CBASP IN THE TREATMENT OF PERSISTENT DEPRESSIVE DISORDER

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CBASP IN THE TREATMENT OF PERSISTENT DEPRESSIVE DISORDER

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EDITORIAL
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Editorial: CBASP in the Treatment of Persistent Depressive Disorder

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Keywords: persistent depressive disorder, cognitive behavioral analysis system of psychotherapy, comorbidity, effectiveness, group

Editorial on the Research Topic

CBASP in the Treatment of Persistent Depressive Disorder

This special issue seeks to contribute to a better understanding of patients with a persistent depressive disorder (PDD) and on how to optimize treatment for this group of patients. Starting with a case description:

John is a 39-year-old man. He is diagnosed with PDD. His depression started by the age of 18. He grew up with a depressed mother, who was in and out of hospital during his childhood. His father had a hard time taking care of him and his siblings and hit them when they did not obey or if they said something he did not like. John learned to stay out of his parents' way and to take care of himself. He is currently working as an accountant in a small firm. He met his wife at the age of 23 and married her straight away. They have a son, now at the age of 15 years, hitting puberty. John has trouble handling him. His depression got worse in the last couple of months and he seeks treatment. During treatment it becomes clear that it is difficult for John to assert himself. He is afraid to get punished or rejected when he expresses something negative. In turn, he withdraws when these situations appear.

John is referred to a Cognitive Behavioral Analysis System of Psychotherapy (CBASP) therapist since CBASP is recommended as first line psychotherapeutic treatment for persistent depressive disorder by several national and international treatment guidelines (e.g., the Danish, German, Canadian guidelines and the European Psychiatric Association). CBASP is developed by James McCullough Jr. who is stating in his contribution for this special issue: "Becoming a successful CBASP psychotherapist is not a simple undertaking." Patients with PDD, like John, are difficult to treat because of the entrenched cognitive-emotional-behavioral patterns they bring to treatment, exhibited in overlearned interpersonal fear and avoidance ("it is better to stay away from others") often due to abusive developmental histories (in John's case a depressed mother and an aggressive father).

McCullough states that these toxic developmental histories derail normal social-emotional maturational development and entrap patients in a preoperational state of functioning. The term "preoperational" stems from Piaget's theory of cognitive development in children. In this preoperational state, patients are not connected to their environment (John withdraws whenever something negatives happens). CBASP practitioners are required to actualize a personal relationship with their patients that seeks to modify this preoperational state of being, this technique is labeled *Disciplined Personal Involvement*. Disciplined Personal Involvement addresses the interpersonal fear and avoidance and teaches patients to connect with others, starting with the therapist.

Like John, many patients grow up with depressed mothers (or fathers). A study on the effects of maternal depression, and more specifically, maternal chronic depression, on offspring's risk for

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depression, anxiety, and externalizing symptoms, by Silver et al., state that given the potential long-term effects of maternal chronic depression on offspring, early identification, appropriate treatment, and follow-up of depressed women and their children should be key priority.

As our patient John grew up with a depressed mother and an aggressive father both not able to handle and take care of their children, John learned to avoid his parents and disconnect with his environment, which kept him in a preoperational state; thinking "whatever I do, nothing will ever change." Sondermann et al. examined the influence of preoperational thinking on depressive symptom severity over 2 years. They found that higher levels of preoperational thinking are associated with higher depressive symptom severity over time. Their results confirm the assumption of CBASP that preoperational thinking is an important factor contributing to the maintenance of depression and therefore needs to be addressed in psychotherapy.

Most PDD patients feel isolated and lonely. Nenov-Matt et al. contribution focusses on the importance of loneliness, since loneliness has been associated with the development of mental disorders and chronic illness trajectories. In a cross-diagnostic study loneliness was examined by comparing PDD and Borderline Personality Disorder (BPD) patients with healthy controls in its interplay with symptom burden, social network characteristics, rejection sensitivity as well as childhood maltreatment. They found that loneliness is highly prevalent in PDD and BPD patients and contributes to the overall symptom burden. In addition, loneliness showed an association with prior experiences of childhood maltreatment as well as current rejection sensitivity. The experience of childhood maltreatment makes PDD patients sensitive to rejection, while their avoidant/submissive interpersonal behavior makes them prone for rejection (Struck et al.) and leads to reduced social connectedness and compassion toward close others (Frick et al.). This cycle needs to be broken.

In CBASP, the focus is on breaking this cycle. Besides individual psychotherapy, CBASP can also be effective in a group format for inpatients and outpatients. For example, Guhn et al. investigated interpersonal change during a multimodal inpatient treatment and found that the majority of their PDD patients reported gain in social competence throughout the CBASP group sessions. In line with these findings is the study by Sürig et al. They examined change in interpersonal and metacognitive skills during treatment with CBASP and metacognitive therapy. They found that especially changes in interpersonal skills seem to be of particular relevance in the treatment of depression. In addition, increases in friendly-dominant behaviors and a less preoperational style of thinking were associated with alleviation of depressive symptoms, thereby, again, supporting McCullough's interpersonal model of depression.

Beside the positive effects of treatment, it is also important to study the negative effects that treatments might have. Herzog et al. focused on the impact of negative effects in a multimodal inpatient CBASP treatment program. They found that most reported negative effects, such as stigmatization, financial concerns and intrapersonal changes, do not appear to have an impact on treatment outcome. However, dependence on the therapist, which was the most frequently reported negative effect, did seem to be negatively linked to treatment response. Glanert et al. also found that care dependency might be associated with a worse treatment outcome in depressed patients. In addition, their results indicate that care dependency is a dynamic construct, as it is changing over time, while the levels of care dependency seem to be independent from the received type of treatment. Future research should continue investigating the mechanisms of care dependency.

Besides PDD, most patients report comorbid disorders, such as comorbid personality disorders. In contrast to other personality disorders, comorbid borderline personality disorder (BPD) is often regarded as an exclusion criterion for CBASP. In clinical settings, however, subthreshold BPD symptoms are prevalent in PDD and may not be obvious at an initial assessment prior to therapy. As data on their impact on CBASP outcome are very limited, this naturalistic study by Konvalin et al. investigates BPD features in PDD and their relevance for the therapeutic outcome of a multimodal CBASP inpatient program. The results show that BPD features at baseline did not limit the clinical response to CBASP. In line with these findings that CBASP might also be useful in patients with other symptom profiles, Sayegh et al. found that patients with bipolar disorder who are currently in a depressive episode can also benefit from CBASP in a group format for outpatients. Finally, Serbanescu et al. investigated the impact of baseline characteristics on the effectiveness of psychotherapy in PDD patients. They compared CBASP with Supportive Psychotherapy and found for both therapies that a poor response was predicted by higher scores of depressive symptoms, suicidality, anxiety, social inhibition, a history of moderate-to-severe emotional or sexual abuse and prior inpatient treatment. In terms of moderators, CBASP was superior over Supportive Psychotherapy for patients with higher depression scores, for patients who had no recurrent depressive episode without complete remission between the episodes, for patients with comorbid axis-I disorders, for patients with a history of at least one antidepressant treatment and for patients with early trauma in the form of moderate-to-severe emotional or physical neglect.

For John, his CBASP treatment taught him how to express negative feelings and how to handle difficult situations with his son, while staying connected with his environment. He knows that he has to keep on working on this, because the patterns that cause his depression are deeply anchored in him.

AUTHOR CONTRIBUTIONS

JW wrote the editorial. PK, ES, TFu, and TFa commented on it and agreed with the final version.

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ORIGINAL RESEARCH
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Preoperational Thinking as a Measure of Social Cognition Is Associated With Long-Term Course of Depressive Symptoms. A Longitudinal Study Involving Patients With Depression and Healthy Controls

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Background: Deficits in social cognition, referred to as preoperational thinking, are assumed to play a key role in the pathogenesis of persistent depression. The aim of this study was to explore the effect of preoperational thinking on the two-year course of depressive symptoms in a sample of persistently depressed, episodically depressed as well as healthy participants.

Methods: We recruited 43 persistently depressed participants, 26 episodically depressed participants and 16 healthy control participants. Preoperational thinking was assessed at baseline with the Luebeck Questionnaire for Recording Preoperational Thinking. Over the period of two years, the course of depressive symptom severity was measured every three months using the Inventory of Depressive Symptomatology.

Results: Using linear mixed model analysis we found a significant effect for the influence of preoperational thinking on the severity of depressive symptoms in the observation period. We found a non-significant statistical trend for an association of preoperational thinking with the change of depressive symptom severity.

Conclusion: Our analyses suggest that a high degree of preoperational thinking is associated with a higher severity of depressive symptoms and possibly less symptom improvement. These findings support the notion that preoperational thinking is a relevant factor for the further course of depression and might indeed contribute to the maintenance of persistent depression.

Keywords: depression, social cognition, preoperational thinking, persistent depressive disorder, Cognitive–Behavioral Analysis System of Psychotherapy, interpersonal behavior

INTRODUCTION

Depressive disorders are frequent mental disorders and one of the main causes of years lived with disability (YLDs), implicating a high burden of disease (1). Approximately 20% of all patients with a depressive disorder develop a persistent depressive disorder (2, 3), with some studies even suggesting rates of up to 30% (4, 5). The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) summarizes the different forms of persistent depression under the diagnosis of persistent depressive disorder (PD). A common feature of all these subgroups is a duration of more than two years (6). A recent systematic review comparing patients with PD to patients with nonpersistent depression (ED) found more comorbidities, more suicide attempts and higher number of previous in- and outpatient treatments in patients with PD (7).

The European Psychiatric Association recommends the Cognitive–Behavioral Analysis System of Psychotherapy (CBASP) as first line psychotherapeutic treatment for persistent depression (8). CBASP was specifically developed for persistent depression (9) combining elements of cognitive behavioral therapy and interpersonal strategies. CBASP assumes that patients with early-onset PD have deficits in social cognition which emerge as a result of adverse childhood experiences (9). It has been observed that patients with PD show higher levels of alexithymia as well as more emotional and behavioral avoidance compared to patients with ED (7, 10), they have more interpersonal fears (11) and are perceived to be more hostile and submissive compared to a normative group as well as in comparison to patients with ED (12).

McCullough (9) suggests that deficits in social cognition should be the target of therapy for PD to improve patients' ability to predict and learn from the consequences of their interpersonal behavior. To conceptualize this, the term preoperational thinking was coined, based on Piaget's theory of cognitive development in children (13, 14). According to observations made by McCullough the cognitive style of patients with PD is similar to preoperational children between the age of two to seven years (9). He describes their thinking as prelogical and precausal, with them being caught in the assumption that all others will respond to them in the same way and in their view, they will always feel like they feel in the present (9). The loss of perspective, to see responses of others as one among many types, is part of the experience that current events are a mere replay of the past. These characteristics are aptly summarized in a patient statement that says: "Whatever I do, nothing will ever change." (9, 11). Another illustration is given by McCullough, who reports a dialog between therapist and patient about an interpersonal conflict, which resulted in the patients statement: "Why are you taking his side? You`re just like all the others—no one understands me." (9). This preoperational thinking is assumed to be the reason for the interpersonal problems in patients with PD because it makes it difficult for them to learn from the actual experience of interpersonal encounters.

Studies that used theory of mind exercises to capture this deficit in social cognition did not find these deficits in patients with persistent depression. In conclusion, Köhler et al. (7) describe the evidence as scarce, with only some evidence for differences between depressed patients in general compared to healthy controls (15–17). Our study aims to provide a more detailed view of social cognition by using a measure developed specifically for preoperational thinking and examining its association with the long-term course of depressive symptoms both in patients and healthy controls. Previous studies using this measure have shown higher levels of preoperational thinking in patients with PD compared to patients with ED or healthy controls (11, 18, 19). Preoperational thinking was also linked to childhood maltreatment with a mediating effect of interpersonal fears (11), as well as mediating the association of childhood maltreatment and a hostile interpersonal style (20).

We did not find existing studies that analyzed the association of preoperational thinking with the course of persistent depression over time. We have therefore conducted a longitudinal study to test the association between baseline preoperational thinking and the two-year course of depressive symptoms. Based on the observation that patients with PD exhibit a higher level of preoperational thinking we hypothesized that preoperational thinking negatively affects the course of depressive symptoms. We were interested if preoperational thinking was associated to the mean levels of depressive symptoms as well as to the change in depressive symptoms in this period.

MATERIALS AND METHODS

Recruitment

We present a prospective, observational, longitudinal study comparing three groups of participants who were matched for age and sex: participants with PD, participants with ED and participants as healthy controls (HC). This study sample was put together from two cross-sectional studies. The first of these (21) recruited depressed participants from in- and outpatient settings, as well as healthy controls *via* local advertisements. The second study (22, 23) recruited patients with depression in a day clinic setting. All participants provided informed consent before enrolling. The ethics committee at the University of Lübeck (Germany) approved the study.

General inclusion criteria were the same as in the underlying studies: Age between 18 and 65 years and adequate proficiency of the German language. Exclusion criteria were somatic conditions requiring acute treatment as well as diagnoses of schizophrenia, schizotypal disorder, bipolar disorder, delusional disorder or substance use disorder. Further criteria for the group of HCs were absence of current mental disorder and no history of psychiatric treatment.

Group assignment was based on a diagnostic interview according to DSM-5 criteria (24) conducted by a trained psychologist for all patients. The group of PD was composed of participants who met the criteria of persistent depressive disorder with: (1) major depressive episode longer than two years without remission; (2)

Abbreviations: CBASP, Cognitive–Behavioral Analysis System of Psychotherapy; CI, Confidence interval; DSM-5, Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition; ED, Episodic depression; HC, Healthy controls; IDS-SR, Inventory of Depressive Symptomatology—Self-rated version; LMM, Linear-mixed models; LQPT, Luebeck Questionnaire for Recording Preoperational Thinking; PD, Persistent depression.

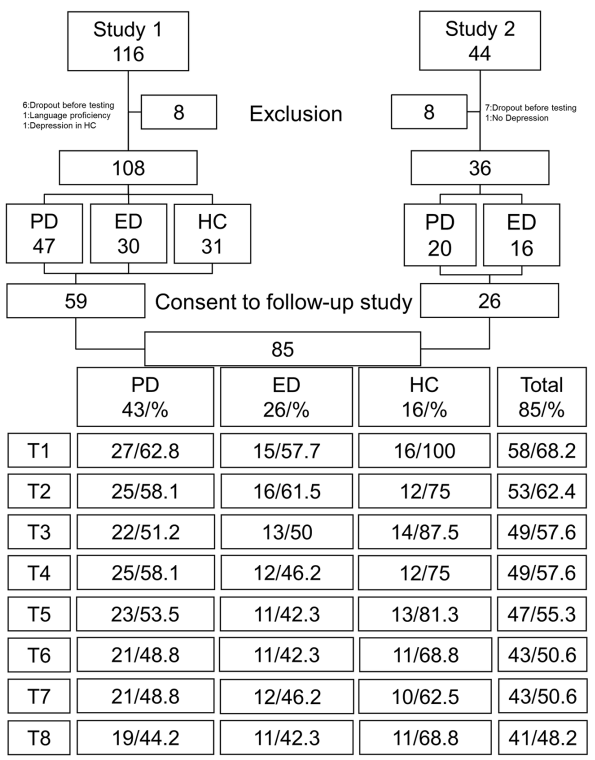
dysthymia; (3) intermittent major depressive episodes with current episode; (4) intermittent major depressive episodes, without current episodes. The group of ED included participants with: (1) a major depressive episode less than 2 years; or (2) a major depressive episode, currently in remission.

Recruitment of study 1 took place between November 2014 and May 2016, while participants in study 2 were recruited between May 2016 and July 2016. In summary, 144 participants of study one and two were invited to participate in this follow-up study; of these, 85 consented to take part (**Figure 1**). The group sizes were 43 participants in group PD, 26 participants in group ED and 16 participants as healthy controls. To test for a systemic bias caused by participants who did not participate, lost to follow-up analyses were performed. Lost to follow-up was defined as a participant who took part less than two times (participation ≤1) after baseline testing. In this analysis all patients who were asked to participate (N = 144) were included. The resulting groups showed no significant differences in the baseline variables of age, diagnosis, gender, secondary education, IDS score and LQPT score (all p-values ≥0.21). For full detail of lost to follow-up analysis see **Supplementary Table 1**.

Measures and Design

LQPT

The Luebeck Questionnaire for Recording Preoperational Thinking (LQPT;19) was used to measure preoperational thinking. Following the description of a short social situation, the participants should respond how they would react in the given situation. It presents a choice between two responses: either indicating a high or a low level of preoperational thinking. For example, in item number 14 a meeting with a new acquaintance is cancelled on short notice by another person. The participant is asked how they would respond to the given situation; they can chose between the following responses: "The acquaintance wouldn't have liked me anyway" indicates a higher level of preoperational thinking while "Too bad it was cancelled, I will call again another time" is indicative of a lower level of preoperational thinking. The LQPT contains 20 items, a low total score shows a high level of preoperational thinking. Recent studies reported the LQPT to be a reliable and valid measure with an excellent internal consistency [Cronbach's alpha 0.901 (19, 21, 25)].



	PD 43/%	ED 26/%	HC 16/%	Total 85/%
T1	27/62.8	15/57.7	16/100	58/68.2
T2	25/58.1	16/61.5	12/75	53/62.4
T3	22/51.2	13/50	14/87.5	49/57.6
T4	25/58.1	12/46.2	12/75	49/57.6
T5	23/53.5	11/42.3	13/81.3	47/55.3
T6	21/48.8	11/42.3	11/68.8	43/50.6
T7	21/48.8	12/46.2	10/62.5	43/50.6
T8	19/44.2	11/42.3	11/68.8	41/48.2

FIGURE 1 | Participant flow with participation rates for each point in time. ED, Episodic depression; HC, Healthy controls; PD, Persistent depression.

IDS-SR

As measurement of the severity of depressive symptoms the Inventory of Depressive Symptomatology, Self-Report (IDS-SR, subsequently abbreviated as IDS (26); was used in its German version (27). It was chosen due to its psychometric properties and its easy administration (26, 28, 29). Multiple studies reported the IDS to be a reliable instrument with Cronbach's alpha coefficients between 0.79 and 0.94 (26, 28, 30).

Further measures used included the DSM-5 based diagnostic interview (24), a demographic questionnaire on age, gender and education, and a short questionnaire about past health care utilization. All measures were used at baseline testing. Subsequently, all participants were notified every three months *via* email over a course of two years to complete the IDS and the questionnaire about health care utilization. In total, this resulted in eight time points of data collection beyond baseline assessment.

Statistical Analysis

All data analyses were performed using SPSS 26 (IBM Corporation, Armonk, NY, USA). Significance levels for all statistical tests were set at $p \leq .05$. Group comparisons are conducted using ANOVAs and t-tests for data with normal distribution and for non-normalized distributed data Kruskal–Wallis tests and Mann–Whitney U tests. The main hypothesis was tested using linear-mixed models (LMM) as they have the advantage of using all available data of each participant. LMM analyses also offer the opportunity to choose an appropriate covariance structure reflecting the potential dependence due to repeated measurements (31). No missing values were substituted in any of the statistical analyses as mixed model analyses based on all observed data are valid and unbiased methods for data missing at random (MAR) (32). In the first analysis, the IDS total score served as dependent variable and was analyzed with time and baseline LQPT as fixed effect. A first order autoregressive structure with homogeneous variances (AR1) was chosen based on Akaike's Information Criterion (AIC) from a fixed set of candidate structures, namely a first order autoregressive (AR1) with either homogeneous or heterogeneous variances; diagonal or scaled identity structure. In a subsequent analysis, we entered time, baseline LQPT, and group as fixed effects with the IDS total score serving as dependent variable. We conducted a third

analysis with IDS change at outcome corrected for baseline IDS score as dependent variable and time, baseline LQPT and baseline IDS as fixed effects.

Sample Description

Demographics and baseline characteristics are shown in **Table 1**. Participants did not differ significantly in age or gender across groups. HC participants had a higher secondary education than participants of the other groups. Significant group differences between all groups were found in LQPT scores, as well as IDS results with mostly large effect sizes. Health care utilization differed between groups with HC participants having lower utilization in comparison to the other groups except for doctor visits of other, non-specified specialties.

RESULTS

Participation and Course of Depressive Symptoms

Participation rate of 56.2% was achieved. Initially at three months (T1) participation rate was 68.2% which decreased over time to a participation rate of 48.2% at the last time point after two years (T8). For full details of participation refer to **Figure 1**. Data from two participants were excluded because of double participation (one instance at T5 and a separate instance at T6). In these cases, only the results of the first participation at each date were considered.

Figure 2 shows the course of depressive symptoms for each group. At all points in time, patients with PD showed higher scores than those with ED who in turn had higher scores than HCs. In multigroup comparisons *via* ANOVA, significant group differences were found for all time points (for time points T5 and T7, Kruskal–Wallis tests were calculated because the normality assumption was violated). In post-hoc analyses, we found that each of the groups (PD, ED, HC) differed from all the others, except for non-significant differences between PD and ED at T4 ($t(35) = 1.875$, $p = .069$), T5 (Mann–Whitney U test: $U = 83{,}000$, $p = .109$) and T8 ($t(28) = 1.738$, $p = .093$).

Health Care Utilization

At all follow-up assessment time points, participants were asked to report their utilization of health care resources in the last three months. At nearly all time points, the three groups differed in the number of visits to a primary care physician (all p-values <.011, except for T2, T5, T7 and T8), to a neurologist or psychiatrist (all p-values <.045, except for T2, T4, and T8) and to a psychotherapist (all p-values <.041). For all the analyses with a significant global effect, post-hoc testing revealed that patients with PD had the highest number of visits (except for the category "neurologist or psychiatrist" at T1; here, patients with ED had more visits than patients with PD). Patients with PD were the only group reporting hospitalizations after the second assessment. The visits at physicians of other specialties showed heterogeneous results.

Preoperational Thinking

In our first LMM analysis, we found a significant effect of the LQPT on IDS ($F_{1,94} = 96.886$, $p < .001$), and of time on the IDS ($F_{1,318} = 17.534$, $p < .001$). This implies that preoperational thinking is associated with the severity of depressive symptoms in the observation period. In the second LMM analysis we added diagnosis group to the fixed effects. We found significant effects of diagnosis ($F_{2,101} = 18.003$, $p < .001$), time ($F_{1,288} = 15.811$, $p < .001$) and LQPT ($F_{1,108} = 28.192$, $p < .001$) on the IDS. Average IDS-scores over the observation period were 1.46 points higher (CI: 0.91, 2.00) for each point decrease in the LQPT-Score. This shows that level of preoperational thinking at baseline is associated to average

TABLE 1 | Sociodemographic data and Baseline test scores with group comparisons.

	Total(*N* = 85)	PD(*n* = 43)	ED(*n* = 26)	HC(*n* = 16)	*P*-value	Test statistics
Age, mean (SD)	36.75 (11.06)	36.51 (9.77)	38.27 (12.96)	34.94 (11.4)	.630	$F_{2,82} = 0.464$
Female, n (%)	50 (58.8)	24 (55.8)	17 (65.4)	9 (56.3)	.717	$\chi^2_2 = 0.667$
Abitur, n (%)	22 (25.9)	5 (11.6)	8 (30.8)	9 (56.3)	.002	$\chi^2_2 = 12.57$
Unemployment, n (%)	29 (34.1)	19 (44.2)	6 (23.1)	4 (25.3)	.139	$\chi^2_2 = 3.941$
Test scores T0						
IDS-SR, mean (SD)	30.18 (17.76)	40.19 (13.58)	29.27 (12.61)	4.75 (2.52)	<.001	$F_{2,82} = 50.887$
LQPT, mean (SD)	14.4 (4.9)	12.26 (4.79)	14.73 (4.06)	19.63 (0.62)	<.001	$\chi^2_2 = 32.739$
Health care utilization in the last 12 months (as number of visits to a physician)						
Primary care physician, mean (SD)	6.94 (7.5)	8.45 (8.97)	7.4 (5.83)	2.25 (1.69)	.016	$F_{2,80} = 4.363$
Psychiatrist or Neurologist, mean (SD)	2.73 (5.7)	3.52 (4.13)	3.16 (8.68)	0	.098	$F_{2,80} = 2.396$
Psychotherapist, mean (SD)	6.55 (11.45)	8.69 (12.98)	7.17 (11.1)	0	.032	$F_{2,79} = 3.603$
Other Physicians, mean (SD)	2.77 (7.96)	3.74 (10.9)	2.2 (2.57)	1.06 (1.18)	.476	$F_{2,81} = 0.749$
Days hospitalized, mean (SD)	23.15 (24.48)	32.58(25.52)	21.76 (20.35)	0	<.001	$F_{2,81} = 13.522$
Group comparisons						
IDS-SR,	**PD/ED**	**PD/HC**	**ED/HC**			
***p*-value (Cohen's *d*)**	.001 (0.826)	<.001 (3.022)	<.001 (2.431)			
LQPT,	**PD/ED**	**PD/HC**	**ED/HC**			
***p*-value (Cohen's *d*)**	.037 (0.516)	<.001 (1.845)	<.001 (1.99)			

ED, Episodic depression; f, Female; HC, Healthy controls; IDS-SR, Inventory of Depressive Symptomatology; LQPT, Luebeck Questionnaire for Recording Preoperational Thinking; PD, Persistent depression; SD, Standard deviation.

symptom severity over the observation period even after correcting for diagnosis. In our third analysis, we found a statistical trend for the association of LQPT to change in IDS corrected for baseline IDS ($F_{1,78} = 3.344$, $p = .071$) and significant effects of time ($F_{1,232} = 8.259$, $p = .004$) and baseline IDS ($F_{1,75} = 14.228$, $p < .001$). The estimated effects of the LQPT are a 0.66 (CI: −0.06, 1.38) higher change in IDS score for each point increase in LQPT score and are higher but with wider confidence intervals than those of the baseline IDS on IDS change (0.36 (CI:0.17, 0.55)).

Table 2 shows the full results of the statistical analyses. For a graphical illustration of the analysis, please refer to **Figure 3** where we have plotted a separate line for the course of depressive symptom severity for each participant with color coding dependent on LQPT scores.

DISCUSSION

Summary of Results

In this study, we examined the influence of preoperational thinking on depressive symptom severity over two years. We found that participants with higher levels of preoperational thinking had a higher baseline symptom severity than participants with lower levels of preoperational thinking. This effect was independent of the diagnosis of PD, suggesting that it might indeed be preoperational thinking and not only a baseline diagnosis of PD that contributes to higher depressive symptoms over the observation period. While we did find a statistical trend, we did not find a significant effect of preoperational thinking on the change of depressive symptom severity over the course of two years. This could suggest that baseline preoperational thinking helps explain changes of depressive symptoms, with higher levels of preoperational thinking leading to less symptom improvement.

Comparison to Existing Studies

Depressive symptoms declined most sharply between baseline and three months later. Reductions in depressive symptoms were modest after that period. This observation is in keeping with previous studies (33, 34), in particular Spijker et al. (35) who showed that rates of remission were highest within the first three months following therapy. As expected, the group of healthy controls exhibited no symptom severity that would indicate depression.

We found higher symptom severity in the group PD at all points in time which ties in well with other studies reporting a higher symptom severity in patients with PD (36, 37). A review comparing PD to non-PD patients concludes that available studies show inconsistent results with about one third of the sources showing higher symptom severity in PD, only a minority showing higher symptom severity in ED but many studies reporting no differences in symptom severity (7). Use of healthcare resources differed across groups with group PD having higher utilization mostly in the categories of visits at a primary care physician, at a neurologist or psychiatrist and visits at a psychotherapist compared to participants of group ED and HC. This higher utilization is consistent with previous studies indicating more treatment as well as longer history of treatment in patients with PD (7).

The differences in level of preoperational thinking at baseline for the groups PD and ED are consistent with other studies (18, 19). We did find a significant group difference, with the group PD showing higher levels of preoperational thinking than the other groups, whereas the group of ED showed significant higher levels of preoperational thinking in comparison to the group HC. Our results show that higher levels of preoperational thinking are associated with higher depressive symptom severity over time. These results are consistent with the view that deficits in social cognition are relevant for the course of depression. The trend we found for the association of baseline LQPT with change in IDS (corrected for baseline IDS) should be examined further by subsequent studies. Our effect estimates suggest a small effect that appears to be stronger than the effect of baseline IDS score on the IDS change. Considering the wider confidence intervals, the true effect size could be weaker or stronger.

Other studies have already demonstrated that social cognition may be associated with symptom severity in episodic depression. In a recent meta-analysis by Bora and Berk patients with ED differed in theory of mind skills from healthy controls; the level of impairment was related to symptom severity (38). Our results

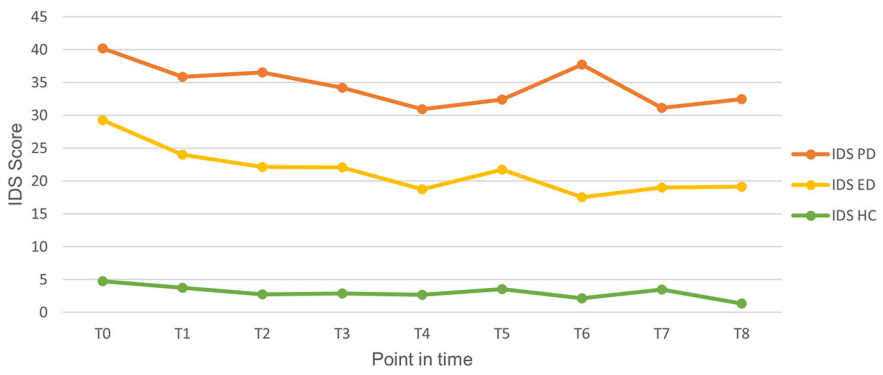


FIGURE 2 | Course of depressive symptom severity for each point in time in the period of two years. ED, Episodic depression; HC, Healthy controls; IDS, Inventory of Depressive Symptomatology; PD, Persistent depression.

TABLE 2 | Results of linear mixed model analyses.

	P	*F*	*dF*	*t*	Estimates (CI)
Analysis one					
Time	<.001	17.534	1, 318	−4.19	−1.24 (−1.83, −0.66)
LQPT	<.001	96,886	1, 94	−9.84	−2.46 (−2.96, −1.96)
Analysis two					
Time	<.001	15.811	1, 288	−3.98	−1.10 (−1.65, −0.56)
LQPT	<.001	28.192	1, 108	−5.31	−1.46 (−2, −0.91)
Group	<.001	18.00	2, 101		
(PD to HC)				5.98	20.71 (13.84, 27.58)
(ED to HC)				3.84	12.54 (6.06, 19.03)
Analysis three					
Time	.004	8.259	1, 232	2.87	1.11 (0.35, 1.87
IDS baseline	<.001	14.228	1, 75	3.77	0.36 (0.17, 0.55)
LQPT	.071	3.344	1, 78	1.83	0.66 (−0.06, 1.38)

Dependent variable in analysis one and two is the IDS score examined with the listed fixed effects. For analysis 3 the dependent variable is change of IDS corrected for baseline IDS, the fixed effects are listed in the table. CI, Confidence interval; dF, Degrees of freedom; ED, Episodic depression; HC, Healthy controls; LQPT, Luebeck Questionnaire for Recording Preoperational Thinking; PD, Persistent depression.

are consistent with the assumptions of CBASP about persistent depression, in particular, that preoperational thinking is a factor contributing to the maintenance of depression and thus plays a key role in its formation. Constantino et al. observed in a study of persistently depressed patients that a decrease of hostile-submissive interpersonal impact messages under therapy was associated with a greater reduction of depressive symptoms over time (39). These findings are consistent with recent results by Klein et al. showing that the association between treatment and outcome was mediated through the reduction of interpersonal problems, in their study measured as change in social inhibition and the improvement of the therapeutic alliance (40). This implies that treatment-induced improvements in interpersonal skills positively affect the course of depression.

The association of preoperational thinking with depressive symptom severity was not specific to patients with PD. Further studies should measure the levels of preoperational thinking repeatedly in addition to depressive symptom severity. This may help to confirm that higher levels of preoperational thinking are associated with higher depressive symptom severity over time in both patients with PD and ED. That approach with a larger sample size would also allow to examine if the statistical trend for association of baseline LQPT to change in IDS is replicable. A possible design could follow the approach of Faissner et al., who used a latent growth model with repeated measurement of cognitive and metacognitive maladaptive beliefs (41). Furthermore, the role of other variables possibly associated with preoperational thinking could also be addressed in a further study. These additional variables include alexithymia (42), because alexithymia has also been associated with interpersonal problems in depression (43). Another potential variable is attachment because both alexithymia and attachment styles (44, 45) have been shown to mediate the association between childhood maltreatment and depression in separate studies (44).

Strengths and Limitations

The prospective longitudinal design of this study enabled us to examine the relationship between the interindividual differences

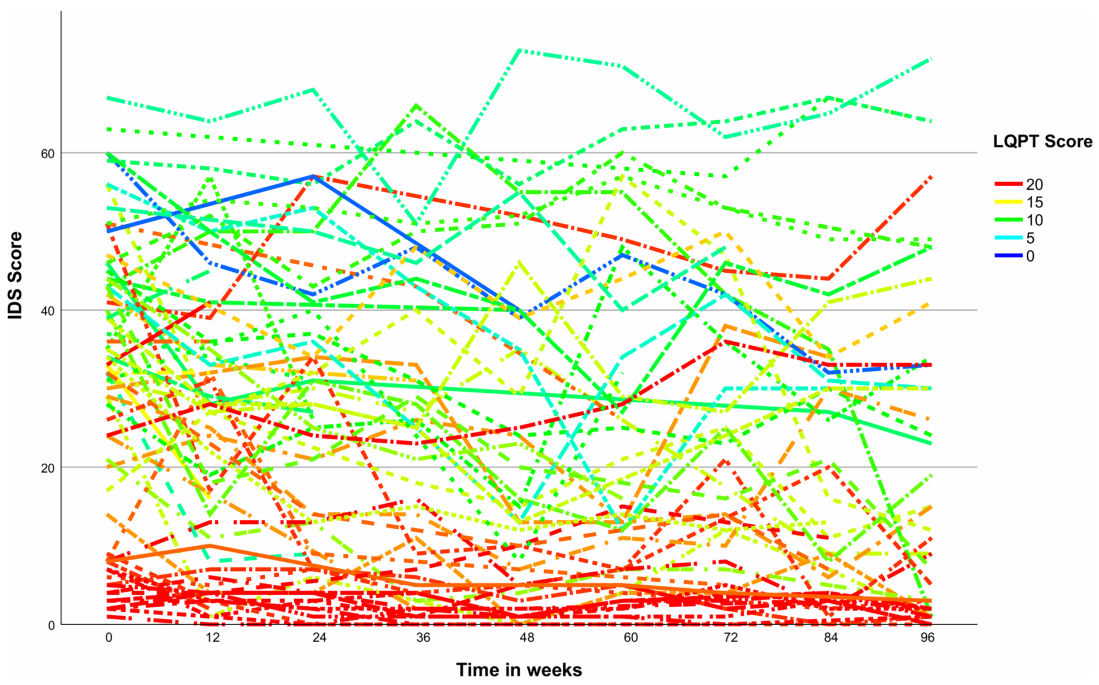


FIGURE 3 | Individual courses of depressive symptoms over time with color coding dependent on level of preoperational thinking. IDS, Inventory of Depressive Symptomatology; LQPT, Luebeck Questionnaire for Recording Preoperational Thinking.

at baseline and the intraindividual changes in depressive symptom severity over two years. The recruitment of two groups with different forms of depression and a group of healthy controls is another strength of this study. Lost to follow-up analyses did not indicate a systematic bias. A possible source of heterogeneity in the group PD relates to group assignment. In our study we divided depressive participants in persistent versus episodic depression based on DSM-5 criteria (6); the group of persistent depression thus included participants with dysthymia alongside participants with PD with current major depressive episode. In line with observations by Klein et al. (42, 46) we decided to use the DSM-5 based assignment because of the similarities between the subgroups of dysthymic and persistent depression with major depressive disorder over the course of time. A possible problem based in the study design is that we did not test for transition of an episodic depression into a persistent depression. The rate of chronification is estimated to be around 15 to 20% (3), with some studies suggesting even higher rates of around 30% (4). This could potentially skew our results and minimize the differences of the depressive groups, if some participants of the group ED had developed a persistent depression across the observation period. Contrary to this we did find significant differences between the group's PD and ED at six out of nine points in time.

Main limitations of this study are the small group size and the low participation rate of the included participants. One of the possible causes for this is the non-personal approach *via* E-Mail. Fricker et al. (43, 47) showed higher participation rates with telephone surveys in comparison to internet survey even if higher incentives where offered in the internet survey. Another possible problem of E-Mail based data collection is failed contacting due to anti-spam procedures of providers. Advantages of an internet survey and in this case contacting *via* E-Mail is the direct acquisition of data which prevents transmission errors and the flexibility and time savings for participant and investigator. As Weightman et al. (48) mention, a problem in studies on social cognition is the multitude of different tools and constructs which lead to a limited comparability across different studies. To the best of our knowledge only Ladegaard et al. (49) examined the course of social cognition abilities in depression. In a sample of patients with a first episode of major depression, they found an improvement of these skills with symptom remission (49). Another limitation is the unbalanced number of participants in the three groups, which was probably a result of already imbalanced group sizes in the two studies from which the participants were recruited. Still, lost to follow-up rates were similar across groups. It is also unclear to what extent the treatment received by study participants affected the course of their depression.

CONCLUSION

Our study suggests that preoperational thinking is associated with symptom severity across the course of depression and possibly with the change of symptom severity, further supporting the evidence for the role of social cognition in the pathogenesis of persistent depression. Other studies should try to verify this association to give a better understanding of social cognition, the extent of its effects on depressive disorders and help identify what kind of deficits distinguish patients with depressive disorders from others.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethics committee University of Lübeck. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

Conception and design: JK with support from SS. Acquisition of data: Study 1—JS and SS, Study 2—UG and JO. Follow-up study: SS with support from SM and JK. Analysis and interpretation of data: SS and JK. Drafting of manuscript: SS with support from JK and SM. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2020.00652/full#supplementary-material

REFERENCES

1. GBD. Disease and Injury Incidence and Prevalence Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet (Lond Engl)* (2018) 392(10159):1789–858. doi: 10.1016/S0140-6736(18)32279-7
2. Gilmer WS, Trivedi MH, Rush AJ, Wisniewski SR, Luther J, Howland RH, et al. Factors associated with chronic depressive episodes: a preliminary report from the STAR-D project. *Acta Psychiatr Scand* (2005) 112(6):425–33. doi: 10.1111/j.1600-0447.2005.00633.x
3. DGPPN B, KBV AWMF. *(Hrsg.). S3-Leitlinie / Nationale VersorgungsLeitlinie Unipolare Depression*. Vol. 2. Auflage. DGPPN, BÄK, KBV, AWMF. (2015). https://www.awmf.org/leitlinien/detail/ll/nvl-005.html; https://www.leitlinien.de/mdb/downloads/nvl/depression/depression-2aufl-vers5-lang.pdf
4. Murphy JA, Byrne GJ. Prevalence and correlates of the proposed DSM-5 diagnosis of Chronic Depressive Disorder. *J Affect Disord* (2012) 139(2):172–80. doi: 10.1016/j.jad.2012.01.033
5. Satyanarayana S, Enns MW, Cox BJ, Sareen J. Prevalence and correlates of chronic depression in the Canadian Community Health Survey: Mental health and well-being. *Can J Psychiatry* (2009) 54(6):389–98. doi: 10.1177/070674370905400606
6. American Psychiatric Association. *Diagnostic and statistical manual of mental disorders: DSM-5*. Arlington, Virginia: American Psychiatric Association (2013).
7. Köhler S, Chrysanthou S, Guhn A, Sterzer P. Differences between chronic and nonchronic depression: Systematic review and implications for treatment. *Depress Anxiety* (2019) 36(1):18–30. doi: 10.1002/da.22835
8. Jobst A, Brakemeier EL, Buchheim A, Caspar F, Cuijpers P, Ebmeier KP, et al. European Psychiatric Association Guidance on psychotherapy in chronic depression across Europe. *Eur Psychiatry* (2016) 33(1):18–36. doi: 10.1016/j.eurpsy.2015.12.003
9. McCullough JP. *Treatment for chronic depression: cognitive behavioral analysis system of psychotherapy (CBASP)* Vol. 326. New York: Guilford Press (2000).
10. van Randenborgh A, Hüffmeier J, Victor D, Klocke K, Borlinghaus J, Pawelzik M. Contrasting chronic with episodic depression: An analysis of distorted socio-emotional information processing in chronic depression. *J Affect Disord* (2012) 141(2–3):177–84. doi: 10.1016/j.jad.2012.02.039
11. Klein JP, Stahl J, Hüppe M, McCullough JP, Schramm E, Ortel D, et al. Do interpersonal fears mediate the association between childhood maltreatment and interpersonal skills deficits? A matched cross-sectional analysis. *Psychother Res* (2020) 30(2):267–78. doi: 10.1080/10503307.2018.1532125
12. Bird T, Tarsia M, Schwannauer M. Interpersonal styles in major and chronic depression: A systematic review and meta-analysis. *J Affect Disord* (2018) 239:93–101. doi: 10.1016/j.jad.2018.05.057
13. Piaget J. *The Language and Thought of the Child*. London: Kegan Paul, Trench, Trubner & co, ltd. (1926). p. 246.
14. Piaget J. Part I: Cognitive development in children: Piaget development and learning. *J Res Sci Teach* (1964) 2(3):176–86. doi: 10.1002/tea.3660020306
15. Wilbertz G, Brakemeier EL, Zobel I, Härter M, Schramm E. Exploring preoperational features in chronic depression. *J Affect Disord* (2010) 124 (3):262–9. doi: 10.1016/j.jad.2009.11.021
16. Zobel I, Werden D, Linster H, Dykierek P, Drieling T, Berger M, et al. Theory of mind deficits in chronically depressed patients. *Depress Anxiety* (2010) 27 (9):821–8. doi: 10.1002/da.20713
17. Wolkenstein L, Schönenberg M, Schirm E, Hautzinger M. I can see what you feel, but i can't deal with it: Impaired theory of mind in depression. *J Affect Disord* (2011) 132(1–2):104–11. doi: 10.1016/j.jad.2011.02.010
18. Klein JP, Kensche M, Becker-Hingst N, Stahl J, Späth C, Mentler T, et al. Development and psychometric evaluation of the Interactive Test of Interpersonal Behavior (ITIB): A pilot study examining interpersonal deficits in chronic depression. *Scand J Psychol* (2016) 57(1):83–91. doi: 10.1111/sjop.12222
19. Kühnen T, Knappke F, Otto T, Friedrich S, Klein JP, Kahl KG, et al. Chronic depression: Development and evaluation of the luebeck questionnaire for recording preoperational thinking (LQPT). *BMC Psychiatry* (2011) 11(1):199. doi: 10.1186/1471-244X-11-199
20. Klein JP, Grasshoff L, Hermanns R, Haeger S, Sondermann S, Kühnen T, et al. Präoperatorisches Denken bei Patienten mit Angststörung oder Chronischem Rückenschmerz: Zwei Querschnittsstudien zum besseren Verständnis des Cognitive Behavioral Analysis System of Psychotherapy (CBASP). *Z für Psychiatr Psychol und Psychother* (2020) 68(3):1–9. doi: 10.1024/1661-4747/a000418
21. Stahl J. *Evaluation eines interaktiven Testsystems zur Erfassung interpersonellen Verhaltens „ Interactive Test of Interpersonal B ehaviour " ITIB*. [thesis]. University of Lübeck (2018). p. 155.
22. Outzen J. *Changes in Interpersonal and Metacognitive Skills during a Day Clinic Treatment in Patients with Depression [master's thesis]*. Universität zu Lübeck (2016). p. 149.
23. Grave U. *Depressionsrelevante Fertigkeitsdefizite bei chronischer Depression Depressionsrelevante Fertigkeitsdefizite bei chronischer Depression [master's thesis]*. Universität zu Lübeck (2016). p. 23.
24. Klein JP, Belz M. *Psychotherapie Chronischer Depression. Praxisleitfaden CBASP*. Göttingen: Hogrefe (2014).
25. Sargin AE, Uca O, Kose S, Türkçapar H. Reliability, validity, and factorial structure of the Turkish version of the Luebeck questionnaire for recording preoperational thinking (Turkish LQPT). *Psychiatry Clin Psychopharmacol* (2018) 28(2):191–8. doi: 10.1080/24750573.2017.1411575
26. Rush AJ, Gullion CM, Basco MR, Jarrett RB, Trivedi MH. The Inventory of Depressive Symptomatology (IDS): psychometric properties. *Psychol Med* (1996) 26(3):477–86. doi: 10.1017/S0033291700035558
27. Drieling T, Schärer LO, Langosch JM. The Inventory of Depressive Symptomatology: German translation and psychometric validation. *Int J Methods Psychiatr Res* (2007) 16(4):230–6. doi: 10.1002/mpr.226
28. Trivedi MH, Rush AJ, Ibrahim HM, Carmody TJ, Biggs MM, Suppes T, et al. The Inventory of Depressive Symptomatology, Clinician Rating (IDS-C) and Self-Report (IDS-SR), and the Quick Inventory of Depressive Symptomatology, Clinician Rating (QIDS-C) and Self-Report (QIDS-SR) in public sector patients with mood disorders: a psych. *Psychol Med* (2004) 34(1):73–82. doi: 10.1017/S0033291703001107
29. Rush AJ, Trivedi MH, Ibrahim HM, Carmody TJ, Arnow B, Klein DN, et al. The 16-Item Quick Inventory of Depressive Symptomatology (QIDS), clinician rating (QIDS-C), and self-report (QIDS-SR): a psychometric evaluation in patients with chronic major depression. *Biol Psychiatry* (2003) 54(5):573–83. doi: 10.1016/S0006-3223(02)01866-8
30. Corruble E, Legrand JM, Duret C, Charles G, Guelfi JD. IDS-C and IDS-SR: Psychometric properties in depressed in-patients. *J Affect Disord* (1999) 56(2–3):95–101. doi: 10.1016/S0165-0327(99)00055-5
31. Gueorguieva R, Krystal JH. Move over ANOVA: Progress in Analyzing Repeated-Measures Data and Its Reflection in Papers Published in the Archives of General Psychiatry. *Arch Gen Psychiatry* (2004) 61(3):310–7. doi: 10.1001/archpsyc.61.3.310
32. Bell ML, Fiero M, Horton NJ, Hsu C-H. Handling missing data in RCTs; a review of the top medical journals. *BMC Med Res Methodol* (2014) 14(1):118. doi: 10.1186/1471-2288-14-118
33. Stegenga BT, Kamphuis MH, King M, Nazareth I, Geerlings MI. The natural course and outcome of major depressive disorder in primary care: The PREDICT-NL study. *Soc Psychiatry Psychiatr Epidemiol* (2012) 47(1):87–95. doi: 10.1007/s00127-010-0317-9
34. Comijs HC, Nieuwesteeg J, Kok R, van Marwijk HW, van der Mast RC, Naarding P, et al. The two-year course of late-life depression; results from the Netherlands study of depression in older persons. *BMC Psychiatry* (2015) 15 (1):1–9. doi: 10.1186/s12888-015-0401-5
35. Spijker J, de Graaf R, Bijl RV, Beekman ATF, Ormel J, Nolen WA. Duration of major depressive episodes in the general population: results from The Netherlands Mental Health Survey and Incidence Study (NEMESIS). *Br J Psychiatry* (2002) 181(Cidi):208–13. doi: 10.1192/bjp.181.3.208
36. Köhler S, Wiethoff K, Ricken R, Stamm T, Baghai TC, Fisher R, et al. Characteristics and differences in treatment outcome of inpatients with chronic vs. episodic major depressive disorders. *J Affect Disord* (2015) 173:126–33. doi: 10.1016/j.jad.2014.10.059
37. Wiersma JE, van Oppen P, van Schaik DJF, van der Does AJW, Beekman ATF, Penninx BWJH. Psychological Characteristics of Chronic Depression. *J Clin Psychiatry* (2011) 72(03):288–94. doi: 10.4088/JCP.09m05735blu
38. Bora E, Berk M. Theory of mind in major depressive disorder: A meta-analysis. Vol. 191. *J Affect Disord* (2016) 191:49–55. doi: 10.1016/j.jad.2015.11.023

39. Constantino MJ, Laws HB, Arnow B, Klein DN, Rothbaum BO, Manber R. The relation between changes in patients' interpersonal impact messages and outcome in treatment for chronic depression. *J Consult Clin Psychol* (2012) 80 (3):354–64. doi: 10.1037/a0028351
40. Klein JP, Probst T, Kriston L, Assmann N, Bailer J, Eich H, et al. Changes in Therapeutic Alliance and in Social Inhibition as Mediators of the Effect of the Cognitive Behavioral Analysis System of Psychotherapy: A Secondary Analysis from a Randomized Clinical Trial. *Psychother Psychosom* (2020) 19:1–2. doi: 10.1159/000506082
41. Faissner M, Kriston L, Moritz S, Jelinek L. Course and stability of cognitive and metacognitive beliefs in depression. *Depress Anxiety* (2018) 35(12):1239–46. doi: 10.1002/da.22834
42. Li S, Zhang B, Guo Y, Zhang J. The association between alexithymia as assessed by the 20-item Toronto Alexithymia Scale and depression: A meta-analysis. *Psychiatry Res* (2015) 227(1):1–9. doi: 10.1016/j.psychres.2015.02.006
43. Spitzer C, Siebel-Jürges U, Barnow S, Grabe HJ, Freyberger HJ. Alexithymia and interpersonal problems. *Psychother Psychosom* (2005) 74(4):240–6. doi: 10.1159/000085148
44. Thomas R, DiLillo D, Walsh K, Polusny MA. Pathways from child sexual abuse to adult depression: The role of parental socialization of emotions and alexithymia. *Psychol Violence* (2011) 1(2):121–35. doi: 10.1037/a0022469
45. Taubner S, Kessler H, Buchheim A, Kächele H, Staun L. The Role of Mentalization in the Psychoanalytic Treatment of Chronic Depression. *Psychiatry Interpers Biol Process* (2011) 74(1):49–57. doi: 10.1521/psyc.2011.74.1.49
46. Klein DN, Shankman SA, Rose S. Ten-Year Prospective Follow-Up Study of the Naturalistic Course of Dysthymic Disorder and Double Depression. *Am J Psychiatry* (2006) 163(5):872–80. doi: 10.1176/ajp.2006.163.5.872
47. Fricker S. An Experimental Comparison of Web and Telephone Surveys. *Public Opin Q* (2005) 69(3):370–92. doi: 10.1093/poq/nfi027
48. Weightman MJ, Air TM, Baune BT. A Review of the Role of Social Cognition in Major Depressive Disorder. *Front Psychiatry* (2014) 11:5(NOV). doi: 10.3389/fpsyt.2014.00179
49. Ladegaard N, Videbech P, Lysaker PH, Larsen ER. The course of social cognitive and metacognitive ability in depression: Deficit are only partially normalized after full remission of first episode major depression. *Br J Clin Psychol* (2016) 55(3):269–86. doi: 10.1111/bjc.12097

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CLINICAL TRIAL
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Group Cognitive Behavioral Analysis System of Psychotherapy (CBASP): A Pilot Study for Bipolar Depression

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Objectives: Cognitive Behavioral Analysis System of Psychotherapy (CBASP) is an individually administered treatment model designed specifically for Persistent Depression however bipolar patients have traditionally been excluded from CBASP studies. There is a perception that bipolar depression will be harder to treat and requires a unique psychological approach. This pilot study reports on the feasibility of administering the same 20-week manualized group CBASP therapy with bipolar patients currently in a depressive episode.

Methods: This non-randomized, single-arm prospective pilot study, reports on an *a posteriori* exploration of benefits to bipolar depressed patients (n=26) of the same 20-week group CBASP intervention administered to unipolar depressed patients (n=81). The clinical trial for the initial phase examining benefits of the manualized 20-week group CBASP intervention with unipolar patients was registered with the ISRCTN registry, study ID: ISRCTN95149444. Results reported here include mixed ANOVA analyses, across group treatment models and diagnostic categories. Changes over time in self-reported depressive symptoms (Inventory of Depressive Symptoms -IDS-SR), self-reported social functioning, interpersonal problems and interpersonal dispositions are documented for all patients. An exploratory longitudinal latent class analysis was used to examine patients' trajectories of improvement in depressive symptoms. Finally, the best predictors of change in reported depressive symptoms were explored with a logistic regression for all patients.

Results: Improvements in depressive symptoms and in social functioning over time were significant for all patients with bipolar patients trending towards a greater improvement in depressive symptoms after controlling for baseline differences. An exploratory Latent Class Analysis identified two different treatment trajectories for the entire sample: 1) moderate to severely depressed patients who improved significantly (49%) and 2) severely depressed patients who did not improve (51%). The best predictors of non-response to

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group therapy include high baseline problems in social functioning and low rates of self-reported Perceived Improvements in overall health.

Conclusion: Bipolar patients in a depressive episode appear to benefit from the same 20-week group CBASP model designed originally for the treatment of Persistent Depressive Disorder. Bipolar patients seem more easily mobilized both during and outside of group therapy sessions and report more interpersonal confidence and more agency than unipolar depressed patients.

Keywords: bipolar depression, unipolar depression, group psychotherapy, severe depression, Cognitive Behavioral Analysis System of Psychotherapy (CBASP)

INTRODUCTION

Severe depression is a debilitating illness whether it is associated with a bipolar or unipolar mood disorder and often becomes recurrent and refractory. More than 300 million people are affected by unipolar depression worldwide (WHO 2018) and about 49 million (WHO 2013) have bipolar disorders globally (1, 2). Bipolar disorders follow Major Depressive Disorder as the fifth leading cause of disability-adjusted life years (DALYs) and are the 16th leading cause of years lost to disability worldwide (2). Furthermore, poor psychosocial functioning is a risk factor for illness progression in both bipolar and unipolar mood disorders (3). With bipolar depression being the most difficult to treat and most impairing phase of bipolar disorder (1, 4–6), psychotherapy is often an important adjunct to pharmacotherapy in the treatment of bipolar depression in the context of relapse prevention (6–8). Effective Psychosocial interventions recommended for acute depressive episodes in bipolar disorder include psychoeducation and Cognitive Behavioral Therapy (9) (CBT), Family-focused therapy (10) (FFT) as maintenance treatment with euthymic patients, Interpersonal and Social Rhythm Therapy (1) (IPSRT) and Mindfulness-Based Cognitive Therapy (11) (MBCT) for residual sub-syndromal symptoms. Cognitive Behavioral Analysis System of Psychotherapy [CBASP, (12, 13)] is the only psychotherapy developed to date specifically for the treatment of persistent depression. CBASP is a first line treatment for persistent depression in Europe due to its reported lower drop-out rates and greater tolerability compared to medication and even to other psychological treatments (14, 15). CBASP uses an interpersonal and behavioral paradigm to improve social functioning and help depressed patients break their isolation and improve executive functions (12). It is a highly structured, skills-oriented approach teaching concrete skills to help patients learn interpersonal problem-solving strategies (16). Keller et al. (17) mounted the first long-term, multi-site clinical trial showing the best-yet response rates for chronic depression when individually-administered CBASP and pharmacotherapy are combined. CBASP has been reported on in several meta-analyses on psychotherapy for persistent depression (18–20). In spite of wide heterogeneity between trials being compared, there is consistent evidence of the effectiveness of CBASP as monotherapy for acute depression but even more effectiveness when combined with medication for persistent depression (19, 21).

Group psychotherapy provides a source of social support and rewards as well as exposure to interpersonal interactions and problem-resolution that are needed to improve social functioning in the treatment of chronic depression. In fact studies of psychotherapy for treatment-resistant depression using a group modality were found to have larger effect sizes than individual modalities according to a recent meta-analysis and meta-regression (22). The feasibility of a maximum of 10 sessions of CBASP group therapy adapted for chronically depressed unipolar inpatients was assessed in a large multicenter study by Sabass et al. (23). The concept of acceptability was measured by self-report questionnaires completed by patients and therapists separately. In addition to significant improvements in clinician-rated depression scores, in self-reported depressive symptoms and in quality of life, results are highly favorable, according to the authors, with regards to acceptability and clinical benefits of group CBASP, considering the lower number of group sessions. Guhn et al. (24) assessed a 12-week multimodal CBASP treatment adapted for inpatients with Persistent Depressive Disorder which included a total of 26 individual and group CBASP sessions with 4 weeks of post-treatment outpatient group CBASP sessions. The group sessions comprised of the same CBASP adaptation used in the previous study by Sabass et al. however the setting in this study was a general psychiatric ward. Guhn et al. (24) report significant treatment response at post-treatment and significant but lower response rates at 6-month follow-up with regards to clinician-rated and to a lesser extent self-rated depressive symptoms. They confirm that their sample of more severely depressed patients than previously reported in a meta-analysis of psychotherapy for chronic depression (21), may have benefitted from an extended duration of treatment to consolidate improvements. Improvements in depressive symptoms were also associated with reduced interpersonal distress.

In a prospective, bi-center, randomized controlled trial, Michalak et al. (25) compared a group adaptation of CBASP plus treatment as usual (TAU) to Mindfulness-Based Cognitive Therapy (MBCT) plus TAU, to TAU alone in a sample of patients with chronic major depression or Persistent Depressive Disorder. Results revealed a large effect size for improvements in clinician-rated depressive symptoms with

eight sessions of group CBASP in addition to treatment as usual for the entire sample while group MBCT was effective in one treatment site more than the other. Comparisons between CBASP and MBCT were complicated by between-site differences discussed by the authors.

There is no published study documenting the effectiveness of group CBASP with bipolar depression. Although McCullough designed and evaluated the effectiveness of CBASP with patients suffering from unipolar persistent depression (17) and a bipolar disorder diagnosis constituted an exclusion criterion in all studies on the effectiveness of CBASP, there is no stipulated contraindication for the use of CBASP for bipolar depression. Furthermore, the same DSM-5 criteria and symptom duration are used to diagnose a major depressive episode in either diagnostic category. Perhaps bipolar patients have been excluded from CBASP treatment due to concerns that patients may switch unexpectedly into hypomania during treatment or to concerns that patients may have cognitive difficulties that make it difficult for them to benefit from cognitive restructuring exercises. The rationale behind staging models for psychiatric disorders sometimes suggests that Bipolar Disorders are more difficult to treat or require different therapeutic interventions or models in relation to the progressive nature of the illness (26–28) Therefore, it remains unknown whether group CBASP can also be beneficial for bipolar depression, a mood state that is often more long-lasting than hypomanic states.

The first author (LS) manualized the group adaptation of CBASP (29, 30) for persistent depression used in this study. In a pilot study administering this group CBASP adaptation over 12 weekly sessions with a sample of unipolar depressed outpatients, it was found to be beneficial in reducing self-reported depressive symptoms and improving self-reported social adjustment and interpersonal self-efficacy (31). However, twelve sessions were found to be insufficient to reach community-based levels of social functioning. A second pilot study was carried out seeking to verify the benefits of increasing this manualized group CBASP adaptation from 12 to 20 weeks considering previous findings of insufficient duration (31). The choice of 20 weeks was based on findings of a meta-analysis of the effectiveness of psychotherapy trials for chronic major depression and dysthymia suggesting 18 treatment sessions to be optimal (21). The second pilot study kept the same outcome measures of self-reported depressive symptoms and social functioning. A sample of unipolar severely depressed patients were non-randomly assigned in a sequential manner to either 20 weeks of manualized group CBASP treatment or to 20 weeks of a manualized group adaptation of Behavioral Activation for depression, also known to be effective in treating depression. Some results of this comparison have been previously published (32). The second pilot study examining the benefits of an extended 20-week group CBASP treatment for unipolar severely depressed patients was registered as a clinical trial with the ISRCTN registry, study ID: ISRCTN95149444.

An exploratory a posteriori phase of this second pilot study, reported in this article, involved administering this group CBASP treatment with bipolar patients in a current depressive episode. This idea emerged largely out of necessity to provide some psychotherapy treatment to severely depressed bipolar patients. This phase followed the completion of data collection with unipolar patients. In this first feasibility, pilot study of group CBASP including bipolar depressed patients, the main objective is to assess whether these patients will benefit from the same 20-weeks of manualized group CBASP treatment, with regards to self-reported improvements in depressive symptoms and in social functioning, as is administered with unipolar depressed patients. The study will also assess whether differences (if any) between patients with bipolar depression or unipolar depression persist after controlling for differences in baseline characteristics. Analyses will explore the nature of the relationship between trajectories of improvement in depressive symptoms and changes in social functioning throughout group therapy for both bipolar and unipolar depressed patients. The best predictors of symptomatic improvements will be examined for all patients. In addition, using a latent class analysis, trajectories of improvements in depression will be explored as well as any associated characteristics.

MATERIALS AND METHODS

Study Design and Participants

This pilot study is a non-randomized, single-arm prospective study. All participants were adult outpatients at the Douglas Mental Health University Institute, Montreal, Quebec, Canada, a specialized, tertiary-care teaching/research psychiatric hospital. Patients with a bipolar depression were treated at the Bipolar Disorders Clinic and patients with a unipolar depression were treated at the Depressive Disorders Clinic. Similar administrative procedures are present in both clinics with regards to admission of patients, semi-structured psychiatric assessments and psychological services available. Participants were included in the study in a sequential manner based on the time of their referral, between 2010 and 2016. The enrolment of participants in both clinics is described in the CONSORT flow-chart in **Figure 1**. Therapy groups consisted entirely of bipolar or of unipolar patients since group therapies were held in each respective clinic where the treating psychiatrists and the patients' charts were situated. Groups were not comprised of patients from both clinics together due to an administrative directive at the time. All participants underwent a comprehensive DSM-IV-TR-based psychiatric evaluation required for admission into the clinics, carried out by their treating psychiatrist. Unipolar patients all received their psychiatric diagnosis before the DSM-5 introduced the diagnosis of Persistent Depressive Disorder to replace several categories for chronic depression. These diagnoses have not been revised for this study. Pharmacological treatments provided for each patient followed clinical guidelines for treatment algorithms developed by the Canadian Network for Mood and Anxiety Treatments (CANMAT) for patients with Major Depressive Disorders (33) and by CANMAT as well as the International Society for Bipolar Disorders (ISBD) regarding patients with a Bipolar Disorder (1).

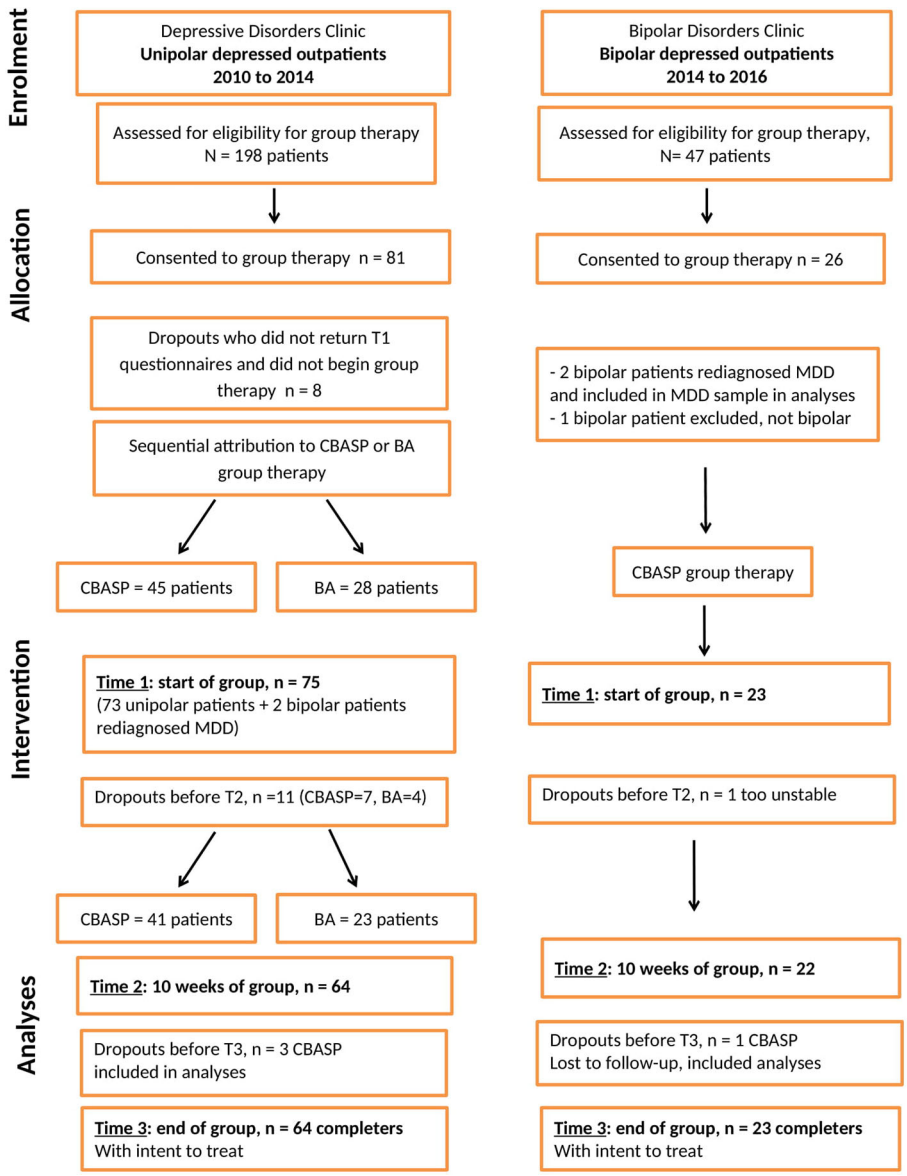

FIGURE 1 | CONSORT flow chart.

Recommendations for concurrent psychosocial therapies are offered, according to CANMAT, as part of best management practices for Bipolar Disorders (8) and for unipolar Major Depressive Disorder (34). Inclusion criteria were patients between ages 18 and 65 with a DSM-IV-TR primary diagnosis of Major Depressive Disorder (MDD), unipolar, or a diagnosis of Bipolar Disorder Type I or Type II, current episode depression, or schizoaffective bipolar type. In addition to primary diagnoses, a second comorbid Axis-I diagnosis was recorded for each patient. Exclusion criteria included the following: psychosis or psychotic symptoms during group therapy, an acute manic or hypomanic episode, a primary diagnosis for any of: anxiety disorders, schizophrenia, acute substance abuse disorder, eating disorder. Patients with a debilitating or unstable medical diagnosis were also excluded. Patients, who were at high risk for suicide at the start of group therapy, including acute suicidal ideation, intent or suicide attempt, were excluded in favor of an individual intervention. This study was approved by the Douglas Institute's Research Ethics Board (REB Protocol 10/19).

Procedures

Patients were referred to group therapy by their treating psychiatrist for a concurrent psychological intervention to their pharmacological treatment due to the severity of their depressive symptoms. Patients from the Depressive Disorders Clinic were met individually by the CBASP-certified psychologist and informed of the benefits of CBASP and BA in a group format

for chronic depression and of the option to participate in the study of their benefits. In accordance with the declaration of Helsinki, patients who accepted to participate in group therapy signed a consent form informing them of the research study and of its impact. Patients who refused group therapy were offered other psychological interventions in an individual modality as they most often refused a group format. A few of the patients who dropped out after giving their consent may have done so in rejection of the group format which they are not always comfortable to admit to. Baseline demographic or clinical information on these dropout cases were included in analyses to assess for potential differences with patients who remained in group therapy. However, personality characteristics, not assessed in this pilot study, may contribute to patients' preferences with regards to treatment modality. Following their informed consent to undergo group therapy, patients from the Depressive Disorders Clinic were assigned to either CBASP or BA group therapy in a sequential manner by constituting one group of six patients for CBASP or BA and then another group of six patients for the other treatment model, etc. Patients were taken from the waiting list and assessed for eligibility for group therapy when the next CBASP or BA group was being constituted. This followed administrative procedures regarding the use of waiting lists for requests for psychotherapy services in this public mental health clinic. Patients did not receive any other psychological treatments while on the waiting list, since group therapy had been recommended, nor during participation in group therapy in order not to confound treatment effects. Medical follow-ups are provided to all patients admitted to the clinic while on a waiting list for psychotherapy.

Patients from the Bipolar Disorders Clinic were offered CBASP group therapy due to a demand for psychological treatment options for the depressive phase of the disorder. Therefore an *a posteriori* exploration of benefits of CBASP for bipolar depression seemed a logical follow-up of this initiative. All bipolar patients participated in CBASP group therapy after all unipolar patients had completed their participation in the study. Bipolar patients also gave their informed consent to complete questionnaires aimed at assessing the benefits of CBASP group therapy.

All patients, unipolar and bipolar, were met for two individual sessions prior to beginning group treatment in order to determine the interpersonal goals they would focus on during group therapy. The group treatment comprised one 2-hour session each week for 20 consecutive weeks, held in each unipolar and bipolar clinics separately. The group CBASP manual adapted by the first author (LS) (29, 30) is based on McCullough's CBASP individual modality (12, 13). The group BA manual developed by Lejuez et al. (35) was adapted by the first author (LS) to accommodate the 20-week group treatment protocol. Each group had a maximum of six patients, with the median and modal group size being five patients. CBASP groups were conducted by a CBASP-certified senior clinical psychologist with a clinical psychology graduate student as co-therapist, receiving training in CBASP or by two CBASP-trained psychology graduate students, all supervised by a CBASP-certified senior clinical psychologist. All BA groups were conducted by either a clinical psychologist or by experienced psychotherapists on staff or by nurse clinicians with a clinical psychology graduate student as co-therapist, also trained and supervised by a clinical psychologist.

All patients received routine medical appointments with their psychiatrist throughout group therapy, examining symptomatology and required minimal changes to their long-term medication regimen. When patients needed to be hospitalized during group therapy, their ongoing participation in group sessions was individually determined. This means that patients could continue attending group sessions during hospitalization and did not drop-out nor were they excluded from participating in group therapy, unless a patient requested to stop group therapy. Patients who completed the initial assessment but subsequently dropped out were included in the current analyses in order to determine whether any characteristics are associated with dropouts.

Patient Selection

A total of 107 outpatients (bipolar n=26, unipolar n=81) admitted into the clinics sequentially accepted to participate in the study. **Figure 1** displays in a CONSORT flow chart enrolment, allocation and intervention stages with dropout cases identified at each level. One bipolar patient, whose primary diagnosis of Bipolar Disorder was changed, was excluded from the study and two bipolar patients had their diagnosis revised to unipolar depression (MDD) and were included in the unipolar sample. One unipolar patient was excluded from analyses due to ongoing psychotic symptoms. The following patients with complete information on clinical and outcome measures, with attrition accounted for, included in analyses at the three assessment periods consisted of: 98 patients at time 1 (23 bipolar, 75 unipolar), 86 patients at time 2 (22 bipolar, 64 unipolar) and 82 patients at time 3 (21 bipolar, 61 unipolar). Patients who did not complete the 20 weeks of group therapy, but attended more than half of the sessions, were included in the analyses using the Intent to Treat principle, as indicated in **Figure 1**. No significant differences were found for both samples between drop-outs due to attrition and patients who completed the 20 weeks of treatment on all demographic and clinical variables. Participants (total N=104) included in the analyses reported below, consisted of 23 bipolar patients in group CBASP, 41 unipolar patients in group CBASP and 23 unipolar patients in group BA. Analyses included demographic and baseline information for non-completers in order to test for differences.

Group Treatments

Cognitive Behavioral Analysis System of Psychotherapy (CBASP), developed by McCullough (12, 13), is the only psychotherapy developed specifically to treat the chronically depressed patient. Based on contemporary learning theory, its primary goal is to connect the patient perceptually to others (the environment) so that others can begin to inform/influence the behaviour of the patient in positive ways. CBASP is based on a Person X Environment Causal Determinant Model of Behavior and promotes the acquisition of stimulus learning (through the

therapeutic and other more adaptive relationships) and response learning (acquiring more adaptive coping behaviours to reduce interpersonal avoidance and increase positive reinforcements) (36).

Both group treatment adaptations, CBASP and BA, comprised two modules. The first module introduces a behavioural activation exercise using an activity calendar and graded task assignments to promote a more active life style. In the case of the CBASP group treatment, the second module introduced the CBASP model with its components including the Situational Analysis, use of the Transference Hypothesis and Interpersonal Discrimination Exercise. The Interpersonal Circumplex is used to demonstrate how complementary interpersonal behaviours result in satisfactory exchanges and how interpersonal motives and goals drive our interpersonal interactions. The Situational Analysis (SA) is used to teach participants the consequences of their interpersonal behaviours. Social skills are also practiced during the SA with participants carrying out role plays together.

The group Behavioral Activation manual used was developed by Lejuez et al. (35, 37) and is based on behavioural principles that examine mechanisms of behavioural change. The goal of this treatment is to gradually increase the frequency of targeted healthy behaviours by increasing the relative value of such behaviours for the individual. This treatment model suggests that the relative frequency of depressed behaviours, compared to non-depressed behaviours (that is all other types of behaviours), is proportional to the relative value of reinforcement obtained for depressed behaviours compared to non-depressed behaviours (37). As explained above, the first module of the group BA treatment introduced a behavioral activation exercise to promote an active life style. The second module introduced the initial stage of BA treatment consisting in assessing the function of depressed behaviours, whether these are maintained by (a) an absence of reinforcement for non-depressed behaviours, (b) reinforcement for depressed behaviours, or (c) some combination of the two. The rest of the group sessions consisted in patients reviewing and setting short-term goals with regards to various aspects of their life (social, leisure, work, personal) and determining how to realize these goals with the use of graded tasks which they reported on each week. BA group sessions did not focus on interpersonal problems or strategies to resolve them.

Primary Outcome Measure

All participants in the study were assessed three times at approximately 10-week intervals: at the beginning of group treatment (baseline T1: time 1), at the 10^{th} week of treatment (mid-treatment T2: time 2), and at the 20th week of treatment (termination T3: time 3). The outcome measure used was changes in depressive symptoms recorded with the Inventory of Depressive Symptoms, Self-Report [IDS-SR, (38)]. This is a 30-item measure of symptoms of depression experienced during the previous week. Items are scored on a 0 to 3 scale, with higher scores reflecting more severe depression. Rush et al. (38) report Cronbach's alpha coefficients of internal consistency of .77 for a sample of symptomatic depressed patients. The authors also report good discriminant validity of the IDS-SR between symptomatic and euthymic patients with MDD and report that the IDS-SR is equivalent to the Hamilton Rating Scale for Depression (39) in detecting symptom change during an acute treatment phase. Rush et al. (40) also report good concurrent and discriminant validity for the IDS-SR and sensitivity to change in patients with major depressive and bipolar disorders. Trivedi et al. (41) reported good psychometric properties for the IDS-SR with a public sector psychiatric outpatient sample of patients with Major Depressive Disorder (MDD) or Bipolar Disorder (BD). In addition, internal consistency scores for the IDS-SR were 0.92 for patients with MDD and 0.89 for the clinician-rated IDS with bipolar patients.

Baseline Characteristics

The same self-report measures were used with both samples of bipolar and unipolar patients. Baseline characteristics were assessed on demographic, clinical and social domains of functioning as well as for perception of improvement with treatment received. Demographic variables include age, gender, marital status, employment status, while clinical variables of interest include symptom severity, duration of current depressive episode, total number of depressive episodes and co-morbid psychiatric diagnoses.

Secondary Outcome Measures

Social Adjustment Scale—Self-Report

The Social Adjustment Scale, self-report [SAS-SR, (42)] is a 54-item self-report questionnaire assessing instrumental and expressive role performance over the past two weeks. Six major areas of functioning are covered: work (paid worker, unpaid homemaker or student); social and leisure activities; relationships with extended family; role as a marital partner; parental role; and role within the family unit, including perceptions about one's economic situations. Each question is rated on a 5-point scale with higher scores indicating more impairment. A mean for each role category is obtained as well as an overall adjustment score. The SAS-SR has a good internal consistency coefficient of 0.74 and a good test-retest reliability coefficient of 0.78 over a period of two weeks. The Alpha coefficient for the current sample of depressed patients is 0.71. Patients' mean total SAS-SR scores at Time 1 in this study's sample, are comparable to the scores reported by Weissman et al. (43) for patients in acute depression.

Perceived Stress Scale

The Perceived Stress Scale (PSS, [(44)] is originally a 14-item scale designed to measure the degree to which situations in one's life are appraised as stressful. Items were designed to tap how unpredictable, uncontrollable and overloaded respondents find their lives with high scores indicating more perceived stress. The shorter 10-item version, with an alpha coefficient for internal reliability of 0.78, is used in the present study (45).

The Coping Inventory for Stressful Situations

The Coping Inventory for Stressful Situations [CISS, (46)] is a 48-item, self-report questionnaire using a 5-point Likert-type rating scale ranging from (1) "not at all" to (5) "very much" with high scores indicating greater use of coping strategies reported.

The CISS is comprised of three coping dimensions: Task, Emotion and Avoidance-oriented coping strategies. There are two subscales for the Avoidance-Oriented scale: Distraction and Social Diversion. High alpha reliability coefficients for internal consistency for a psychiatric normative group range from 0.69 to 0.91. Test-retest reliabilities were moderate to high for the Task and Emotion scales (0.68 to 0.73) and moderate for the Avoidance scale (0.51 to 0.60). Good construct validity was found when comparing the CISS with the Ways of Coping Questionnaire [WCQ, (47, 48)], in the directions predicted.

Perceptions of Improvement Questionnaire

The Perceptions of Improvement Questionnaire (PIQ) is a self-report questionnaire measuring patients' perceptions of improvements of their physical and mental health symptoms (49). It was administered at 10 and 20 weeks of group therapy. Patients rate on a 4-point rating scale, ranging from "worse than before" to "much better than before", the extent to which they perceive improvement in 20 areas of their life, since the start of group therapy. High scores indicate more reported improvements. In a study with 232 participants in a methadone maintenance program, a factor analysis of this scale generated three main factors, accounting for 60.1% of the variance, including emotional health, social relations and physical health (49). Internal consistency coefficient for the overall scale is 0.91 and for the three subscales were 0.91 for "emotional health", 0.79 for "social relations", and 0.79 for "physical health". Cronbach's alpha coefficients for the current study sample are 0.90, 0.78, 0.68 and 0.63 for the overall scale, emotional health, social relations and physical health respectively.

Circumplex Scales of Interpersonal Problems, Values and Efficacy

The 32-item circumplex version of the Inventory of Interpersonal Problems used in this study [IIP-32, (50)] is a self-report questionnaire assessing interpersonal difficulties and distress generated. Respondents rate 4 items, for each of 8 octants in the circumplex, on 0 (not at all) to 4 (extremely) scales with high scores indicating high interpersonal distress. The internal consistency for the IIP-32 is high with reliability coefficients ranging from 0.68 to 0.93. The Circumplex Scales of Interpersonal Values [CSIV, (51)] is a 64-item self-report measure of interpersonal goals or values (8 items for each of 8 octants) for which respondents rate the importance for themselves (on a scale from 0, not important, to 4, extremely important). The scale demonstrates very good internal consistency for the eight octants of the circumplex, with a Cronbach's alpha ranging from 0.76 to 0.86. The Circumplex Scales of Interpersonal Efficacy [CSIE, (52)] is a 32-item self-report measure of individuals' confidence in their ability to perform interpersonal behaviours successfully. Respondents were asked to rate (on a 0, not at all confident, to 10, absolutely confident) 4 interpersonal actions for each of 8 octants. Responses were transformed to 0-to-4 scales to make them comparable to the IIP and CSIV scales. In the current study respondents were asked to think of the group therapy setting as an example of interpersonal situations they were asked to rate for the CSIV and CSIE. The scales of the CSIE have been shown to have internal consistency (Cronbach alphas ranging from 0.66 to 0.83 for each of the 8 octants). Satisfactory Cronbach alphas for a similar sample of persistently depressed outpatients, taken from the same mental health institute as the current study sample, were previously reported for these three circumplex measures (53).

A structural summary approach for calculating scores derived from these circumplex scales yields vector lengths for each scale which can represent indicators of a person's interpersonal style (54). Longer vector lengths on any scale suggest a more limited interpersonal repertoire with high scores in one particular region of the circumplex but low scores in the opposite regions. Shorter vector lengths suggest an equal distribution of scores on opposite sides of the circumplex. Therefore, individuals with personality dispositions in all regions of the circumplex (shorter vector lengths) can be described as more interpersonally flexible and more able to adapt to the demands of a situation. Whereas individuals with a more limited interpersonal repertoire may only be able to express the same set of behaviors even if these are inappropriate to the situation (54).

Weekly Journal

All patients were asked to complete a Weekly Journal at the beginning of each of the 20 group sessions, consisting of 20 items, on a 5-point Likert-type scale ranging from "not at all" to "every day." Six items assessed *behavioral activation* (e.g., "I have completed my household chores and/or professional/student work"). Six items assessed *depressive symptoms* similar to DSM criteria (e.g., "I have been in a sad, depressed mood"). Eight items assessed interpersonal *self-efficacy* (CSIE), one item for each of the 8 CSIE octants; (eg., "This week in the group I can be helpful, I can take an active part in the group, I can ease the pain of others, and I can understand their feelings"). Whereas the *self-efficacy* items referred to expectations for the coming week, the *activation* and *depression* items referred to experiences over the preceding week. Cronbach's Alpha coefficients of reliability obtained for this study sample for each of these three subscales are 0.78, 0.81 and 0.60 for BA, DSM symptoms and CSIE, respectively.

Data Analyses

Using SPSS 25 (Statistical Package for the Social Sciences), a series of chi square and ANOVAs were used to compare bipolar patients who underwent group CBASP, unipolar patients who underwent group CBASP, and unipolar patients who underwent group BA using frequencies/means for demographic and clinical baseline measures. Cramer's V, Cohen's D and Eta Square were used as association measures to assess effect sizes of significant differences between groups.

Measures of depressive symptoms over time (T1, T2, and T3) were compared between the two diagnostic groups using a mixed multivariate ANOVA (repeated measures and groups analysis), controlling for covariates which comprised total number of depressive episodes and comorbid diagnoses (SPSS).

Then, a mixed ANOVA (repeated measures by diagnostic groups) was performed to assess changes in each clinical and social measure (SAS, CISS, PSS, IIP-32, CSIE, CSIV, PIQ, and Weekly Journal) over time across bipolar and unipolar patients.

Partial Eta square is used as an association measure to assess effect size of main or interaction effects.

Mplus 8.1 (55) was used to perform an exploratory longitudinal latent class analysis to identify subgroups of patients' trajectories of improvement in depressive symptoms. The structural software maximizes the information available in the data, concerning IDS-SR, so as to complete the missing repeated measurements (n=98) for patients who did not complete 20 weeks of treatment. To select the optimal solution of latent classes of depressive symptoms over time, we used at least three statistical indexes: Bayesian Information Criterion (BIC), Entropy, and Lo Mendel Rubin (LMR) adjusted test. The best solution chosen is the model with the lowest BIC, an entropy or rate of classification larger than 0.70, to which an additional class does not improve statistically the retained model after an LMR test. For this exploratory analysis, the selected model must be substantively meaningful for robustness.

Two optimal latent classes obtained were used to perform a mixed ANOVA in order to confirm whether the latent class trajectories are significantly different with regards to depressive symptoms over time. Finally, multiple comparisons were performed to validate statistically and clinically these two latent classes. We conducted several t-tests and chi-square tests to assess differences between these latent classes with regards to demographic and clinical characteristics.

A Logistic Regression Analysis was carried out to identify, among baseline social functioning variables the ones that best predict the trajectory group of patients who benefit most from group therapy with regards to self-reported improvements in depressive symptoms. Given the relatively small sample size (n=104), only the most important variables are included in the multivariate model to assess class membership. These variables must be significant in the bivariate analysis.

RESULTS

Demographic and baseline information on the sample (N=104) are outlined in **Tables 1A**, **B**. At baseline, patients with bipolar depression (n=23) did not differ significantly from those with

TABLE 1A | Participant characteristics by treatment groups: Comparison of frequencies.

T1-Characteristics	Treatment groups					
n	Bipolar CBASP 23	Unipolar CBASP 41	Unipolar BA 23	All sample 87	Chi-2	Cramer V
Gender						
Female	11 (48)	20 (49)	17 (74)	48 (55)	4.44	–
Male	12 (52)	21 (51)	6 (26)	39 (45)		
Marital status					7.87	–
Maried	4 (18)	12 (29)	11 (48)	27 (31)		
Single/divorced	12 (52)	21 (51)	11 (48)	44 (51)		
In a relationship	7 (30)	8 (20)	1 (4)	16 (18)		
Employment status					11.48	–
Employed	3 (13)	8 (19)	1 (4)	12 (14)		
Unemployed	7 (30)	16 (39)	16 (70)	39 (45)		
Sick leave	10 (44)	15 (37)	6 (26)	31 (36)		
Student/retired	3 (13)	2 (5)	0 (0)	5 (6)		
Psychiatric Comorbidity					20.48***	.49
Yes	20 (87)	12 (29)	9 (39)	41 (47)		
No	3 (13)	29 (71)	14 (61)	46 (53)		
Type of comorbidity					–	–
Anxiety only	5 (23)	2 (5)	1 (4)	8 (9)		
Anxiety & other	6 (27)	1 (2)	0 (0)	7 (8)		
Alcohol	0 (0)	1 (2)	0 (0)	1 (1)		
Alcohol in remission	1 (4)	2 (5)	2 (9)	5 (6)		
Substance abuse	1 (4)	4 (10)	6 (26)	11 (13)		
Substance in remission	5 (23)	0 (0)	0 (0)	5 (6)		
Situational disorder	0 (0)	1 (2)	0 (0)	1 (1)		
Gambling	1 (4)	0 (0)	0 (0)	1 (1)		
No comorbidity	3 (14)	29 (73)	14 (61)	46 (54)		
Type of diagnostic					–	–
MDD	0 (0)	20 (49)	15 (65)	35 (40)		
MDD recurring	0 (0)	18 (44)	8 (35)	26 (30)		
MDD single	0 (0)	2 (5)	0 (0)	2 (2)		
Double depression	0 (0)	1 (2)	0 (0)	1 (1)		
Bipolar Type I	8 (35)	0 (0)	0 (0)	8 (9)		
Bipolar Type II	13 (57)	0 (0)	0 (0)	13 (15)		
Schizoaffective bipolar	1 (4)	0 (0)	0 (0)	1 (1)		
Bipolar rapid cycles	1 (4)	0 (0)	0 (0)	1 (1)		

*Entries are frequencies (with percentages in parenthesis). Percentages are calculated among the diagnostic variable. The Cramer's V statistic is a measure of association. ***p ≤ 0.001 (two tailed-test). For type of comorbidity and type of diagnostic variables, no chi-square test is calculated because there is zero in the cellules.*

TABLE 1B | Participant characteristics by treatment groups: Comparison of means.

T1-Characteristics	Treatment groups					
n	Bipolar CBASP 23	Unipolar CBASP 41	Unipolar BA 23	All sample 104	F	Eta square
Age	48.5 (11.1)	43.4 (11.1)	48.3 (8.5)	46.0 (10.6)	2.51	–
Duration of current episodes (months)	20.6 (16.3)	28.8 (26.5)	24.7 (19.7)	25.5 (22.5)	0.99	–
Total depressive episodes	4.81 (3.23)	3.10 (1.37)	2.70 (0.82)	3.43 (2.09)	7.88***	0.16
IDS-SR	37.3 (10.9)	39.0 (12.5)	36.1 (13.9)	37.8 (12.4)		–
SAS mean	2.46 (0.55)	2.66 (0.58)	2.58 (0.44)	2.59 (0.54)	0.97	–
Work Role	2.97 (1.15)	3.22 (1.27)	3.57 (1.29)	3.25 (1.25)	1.30	–
Social leisure	3.13 (0.82)	2.97 (0.59)	2.81 (0.81)	2.97 (0.72)	1.22	–
Extended family	2.14 (0.56)	2.27 (0.53)	2.18 (0.61)	2.21 (0.56)	0.43	–
Primary relation	2.12 (0.60)	2.54 (0.67)	2.32 (0.50)	2.37 (0.62)	1.99	–
Parental role	1.86 (0.48)	2.05 (0.63)	1.83 (0.58)	1.96 (0.57)	0.42	–
Family unit	1.93 (0.76)	2.43 (1.10)	2.02 (1.06)	2.19 (1.03)	2.23	–
Vector Length CSIE	3.31 (1.79)	3.51 (1.62)	4.05 (1.47)	3.58 (1.64)		–
Vector Length CSIV	1.20 (0.61)	1.24 (0.53)	1.20 (0.39)	1.22 (0.52)	0.17	–
Vector Length IIP	1.90 (0.95)	1.81 (0.84)	2.14 (0.69)	1.93 (0.83)	0.02	–
CISS coping						
Task oriented	42.9 (11.7)	44.5 (9.7)	41.8 (9.45)	43.4 (10.2)	0.55	–
Emotion oriented	53.2 (8.4)	54.1 (8.3)	51.3 (9.84)	53.1 (8.7)	0.74	–
Avoidance oriented	36.8 (9.9)	38.7 (8.0)	37.4 (8.23)	37.9 (8.5)	0.40	–
Distraction	19.3 (6.4)	19.8 (4.7)	19.6 (4.42)	19.6 (5.1)	0.08	–
Social diversion	10.6 (3.5)	12.7 (4.9)	11.0 (3.76)	11.7 (4.3)	2.14	–
PSS stress	26.5 (6.0)	26.7 (5.7)	26.04 (3.83)	26.5 (5.3)	0.10	
T2-Perceived efficacy	29.3 (7.8)	26.2 (8.11)	27.04 (5.90)	27.2 (7.5)	1.20	–
Emotional health	8.1 (2.4)	7.2 (2.6)	6.91 (2.31)	7.4 (2.5)	1.52	–
Social relations	5.2 (1.6)	4.9 (1.8)	4.60 (1.5)	4.9 (1.7)	0.76	–
Physical health	6.5 (2.4)	5.6 (2.0)	5.65 (1.5)	5.8 (2.0)	1.54	–
Weekly Journal						
Behavioral activation	3.74 (5.83)	8.19 (5.74)	9.74 (4.41)	7.20 (5.9)	7.1**	0.17
Depressive symptoms	4.78 (7.46)	13.06 (7.02)	14.58 (5.82)	10.9 (7.9)	13.4***	0.27
CSIE	5.61 (8.34)	13.5 (7.16)	15.42 (2.82)	11.5 (7.8)	13.2***	0.27

*Entries are means (with standard deviation in parenthesis). The Cohen's statistic is a measure of effect size: 0.20 = Small effect; 0.50 = Medium effect; 0.80 = Large effect. ***p ≤ 0.001 (two tailed-test) **p ≤ .01.*

unipolar depression who received group CBASP (n=41) or from unipolar patients who received group BA (n=23) with regards to most demographic, clinical and social functioning characteristics. However, bipolar depressed patients had a greater total number of depressive episodes (4.8 bipolar vs. 2.9 unipolar, t=4.33, p≤.001, Cohen's D=0.88), more comorbid psychiatric diagnoses (primarily Anxiety Disorders and Substance Abuse Disorders in remission, 87% bipolar vs. 28% unipolar, $Chi^2 = 25.3$, $p \leq 0.001$, Cramer's V=0.49), and the week prior to beginning group therapy bipolar patients reported in the Weekly Journal lower levels of behavioral activation on a daily basis (3.7 bipolar vs. 8.3 unipolar, t=3.34, $p \leq 0.001$, Cohen's D=0.76) but fewer self-reported depressive mood symptoms (4.8 bipolar vs. 13.3 unipolar, t=4.88, $p \leq 0.001$, Cohen's D=1.11) compared to unipolar depressed patients. All patients had similar IDS-SR depression severity at baseline.

Both bipolar and unipolar patients had a similar duration of the current depressive episode for which they were in group therapy, with a slightly higher duration for unipolar patients, the mean duration being 25 months for the entire sample. Bipolar patients had an average of almost two hypo/manic episodes (SD=1.82).

The absence of significant differences between CBASP and BA group therapies on all baseline measures allowed us to combine results for all unipolar patients and to focus on trajectories of change in depressive symptoms and social functioning in bipolar and unipolar patients.

A mixed repeated measures analysis of variance revealed significant improvements in self-reported depressive symptoms (IDS-SR) over time for all patients in group therapy (F=17.2, p<0.001, partial eta square=0.18) with a mean of 37.6 at T1, 32.6 at T2, and 29.9 at T3, all scores remaining within the moderate level of symptom severity at the end of group therapy. Although no significant differences are found between bipolar and unipolar patients with regards to their trajectories of improvement, closer observation of the means suggests a trend for unipolar patients to report higher depressive severity scores than bipolar patients across the three measurement periods. Furthermore, after controlling for total number of depressive episodes and comorbid diagnoses, bipolar patients trended towards greater improvement in depressive symptoms compared with unipolar patients while the interaction effect is marginally significant (F=2.86, p=0.06, partial eta square=0.04, **Figure 2**). Results also reveal a significant interaction between depressive symptoms over time and number of comorbid diagnoses (F=3.68, p=0.03, partial eta square=0.09).

According to a mixed ANOVA analysis, social functioning (SAS-SR total mean) improved significantly over time with

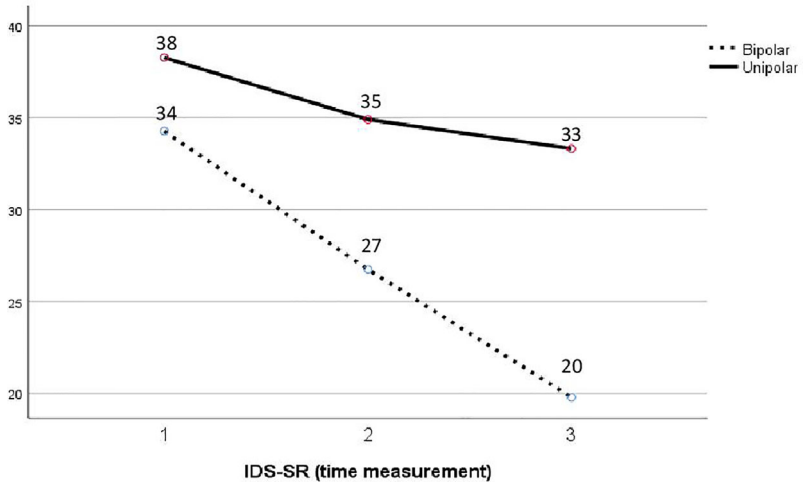

FIGURE 2 | Mean trajectories of depressive symptoms (IDS-SR) over time for diagnostic groups, controlling for psychiatric comorbidity and total number of depressive episodes.

group interventions for all patients (F=8.81, p=0.001, partial Eta square=0.10) with no significant differences between bipolar and unipolar depressed patients. Changes in social functioning over the course of group therapy are positively correlated with changes in self-reported depressive symptoms (Pearson R=0.582, $p \leq 0.01$) for all patients. In addition to the overall mean for social functioning, all patients significantly improved in areas of SAS-work role (F=6.53, p=0.002, partial Eta square=0.08) and SAS-social leisure activities (F=14.1; p=0.001; partial Eta square=0.15) with bipolar patients engaging in significantly more social leisure activities than unipolar patients ($F_{interaction}$=5.54; p=0.005; partial Eta square=0.07). Group therapy treatments contributed as well to significantly lowering perceived stress (PSS; F=12.87, p=0.001, partial Eta square=0.14) with a post-treatment mean for the entire sample (M=23, SD=6.4) only slightly above rates reported for a large non-psychiatric sample in the US (M=22, SD=6.3) (56).

All patients also significantly increased their use of problem-solving coping strategies (CISS; F=6.18, $p \leq 0.003$, partial Eta square=0.07), lowered their emotion-oriented strategies (CISS; F=8.69, p=0.001, partial Eta square=0.10), and increased use of social diversion (CISS; F=10.27; p=0.001; partial Eta square=0.12) over distraction as a preferred form of avoidance-oriented coping strategies. Bipolar patients used significantly more social diversion compared to unipolar patients ($F_{interaction}$=4.40; p=0.014; partial Eta square=0.05). Post-treatment means obtained for the CISS in this sample are slightly better than means reported for a unipolar depressed sample by McWilliams et al. (57) particularly in the greater use of task-oriented strategies and lower use of emotion-oriented strategies in the current sample. Bipolar patients also show significantly more interpersonal flexibility than unipolar patients, over the course of group therapy, by endorsing the value of having a wider range of interpersonal behaviors related to the group therapy situation (vector length_CSIV; $F_{interaction}$=2.69; p=0.035; partial Eta square=0.08). Bipolar patients also have baseline measures of interpersonal self-efficacy that are more agentic (CSIE-unagentic score; t=2.33, p=0.01; Cohen's d=0.48) and less submissive (CSIE-HI-nonassertive; t=2.14, p=0.01; Cohen's d=0.44) than interpersonal self-efficacy reported by unipolar patients.

All patients reported significant Perceived Improvements with their overall state of health (PIQ; F=3.93, p=0.05, partial Eta square=0.05) over the course of group therapy. The subscale of emotional health improved significantly (F=4.40, p=0.04, partial Eta square=0.05) over 20 weeks of group therapy, while the subscale of social relations improved more slowly but not significantly and the subscale of physical health did not appear to change over time for all patients. All Perceived Improvement scores (PIQ) obtained at the end of group therapy are much lower than scores reported for a sample of patients treated in a methadone maintenance program also receiving psychosocial services, in the same city where the current sample is taken from (49).

Repeated measures ANOVAs using the Weekly Journal over all 20 weeks of group therapy show significant improvements in self-reported behavioral activation from one week to the next (F=2.52; p=0.002) for all patients. All patients also reported significantly fewer depressive symptoms experienced the week prior to each group session over the course of group therapy (F=2.30, p=0.006). A mixed-model ANOVA showed significant differences between both diagnostic groups (F=1.93; p=0.025). Results suggest that unipolar patients report more depressive symptoms each week overall. Results also suggest that bipolar patients gain more interpersonal confidence (CSIE) throughout group therapy as indicated by significantly higher rates compared to unipolar patients (F=2.04; p=0.016).

A longitudinal Latent Class Analysis was used to explore underlying classes of trajectories using the self-report measure of symptom severity (IDS-SR) for both samples. Results outlined in

TABLE 2 | Number of optimal latent classes – trajectories of depressive symptoms (IDS-SR).

Parameters	Number of latent classes			
	1	2	3	4
BIC	2,121.6	2,100.5	2,102.7	2,106.2
Entropy	–	0.76	0.72	0.78
LMR adjusted test (p-value)	–	0.004	0.24	0.10

BIC, Bayesian Information criterion; LMR, Lo Mendel Rubin.

Table 2 demonstrate two latent classes of patients as the most optimal solution: lowest BIC, good entropy, significantly different from the 1-class solution, and not different from a 3-class solution. As shown in **Figure 3**, the first latent class represents moderate to severely depressed patients (49%, mean=32) at the start of group therapy who improved significantly over time, ending group therapy in the mild symptoms range (mean=19). The second latent class represents severely depressed patients (51%, mean=44) at the start of group therapy who did not improve over time (mean=40). A mixed ANOVA confirms significant differences between trajectories of these two latent classes with regards to depressive symptoms ($F=16.7$; $p \leq 0.001$; Partial Eta square=0.17) and almost all baseline social functioning measures (**Tables 3A–C**). Patients in the first trajectory group who improved significantly over the course of treatment, also improved significantly more in social functioning (overall mean) than patients in the second trajectory group ($T= -2{,}27$, $p \leq 0.03$, standard error=0.12, 95% confidence).

None of the baseline demographic variables, including bipolar vs unipolar diagnosis, duration of current depressive episode, total number of depressive episodes, distinguish these two latent classes as apparent in **Tables 3A**, **B**. Patients in trajectory group 2 have a higher rate of comorbid psychiatric diagnoses, although this did not reach significance. These patients also report more baseline problems with social functioning (SAS-SR overall mean), particularly in areas of reduced motivation and interest for social and leisure activities (SAS-social-leisure), withdrawal, avoidance and/or interpersonal conflicts with extended family members (SAS-extended family) and excessive worrying or guilt about one's current situation (SAS-family unit) over the past two weeks. They report significantly more perceived stress (PSS) over the past month and tend to use significantly fewer task-oriented coping strategies (CISS-task) than patients in the first trajectory group who report improvements with group therapy.

Patients in trajectory group 1 who benefit most from group therapy also report significantly higher rates of Perceived

TABLE 3A | Latent classes for depressive symptoms trajectories by participant characteristics: frequencies comparison (n=98).

T1-Characteristics	Latent classes		
	Class 1:Low depression with decreasing trajectory	Class 2:High depression with stable trajectory	Chi-2
n	48	50	
Gender			1.96
Female	23 (43)	31 (57)	
Male	25 (57)	19 (43)	
Marital status			
Maried	16 (50)	16 (50)	0.04
Single/divorced	24 (48)	26 (52)	
In a relationship	8 (50)	8 (50)	
Employment status			
Employed	9 (69)	4 (31)	3.51
Unemployed	22 (49)	23 (51)	
Sick leave	14 (40)	21 (60)	
Student/retired	3 (60)	2 (40)	
Diagnosis			0.68
Unipolar	35 (47)	40 (53)	
Bipolar	13 (57)	10 (43)	
Prevalence depression			
3 episodes or more	30 (50)	30 (50)	0.02
2 episodes or less	17 (49)	18 (51)	
Comorbidity			0.41
Yes	19 (45)	23 (55)	
No	29 (52)	27 (48)	

Entries are frequencies (percentages in parenthesis, calculated across 2 latent classes).

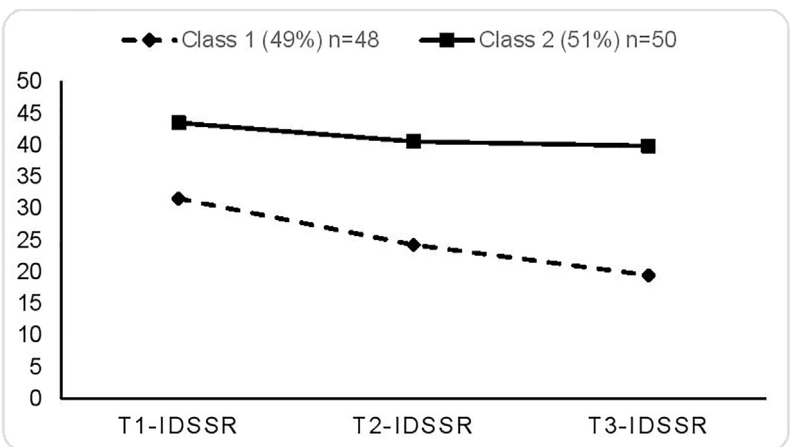

FIGURE 3 | Treatment trajectories for two latent classes of responders and non-responders. Entries are conditional means.

TABLE 3B | Latent classes of depressive symptoms trajectories by participant characteristics: Means comparison (n=98).

T1- Characteristics	Latent classes			
	Class 1: Low depression with decreasing trajectory	Class 2: High depression with stable trajectory	t	Cohen's d
n	48	50		
Age	45.3 (9.41)	46.1 (11.1)	0.43	–
Duration of current episode (months)	27.7 (27.5)	24.0 (16.1)	0.83	–
Total depressive episodes	3.30 (1.52)	3.33 (2.43)	0.09	–
SAS mean	2.33 (0.46)	2.84 (0.51)	5.16***	1.06
Work Role	3.02 (1.42)	3.51 (1.09)	1.88	–
Social leisure	2.70 (0.67)	3.19 (0.65)	3.67***	0.75
Extended family	1.98 (0.54)	2.41 (0.51)	4.05***	0.83
Primary relation	2.15 (0.41)	2.61 (0.66)	3.01**	0.83
Parental role	1.84 (0.66)	2.25 (0.53)	1.80	–
Family unit	1.85 (0.69)	2.51 (1.20)	3.31***	0.68
Vector Length CSIE	3.07 (1.40)	4.08 (1.71)	3.15**	0.66
Vector Length CSIV	1.11 (0.49)	1.32 (0.54)	1.91	–
Vector Length IIP	1.64 (0.78)	2.18 (0.82)	3.26**	0.68
CSIE_BC (dominant-distant)	4.31 (2.10)	3.38 (1.93)	2.27*	0.47
CSIE_NO (dominant-friendly)	5.32 (2.30)	4.36 (2.06)	2.18*	0.45
CSIE Agency_Y	–1.75 (1.90)	–3.05 (1.80)	3.33**	0.71
CSIV mean	2.12 (0.46)	1.88 (0.55)	2.20*	0.47
CSIV_BC (dominant-distant)	1.35 (0.64)	0.91 (0.69)	3.23**	0.67
CSIV raw agentic	2.07 (0.63)	1.75 (0.59)	2.54*	0.53
IIP mean	1.56 (0.52)	1.68 (0.52)	1.12	–
IIP PA (domineering)	0.77 (0.66)	0.51 (0.58)	2.09*	0.43
IIP FG (avoidant)	1.94 (0.90)	2.54 (1.09)	2.98**	0.61
IIP HI (non-assertive)	2.22 (1.01)	2.64 (1.08)	2.11*	0.43
IIP NO (intrusive)	1.17 (0.96)	2.17 (1.04)	2.61**	0.53
IIP raw unagentic	2.15 (0.78)	2.58 (0.84)	2.66**	0.54
IIP Agency_Y	–1.19 (0.82)	1.88 (0.86)	3.98**	0.82

*Entries are means (with standard deviation in parenthesis). The Cohen's statistic is a measure of effect size: 0.20=Small effect; 0.50=Medium effect; 0.80=Large effect. *p ≤ 0.05, **p ≤ 0.01, ***p ≤ 0.001 (two tailed-test).*

TABLE 3C | Latent classes of depressive symptoms trajectories by participant characteristics: means comparison (n=98).

T1-Characteristics	Latent classes			
	Class 1:Low depression with decreasing trajectory	Class 2:High depression with stable trajectory	t	Cohen's d
n	48	50		
CISS coping				
Task oriented	45.65 (10.27)	40.88 (9.70)	2.36*	0.48
Emotion oriented	52.08 (7.61)	54.06 (9.21)	1.16	–
Avoidance oriented	39.44 (8.68)	36.36 (8.01)	1.83	–
Distraction	20.35 (5.23)	19.22 (4.98)	1.10	–
Social Diversion	12.42 (4.04)	10.86 (4.54)	1.79	–
PSS stress	24.83 (5.28)	28.28 (4.88)	3.36***	0.68
T2-Perceived efficacy -PIQ	29.5 (8.51)	24.98 (5.68)	2.89**	0.63
Emotional health	7.93 (2.72)	6.79 (2.12)	2.15*	0.48
Social relations	5.62 (1.85)	4.23 (1.17)	4.14***	0.91
Physical health	6.17 (2.25)	5.47 (1.72)	1.62	–
Weekly Journal				
Behavioral activation	8.45 (6.52)	5.63 (4.77)	2.17*	0.50
Depressive symptoms	9.03 (7.04)	12.92 (8.39)	2.23*	0.51

*Entries are means (with standard deviation in parenthesis). The Cohen's statistic is a measure of effect size: 0.20=Small effect; 0.50=Medium effect; 0.80=Large effect. *p ≤ 0.05, **p ≤ 0.01, ***p ≤ 0.001 (two tailed-test).*

Improvements (PIQ) in overall health, in emotional health and in social relations compared to more severely depressed patients, even after 10 weeks of group therapy. Furthermore, increasingly endorsing the importance of a wider range of interpersonal behaviors (CSIV vector length), over the course of group therapy, was significantly correlated with improvements in emotional health by the end of treatment (Pearson R=0.330, p=0.001). In fact, reported improvements over time in overall health, emotional health and physical health were significantly correlated with lower levels of reported interpersonal problems over time that are associated with a more rigid behavioral repertoire (IIP vector length). This is an important finding considering how resistant to change physical symptoms have proven to be.

The Logistic Regression Analysis (**Table 4**) revealed that, after controlling for other variables, high baseline problems in social functioning (SAS-SR mean) increase the chances of membership in the severely depressed trajectory group 2 (OR =12.6; 95% CI=1.83–86.7). In addition, low rates of Perceived Improvements with treatment (PIQ) by the end of group therapy also increase the likelihood of membership in this more severe trajectory group 2 (OR=0.75; 95%CI=0.65–0.87). Therefore, higher baseline problems in social functioning represent the most important clinical predictor of membership in the second trajectory group of severely depressed patients who do not report improvements in depressive symptoms over the course of group therapy and who perceive their treatment as ineffective.

DISCUSSION

This is the first pilot study examining the feasibility of CBASP in a group format with bipolar patients currently in a depressive episode, using the same manualized treatment administered to a sample of unipolar depressed patients within the same psychiatric institution. Bipolar and unipolar moderately depressed patients report significant improvements in self-reported depressive symptoms and social functioning with 20 weeks of group psychotherapies, both CBASP and BA. After controlling for baseline differences, bipolar disorder patients trended towards a greater improvement in depressive symptoms. Similar to previous studies (58–60), bipolar disorder patients in this study report significantly fewer depressive symptoms than unipolar patients in their daily functioning the week prior to beginning group therapy. Bipolar patients in this study were mobilized, resorted to more social activities and used social diversion as a coping strategy while increasingly endorsing the importance of widening their repertoire of interpersonal behaviors over the course of CBASP group

TABLE 4 | Logistic Regression models predicting trajectory group 2 of non-responders.

T1-Predictors	Model 1		Model 2	
	B (se)	OR	B (se)	OR
SAS mean	2.08*** (0.56)	8.00	2.53** (0.98)	12.6
Vector Length CSIE	0.27 (0.21)	0.19	0.31 (0.28)	1.37
Vector Length IIP	0.44 (0.38)	0.25	0.54 (0.58)	1.71
PSS stress	–	–	0.09 (0.08)	1.09
CISS coping	–	–	0.02 (0.04)	1.02
T3- Perceived efficacy PIQ	–	–	–0.29*** (0.08)	0.75
Intercept	–7.23*** (1.67)	0.001	–3.46 (3.56)	0.03
N	91		77	
Nagelkerke R-square	0.38		0.68	
% ranking	74		83	

*Entries are logistic regression coefficients (B) with standard errors (se) in parenthesis, and odds ratios (OR). T1= time 1, T3= time 3. **p ≤ .01; ***p ≤ .001.*

therapy. Indeed, treatment outcome was more dependent on the severity of the depressive episode at baseline than on diagnosis alone.

Close to half of patients responded to group therapy (49%, mean=19) in this study reporting a mild level of symptom severity after group therapy. These results are comparable to percentages of responders (48%, mean=10 at posttreatment, 12 weeks) reported by the large multi-site Keller et al. (17) study for individually administered CBASP in combination with pharmacotherapy. However, Keller et al. used the clinician-rated Hamilton Rating Scale for Depression [HRSD-24, (61)]. Posttreatment means (M=22) reported by Michalak et al. (25) for 8 sessions of group CBASP added to treatment as usual, using the self-report Beck Depression Inventory [BDI, (62)], are lower than those reported by the entire sample at posttreatment (M=30) in this study using the IDS-SR. However, Michalak et al.'s outcome scores are higher than means for responders to group therapy according to the Latent Class Analysis in this study (M=19). Estimated comparisons of scores on the IDS-SR, the BDI and the HRSD-24 (63) suggest that posttreatment means cited for the Michalak et al. sample and for this study are both in the moderate range of symptom severity at posttreatment. However, responders in this study within the first latent class group ended therapy in the mild level of symptom severity, comparable to HRSD-24 scores reported by Keller et al. (mean=10). Results reported by Sabass et al. (23) for inpatient group CBASP reveal a comparable large effect size (d=1.11) at posttreatment for 24 sessions of group CBASP using the BDI-II (64) as is reported for this study sample (eta square=0.18).

Results confirm studies (26) showing that patients in both diagnostic groups with more severe baseline depressive symptoms do not appear to make significant progress (6, 28) with a 20-week psychological intervention concurrent with pharmacotherapy. Similar to Sabass et al.'s findings, this study also finds that patients with a moderate level of depression severity at baseline and therefore fewer problems with social functioning also tend to perceive benefits gained from group therapy. The more severely depressed patients, comparatively, tend to perceive group therapy as ineffective, perhaps related to feelings of defeatism and hopelessness described by McCullough in chronically depressed patients with early trauma. Furthermore, previous research indicates that 12 sessions of group (31, 65) or individually delivered CBASP (20, 66) may not be enough to promote remission in patients with chronic unipolar depression. Miklowitz et al. (7) reported beneficial effects of 30 sessions in 9 months, of intensive psychotherapy for bipolar depression. It would be worthwhile to examine whether more severely depressed patients might benefit more from individually administered CBASP instead of a group format or from prolonged maintenance treatment.

Good baseline social functioning is the most important predictor of reported improvements in depressive symptoms for all patients, with a strong effect size, although post-treatment levels of social functioning remain below levels reported for a non-psychiatric population in all subscales, with work role being the most problematic (42). These results are comparable to those obtained by Michalak et al. who reported no effects with CBASP regarding social functioning. Patients in the current study who respond to group therapy by reporting lower levels of depressive symptoms also make significantly more improvements in social functioning than non-responders. Other studies have shown that functional impairment predicts clinical outcome in unipolar depression (67) and has been used as an outcome measure to classify a sample of bipolar remitted patients into good versus poor functional outcome and then comparing individual characteristics of each group (68). These results also support research on staging of mood disorders pointing to deteriorating social functioning as a contributor to illness progression (26).

These encouraging results regarding group therapy contributing to improved social functioning in moderate to severely depressed patients, underscore the importance of extending the duration of psychosocial interventions for individuals with severe depression knowing that interpersonal changes need more time to consolidate (69). Patients' reports of Perceived Improvements in overall and physical health, over the course of group therapy in this study, are also related to improvements in their interpersonal problems through the acquisition of a wider range of interpersonal behaviors such as group CBASP promotes with interpersonal problem-solving skills. These results are supported by previous findings of the beneficial impact of psychotherapy in reducing interpersonal problems of depressed individuals (70) and underline the importance of addressing social functioning in psychotherapy for moderate to severe depression.

Results also support previous research that interpersonal dispositions of low agency, social avoidance (71, 72) and a limited repertoire of interpersonal behaviors contribute to the severity of depressive symptoms (73) and treatment non response (74). McCullough (12) describes a similar unagentic profile regarding interpersonal functioning of persistently

depressed individuals. Unipolar patients reported significantly more baseline unagentic and submissive interpersonal dispositions than bipolar patients, in this study, which may explain their lower gains in interpersonal self-efficacy over the course of group therapy. Although no differences in baseline social functioning between the two diagnostic groups are observed and unipolar patients reported being significantly more behaviorally active the week prior to the start of group therapy, bipolar patients appear to attribute more value to interpersonal interactions and mobilize themselves towards change over the course of group therapy demonstrating increased interpersonal confidence. These findings need to be replicated with a larger sample of bipolar patients to further explore interpersonal dispositions of bipolar depressed patients.

Findings reported in this pilot study do not support the exclusion of bipolar patients in a depressive episode from treatment with CBASP for moderate to severe depression. The perception of bipolar depression as being difficult to treat may be a result of the higher medical and psychiatric comorbidities with Bipolar Disorders. However, according to these preliminary results, this perception seems to be unwarranted with regards to providing CBASP in a group format to bipolar depressed outpatients. Indeed, this study suggests that bipolar patients in a depressive episode can benefit as much from the same psychological treatment provided to unipolar patients with chronic depression. No assertion is made as to the recommendation of using CBASP to treat Bipolar Disorders. Rather, CBASP addresses the social withdrawal, interpersonal difficulties and cognitive distortions associated with a severe depressive episode observed in both diagnostic groups. These findings suggest that when controlling for psychiatric comorbidities and number of depressive episodes, perhaps bipolar depressed patients might benefit even more form group CBASP compared to unipolar depressed patients. This study merits to be repeated with a larger sample of bipolar patients currently in a depressive episode. Perhaps bipolar depressed patients can join unipolar depressed patients in group CBASP together and benefit from sharing their similar and different characteristics.

LIMITATIONS

This pilot study is the first to document treatment benefits with group CBASP for bipolar outpatients currently in a depressive episode, using the same manualized group CBASP administered to unipolar depressed patients. Its strength is in its prospective nature, the inclusion of moderately to severely depressed patients and in an extended 20-week treatment duration (instead of the shorter, 12-week duration previously reported as insufficient) provided under similar conditions and following similar procedures for all patients. Limitations of the study include a relatively small sample of bipolar patients, however comparable ($n \leq 100$) to other bipolar psychotherapy studies (7, 9). Another limitation is the use of only self-report measures of improvements in depressive symptoms and social functioning. Adding clinician-rated measures of improvements provides a more objective measure of change that is known to be different from subjective measures. This study did not assess patients at a follow-up period for possible deterioration in mood or in gains achieved and did not use a control or comparison group. Following this pilot study, future research objectives need to demonstrate the effectiveness of group CBASP for unipolar and bipolar depression in a randomized controlled study using a comparison group. Longer treatment duration, including maintenance sessions and long-term follow-up may benefit the more severely depressed patients and is also recommended. Offering the more severely depressed patients individual sessions after group therapy may also help address early trauma or social anxiety that require further interventions.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by: The Douglas Mental Health University Institute's Research Ethics Board (REB Protocol 10/19). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

LS is the principal investigator responsible for design, conceptualization, and research objectives, and played a leading role in all drafts of the manuscript. ET is the statistician responsible for all data analyses, synthesizing results, and presentation of tables and figures. EF had a substantial role in data acquisition: carried out all data organization and entry into SPSS and again in REDCap software. SB is the medical consultant on design, methodology, and discussion of results, and revision and editing of manuscript. SRen is a medical consultant and made contributions in presentation of results. SRej was involved in writing, reviewing, and editing the manuscript, and contributed to interpretation of data and design/presentation of analyses. MP played a substantial role in conception and design of statistical analyses. All authors revised the work critically for important intellectual content, gave final approval of the version to be published, and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work were appropriately investigated and resolved.

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REFERENCES

1. Yatham LN, Kennedy SH, Parikh SV, Schaffer A, Bond DJ, Frey BN, et al. Canadian Network for Mood and Anxiety Treatments (CANMAT) and International Society for Bipolar Disorders (ISBD) 2018 guidelines for the management of patients with bipolar disorder. *Bipolar Disord* (2018) 20 (2):97–170. doi: 10.1111/bdi.12609
2. Ferrari AJ, Stockings E, Khoo JP, Erskine HE, Degenhardt L, Vos T, et al. The prevalence and burden of bipolar disorder: findings from the Global Burden of Disease Study 2013. *Bipolar Disord* (2016) 18(5):440–50. doi: 10.1111/bdi.12423
3. Hartmann JA, Nelson B, Ratheesh A, Treen D, McGorry PD. At-risk studies and clinical antecedents of psychosis, bipolar disorder and depression: a scoping review in the context of clinical staging. *Psychol Med* (2019) 49 (2):177–89. doi: 10.1017/S0033291718001435
4. Tondo L, Vazquez GH, Baldessarini RJ. Options for pharmacological treatment of refractory bipolar depression. *Curr Psychiatry Rep* (2014) 16 (2):431. doi: 10.1007/s11920-013-0431-y
5. McMahon K, Herr NR, Zerubavel N, Hoertel N, Neacsiu AD. Psychotherapeutic Treatment of Bipolar Depression. *Psychiatr Clin North Am* (2016) 39(1):35–56. doi: 10.1016/j.psc.2015.09.005
6. Hidalgo-Mazzei D, Berk M, Cipriani A, Cleare AJ, Florio AD, Dietch D, et al. Treatment-resistant and multi-therapy-resistant criteria for bipolar depression: consensus definition. *Br J Psychiatry* (2019) 214(1):27–35. doi: 10.1192/bjp.2018.257
7. Miklowitz DJ, Otto MW, Frank E, Reilly-Harrington NA, Wisniewski SR, Kogan JN, et al. Psychosocial treatments for bipolar depression: a 1-year randomized trial from the Systematic Treatment Enhancement Program. *Arch Gen Psychiatry* (2007) 64: (4):419–26. doi: 10.1001/archpsyc.64.4.419
8. Murray G. *Adjunctive psychosocial interventions for bipolar disorder: Some psychotherapeutic context for the Canadian Network for Mood and Anxiety Treatments (CANMAT) & International Society for Bipolar Disorders (ISBD) guidelines*. (2018).
9. Chiang KJ, Tsai JC, Liu D, Lin CH, Chiu HL, Chou KR. Efficacy of cognitive-behavioral therapy in patients with bipolar disorder: A meta-analysis of randomized controlled trials. *PLoS One* (2017) 12(5):e0176849. doi: 10.1371/journal.pone.0176849
10. Miklowitz DJ, Chung B. Family-Focused Therapy for Bipolar Disorder: Reflections on 30 Years of Research. *Fam Process* (2016) 55(3):483–99. doi: 10.1111/famp.12237
11. Deckersbach T, Hansen N, Holzel B. Mindfulness-based Cognitive Therapy for Bipolar Disorder, In, Mindfulness-based Treatment Approaches. *Clinician's Guide to Evidence Base and Applications* Baer Ruth A. Academic Press (2014). pp. 77–94.
12. McCullough JP. *Treatment for chronic depression: cognitive behavioral analysis system of psychotherapy (CBASP)* Vol. xxii. New York: Guilford Press (2000). 326 p. p.
13. McCullough JPJr. *Treating chronic depression with disciplined personal involvement: Cognitive Behavioral Analysis System of Psychotherapy (CBASP)*. New York: Springer (2006).
14. Jobst A, Brakemeier E-L, Buchheim A, Caspar F, Cuijpers P, Ebmeier KP, et al. European Psychiatric Association Guidance on psychotherapy in chronic depression across Europe. *Eur Psychiatry* (2016) 33:18–36. doi: 10.1016/j.eurpsy.2015.12.003
15. Cuijpers P, Huibers MJ, Furukawa TA. The Need for Research on Treatments of Chronic Depression. *JAMA Psychiatry* (2017) 74(3):242–3. doi: 10.1001/jamapsychiatry.2016.4070
16. McCullough JPJr. *Chronic Depression and the Cognitive Behavioral Analysis System of Psychotherapy. A casebook of psychotherapy integration*. American Psychological Association; US: Washington, DC (2006) p. 137–51.
17. Keller MB, McCullough JP, Klein DN, Arnow B, Dunner DL, Gelenberg AJ, et al. A comparison of nefazodone, the cognitive behavioral-analysis system of psychotherapy, and their combination for the treatment of chronic depression. *New Engl J Med* (2000) 342(20):1462–70. doi: 10.1037/e492572004-001
18. Kriston L, von Wolff A, Westphal A, Holzel LP, Harter M. Efficacy and acceptability of acute treatments for persistent depressive disorder: a network meta-analysis. *Depress Anxiety* (2014) 31(8):621–30. doi: 10.1002/da.22236
19. Furukawa TA, Efthimiou O, Weitz ES, Cipriani A, Keller MB, Kocsis JH, et al. Cognitive-Behavioral Analysis System of Psychotherapy, Drug, or Their Combination for Persistent Depressive Disorder: Personalizing the Treatment Choice Using Individual Participant Data Network Metaregression. *Psychother Psychosom* (2018) 87(3):140–53. doi: 10.1159/000489227
20. Negt P, Brakemeier EL, Michalak J, Winter L, Bleich S, Kahl KG. The treatment of chronic depression with cognitive behavioral analysis system of psychotherapy: a systematic review and meta-analysis of randomized-controlled clinical trials. *Brain Behav* (2016) 6(8):e00486. doi: 10.1002/brb3.486
21. Cuijpers P, van Straten A, Schuurmans J, van Oppen P, Hollon SD, Andersson G. Psychotherapy for chronic major depression and dysthymia: a meta-analysis. *Clin Psychol Rev* (2010) 30(1):51–62. doi: 10.1016/j.cpr.2009.09.003
22. van Bronswijk S, Moopen N, Beijers L, Ruhe HG, Peeters F. Effectiveness of psychotherapy for treatment-resistant depression: a meta-analysis and meta-regression. *Psychol Med* (2019) 49(3):366–79. doi: 10.1017/S003329171800199X
23. Sabass L, Padberg F, Normann C, Engel V, Konrad C, Helmle K, et al. Cognitive Behavioral Analysis System of Psychotherapy as group psychotherapy for chronically depressed inpatients: a naturalistic multicenter feasibility trial. *Eur Arch Psychiatry Clin Neurosci* (2018) 268 (8):783–96. doi: 10.1007/s00406-017-0843-5
24. Guhn A, Kohler S, Brakemeier EL, Sterzer P. Cognitive Behavioral Analysis System of Psychotherapy for inpatients with persistent depressive disorder: a naturalistic trial on a general acute psychiatric unit. *Eur Arch Psychiatry Clin Neurosci* (2019) 12:1-1. doi: 10.1007/s00406-019-01038-5
25. Michalak J, Schultze M, Heidenreich T, Schramm E. A randomized controlled trial on the efficacy of mindfulness-based cognitive therapy and a group version of cognitive behavioral analysis system of psychotherapy for chronically depressed patients. *J Consult Clin Psychol* (2015) 83(5):951–63. doi: 10.1037/ccp0000042
26. Muneer A, Mazommil R. The Staging of Major Mood Disorders: Clinical and Neurobiological Correlates. *Psychiatry Investig* (2018) 15(8):747–58. doi: 10.30773/pi.2018.05.26
27. Berk M, Berk L, Udina M, Moylan S, Stafford L, Hallam K, et al. Palliative models of care for later stages of mental disorder: maximizing recovery, maintaining hope, and building morale. *Aust N. Z. J Psychiatry* (2012) 46 (2):92–9. doi: 10.1177/0004867411432072
28. Deckersbach T, Peters AT, Sylvia LG, Gold AK, da Silva Magalhaes PV, Henry DB, et al. A cluster analytic approach to identifying predictors and moderators of psychosocial treatment for bipolar depression: Results from STEP-BD. *J Affect Disord* (2016) 203:152–7. doi: 10.1016/j.jad.2016.03.064
29. Sayegh L, Penberthy JK. *Group treatment manual for persistent depression: Cognitive behavioral analysis system of psychotherapy (CBASP) therapist's guide*. New York: Routledge (2016).
30. Sayegh L, Penberthy JK. *Group Workbook for Treatment of Persistent Depression: Cognitive Behavioral Analysis System of Psychotherapy-(CBASP) Patient's Guide*. New York: Routledge (2016).
31. Sayegh L, Locke KD, Pistilli D, Penberthy JK, Chachamovich E, McCullough JPJr., et al. Cognitive Behavioural Analysis System of Psychotherapy for Treatment-Resistant Depression: Adaptation to a Group Modality. *Behav Change* (2012) 29(2):97–108. doi: 10.1017/bec.2012.2
32. Locke KD, Sayegh L, Penberthy JK, Weber C, Haentjens K, Turecki G. Interpersonal Circumplex Profiles Of Persistent Depression: Goals, Self-Efficacy, Problems, And Effects Of Group Therapy. *J Clin Psychol* (2017) 73 (6):595–611. doi: 10.1002/jclp.22343
33. Kennedy SH, Lam RW, McIntyre RS, Tourjman SV, Bhat V, Blier P, et al. Canadian Network for Mood and Anxiety Treatments (CANMAT) 2016 Clinical Guidelines for the Management of Adults with Major Depressive Disorder: Section 3. Pharmacological Treatments. *Can J Psychiatry* (2016) 61 (9):540–60. doi: 10.1177/0706743716659417
34. Parikh SV, Quilty LC, Ravitz P, Rosenbluth M, Pavlova B, Grigoriadis S, et al. Canadian Network for Mood and Anxiety Treatments (CANMAT) 2016 Clinical Guidelines for the Management of Adults with Major Depressive Disorder: Section 2. Psychological Treatments. *Can J Psychiatry* (2016) 61 (9):524–39. doi: 10.1177/0706743716659418
35. Lejuez CW, Hopko DR, Hopko SD. A brief behavioral activation treatment for depression. Treatment manual. *Behav Modif* (2001) 25(2):255–86. doi: 10.1177/0145445501252005

36. McCullough JPJr. The Cognitive Behavioral Analysis System of Psychotherapy: A value-added strategy for chronic depression. *Psychiatr Times* (2008) 25 (10): 26.
37. Lejuez CW, Hopko DR, LePage JP, Hopko SD, McNeil DW. A brief behavioral activation treatment for depression. *Cogn Behav Pract* (2001) 8:164–75. doi: 10.1016/S1077-7229(01)80022-5
38. Rush AJ, Gullion CM, Basco MR, Jarrett RB, Trivedi MH. The Inventory of Depressive Symptomatology (IDS): psychometric properties. *Psychol Med* (1996) 26(3):477–86. doi: 10.1017/S0033291700035558
39. Hamilton M. Development of a rating scale for primary depressive illness. *Br J Soc Clin Psychol* (1967) 6(4):278–96. doi: 10.1111/j.2044-8260.1967.tb00530.x
40. Rush AJ, Carmody T, Reimitz PE. The Inventory of Depressive Symptomatology (IDS): Clinician (IDS-C) and Self-Report (IDS-SR) ratings of depressive symptoms. *Int J Methods Psychiatr Res* (2000) 9(2):45–59. doi: 10.1002/mpr.79
41. Trivedi MH, Rush AJ, Ibrahim HM, Carmody TJ, Biggs MM, Suppes T, et al. The Inventory of Depressive Symptomatology, Clinician Rating (IDS-C) and Self-Report (IDS-SR), and the Quick Inventory of Depressive Symptomatology, Clinician Rating (QIDS-C) and Self-Report (QIDS-SR) in public sector patients with mood disorders: a psychometric evaluation. *Psychol Med* (2004) 34(1):73–82. doi: 10.1017/S0033291703001107
42. Weissman MM, Bothwell S. Assessment of social adjustment by patient self-report. *Arch Gen Psychiatry* (1976) 33(9):1111–5. doi: 10.1001/archpsyc.1976.01770090101010
43. Weissman MM, Prusoff BA, Thompson WD, Harding PS, Myers JK. Social adjustment by self-report in a community sample and in psychiatric outpatients. *J Nerv Ment Dis* (1978) 166(5): 317–26. doi: 10.1097/00005053-197805000-00002
44. Cohen S, Kamarck T, Mermelstein R. A global measure of perceived stress. *J Health Soc Behav* (1983) 24(4):385–96. doi: 10.2307/2136404
45. Cohen S, Williamson GM. Perceived Stress in a probability sample of the United States. In: Spacapan SO,S, editor. *The Social Psychology of Health*. Newbury Park: Sage (1988). p. 31–67.
46. Endler NS, Parker JDA. State and trait anxiety, depression and coping styles. *Aust J Psychol* (1990) 42:207–20. doi: 10.1080/00049539008260119
47. Folkman S, Lazarus RS. *Manual for the Ways of Coping Questionnaire*. Consulting Psychologists Press: Palo Alto, CA (1988).
48. Folkman S, Lazarus RS. If it changes it must be a process: study of emotion and coping during three stages of a college examination. *J Pers Soc Psychol* (1985) 48(1):150–70. doi: 10.1037/0022-3514.48.1.150
49. Perreault M, White ND, Fabres E, Landry M, Anestin AS, Rabouin D. Relationship between perceived improvement and treatment satisfaction among clients of a methadone maintenance program. *Eval Program Plann* (2010) 33(4):410–7. doi: 10.1016/j.evalprogplan.2009.12.003
50. Horowitz LM, Alden LE, Wiggins JS, Pincus AL. *Inventory of Interpersonal Problems (IIP) - Manual*. San antonio, Texas: The Psychological Corporation a Harcourt Assessment Company (2000).
51. Locke KD. Circumplex scales of interpersonal values: reliability, and applicability to interpersonal problems and personality disorders. *J Pers Assess* (2000) 75((2):249–67. doi: 10.1207/S15327752JPA7502_6
52. Locke KD, Sadler P. Self-efficacy, values, and complementarity in dyadic interactions: Integrating interpersonal and social-cognitive theory. *Pers Soc Psychol Bull* (2007) 33(1):94–109. doi: 10.1177/0146167206293375
53. Locke KD, Sayegh L, Weber C, Turecki G. Interpersonal Self-Efficacy, Goals, and Problems of Persistently Depressed Outpatients: Prototypical Circumplex Profiles and Distinctive Subgroups. *Assessment* (2018) 25(8):988–1000. doi: 10.1177/1073191116672330
54. Locke KD, Adamic EJ. Interpersonal circumplex vector length and interpersonal decision making. *Pers Individ Dif* (2012) 53(6):764–9. doi: 10.1016/j.paid.2012.06.001
55. Muthén L, Muthén B. *Statistical analysis with latent variables: Mplus user's guide*. Muthén & Muthén: Los Angeles, CA (2012).
56. Ryff CD, Seeman T, Weinstein M. *Midlife in the United States (MIDUS 2): Biomarker Project, 2004-2009. Inter-university Consortium for Political and Social Research [distributor]*. (2019). doi: 10.3886/ICPSR29282.v9
57. McWilliams LA, Cox BJ, Enns MW. Use of the Coping Inventory for Stressful Situations in a clinically depressed sample: Factor structure, personality correlates and prediction of distress. *J Clin Psychol* (2003) 59(4):423–37. doi: 10.1002/jclp.10080
58. Vohringer PA, Perlis RH. Discriminating Between Bipolar Disorder and Major Depressive Disorder. *Psychiatr Clin North Am* (2016) 39(1):1–10. doi: 10.1016/j.psc.2015.10.001
59. Kessing LV, Andersen PK. Evidence for clinical progression of unipolar and bipolar disorders. *Acta Psychiatr Scand* (2017) 135(1):51–64. doi: 10.1111/acps.12667
60. Nunez NA, Comai S, Dumitrescu E, Ghabrash MF, Tabaka J, Saint-Laurent M, et al. Psychopathological and sociodemographic features in treatment-resistant unipolar depression versus bipolar depression: a comparative study. *BMC Psychiatry* (2018) 18(1):68. doi: 10.1186/s12888-018-1641-y
61. Hamilton M. A rating scale for depression. *J Neurol Neurosurg Psychiatry* (1960) 23:56–62. doi: 10.1136/jnnp.23.1.56
62. Beck AT, Ward CH, Mendelson M, Mock J, Erbaugh J. An inventory for measuring depression. *Arch Gen Psychiatry* (1961) 4:561–71. doi: 10.1001/archpsyc.1961.01710120031004
63. Rush AJ, Trivedi MH, Ibrahim HM, Carmody TJ, Arnow B, Klein DN, et al. The 16-Item Quick Inventory of Depressive Symptomatology (QIDS), clinician rating (QIDS-C), and self-report (QIDS-SR): a psychometric evaluation in patients with chronic major depression. *Biol Psychiatry* (2003b) 54(5):573–83. doi: 10.1016/S0006-3223(02)01866-8
64. Beck AT, Steer RA, Brown GK. *Manual for the Beck Depression Inventory-II*. Psychological Corporation: San Antonio, Texas (1996).
65. Brakemeier EL, Radtke M, Engel V, Zimmermann J, Tuschen-Caffier B, Hautzinger M, et al. Overcoming Treatment Resistance in Chronic Depression: A Pilot Study on Outcome and Feasibility of the Cognitive Behavioral Analysis System of Psychotherapy as an Inpatient Treatment Program. *Psychother Psychosom* (2015) 84(1):51–6. doi: 10.1159/000369586
66. Schramm E, Zobel I, Dykierek P, Kech S, Brakemeier EV, Külz A, et al. Cognitive behavioral analysis system of psychotherapy versus interpersonal psychotherapy for early-onset chronic depression: A randomized pilot study. *J Affect Disord* (2011) 129:109–16. doi: 10.1016/j.jad.2010.08.003
67. Peeters FP, Ruhe HG, Wichers M, Abidi L, Kaub K, van der Lande HJ, et al. The Dutch Measure for quantification of Treatment Resistance in Depression (DM-TRD): an extension of the Maudsley Staging Method. *J Affect Disord* (2016) 205:365–71. doi: 10.1016/j.jad.2016.08.019
68. Reinares M, Papachristou E, Harvey P, Mar Bonnin C, Sanchez-Moreno J, Torrent C, et al. Towards a clinical staging for bipolar disorder: defining patient subtypes based on functional outcome. *J Affect Disord* (2013) 144(1-2):65–71. doi: 10.1016/j.jad.2012.06.005
69. Renner F, Cuijpers P, Huibers M. The effect of psychotherapy for depression on improvements in social functioning: a meta-analysis. *Psychol Med* (2014) 44(14):2913. doi: 10.1017/S0033291713003152
70. McFarquhar T, Luyten P, Fonagy P. Changes in interpersonal problems in the psychotherapeutic treatment of depression as measured by the Inventory of Interpersonal Problems: A systematic review and meta-analysis. *J Affect Disord* (2018) 226:108–23. doi: 10.1016/j.jad.2017.09.036
71. Simon S, Cain NM, Wallner Samstag L, Meehan KB, Muran JC. Assessing interpersonal subtypes in depression. *J Pers Assess* (2015) 97(4):364–73. doi: 10.1080/00223891.2015.1011330
72. Grosse Holtforth M, Altenstein D, Krieger T, Flückiger C, Wright AG, Caspar F. Interpersonal differentiation within depression diagnosis: Relating interpersonal subgroups to symptom load and the quality of the early therapeutic alliance. *Psychother Res* (2014) 24(4):429–41. doi: 10.1080/10503307.2013.829253
73. Barrett MS, Barber JP. Interpersonal profiles in major depressive disorder. *J Clin Psychol* (2007) 63(3):247–66. doi: 10.1002/jclp.20346
74. Quilty LC, Mainland BJ, McBride C, Bagby RM. Interpersonal problems and impacts: Further evidence for the role of interpersonal functioning in treatment outcome in major depressive disorder. *J Affect Disord* (2013) 150 (2):393–400. doi: 10.1016/j.jad.2013.04.030

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Offspring of Mothers With Histories of Chronic and Non-chronic Depression: Symptom Trajectories From Ages 6 to 15

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Several studies have reported that individuals with chronic depression have higher rates of depressive disorders, and particularly chronic depression, in their first-degree relatives, compared to those with non-chronic (episodic) major depression. In addition, a few studies have suggested that offspring of parents with chronic depression have elevated rates of depression and other psychopathology. Most of this work uses the Diagnostic and Statistical Manual of Mental Disorders (DSM), which defines chronicity as persistence for at least 2 years. An alternative is a life-course, approach, which evaluates overall course since first onset. We examined the trajectories of depressive, anxiety, and externalizing symptoms in a community sample of 577 offspring of mothers with histories of chronic depression, non-chronic (or episodic) major depression, and no depression using prospective, multi-informant assessments from age 6 to age 15. Offspring of mothers with a history of depression exhibited higher levels of depression, anxiety, and externalizing symptoms than offspring of mothers who were never depressed. Moreover, the effects of maternal depression on offspring depression, anxiety, and externalizing symptoms were more pronounced for mothers with histories of chronic than non-chronic depression, particularly when the life-course approach to classifying chronicity was used. These data suggest that research that combines chronic and non-chronic depressions includes significant heterogeneity that may hinder understanding of etiology and reduce the likelihood of developing a cumulative and replicable literature. In addition, these findings have significant implications for prevention and treatment.

Keywords: chronic depression, maternal depression, offspring, intergenerational transmission, persistent depression

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INTRODUCTION

An extensive body of research has documented the familial aggregation and intergenerational transmission of depressive disorders (1, 2). A smaller group of studies have reported that the relatives of individuals with chronic forms of depression, such as chronic major depression or dysthymic disorder, referred to as "persistent depressive disorder" in the Diagnostic and Statistical Manual of Mental Disorders, 5th edition [DSM-5, (3)] experience even higher rates of depressive disorders than relatives of persons with non-chronic, or episodic, major depression (4–7). In

addition to being at greater risk for depression in general, relatives of people with chronic depression have higher rates of chronic depression than relatives of individuals with non-chronic major depression, suggesting some degree of specificity of familial aggregation (5, 6, 8).

There has been particular interest in examining the development of depression in the offspring of depressed parents, especially depressed mothers, as this is a high risk group that offers critical opportunities for prevention and early intervention, as well as for examining risk factors and mechanisms prior to the onset of the disorder (2). Studies of clinical and community samples indicate that the rate of depressive disorders in offspring of depressed parents is 2–3 times greater than in the offspring of non-depressed parents (9–12). Moreover, this increase in risk is particularly pronounced among offspring of depressed mothers (13). Children of mothers with depressive disorders are also at increased risk for anxiety, behavior, and substance disorders (11, 14, 15).

Paralleling the literature on the familial aggregation of chronic depression, a handful of studies have reported that the children of chronically depressed parents are at even higher risk than offspring of non-chronically depressed parents. Compared to offspring of non-chronically depressed mothers, offspring of chronically depressed mothers have higher rates of depression, recurrent major depressive episodes, and chronic depression (4, 10). Moreover, offspring of chronically depressed mothers also exhibit higher rates of behavioral problems and substance use disorders (4, 16, 17).

However, a problem plaguing the literature on chronic depression is the wide variation in how chronicity is defined (18). While many studies classify chronic depression using the DSM, which itself has changed across editions, a number define chronicity on the basis of mean scores on repeated assessments of self-reported (19) or interviewer-rated (17) symptoms.

The most widely-used approach in the literature on chronic depression utilizes DSM-III, DSM-III-R, and DSM-IV categories and episode and course specifiers (20–22), which were combined under the rubric of Persistent Depressive Disorder in DSM-5 (3). The DSMs define chronicity as a duration of at least 2 years, which, while reasonable, is arbitrary and is not based on evidence (23). This approach may be most useful for clinical samples, when patients present in a current episode. However, in non-clinical samples, it is possible for individuals to have past episodes that meet DSM criteria for chronic depression while still having a life course that is relatively depression-free (e.g., an individual who experienced a 2-year period of dysthymia at age 30, followed by full recovery and no recurrences over the next 20 years) (23). Hence, Mondimore et al. (24) suggested an alternative approach to defining chronicity using a life course perspective, where chronicity is evaluated on the basis of the individual's course since their first onset of depression. Mondimore et al. (24) reported that this approach exhibited good interrater reliability (Kappa = 0.76). Applying Robins and Guze (25) classic framework for validating psychiatric diagnoses, they compared the familial aggregation of chronic depression using the lifetime and DSM approaches to defining chronic depression. Mondimore et al. (24) found that their approach yielded higher levels of familial aggregation, as indexed by the odds of a relative exhibiting chronic depression, than the DSM approach.

In the present study, we examine the trajectories of depressive, anxiety, and externalizing symptoms in a community sample of offspring of mothers with histories of chronic depression, non-chronic (or episodic) major depression, and no depression using prospective, multi-informant assessments conducted every 3 years from age 6 to age 15. In addition to defining chronic and non-chronic depression using DSM-IV, we conducted parallel analyses using a life-course approach to classifying chronic and non-chronic depression (24). Based on previous literature, we expected that offspring of depressed mothers would exhibit higher levels of depressive symptoms over the course of childhood into adolescence than offspring of never-depressed mothers, and that these effects would be most pronounced among offspring of mothers with a history of chronic depression. We also expected that offspring of depressed mothers would exhibit higher levels of anxiety and externalizing symptoms, and that these effects would be particularly prominent among the offspring of mothers with chronic depression. Finally, given preliminary evidence that a life-course approach to defining chronicity may enhance the differences in familial aggregation between chronic and non-chronic depression compared to DSM classification (24), we conjectured that the hypothesized effects would be more pronounced when chronic and non-chronic depression are classified using a life-course perspective.

METHODS

Participants

Families with a 3-year-old child living within 20 miles of Stony Brook, NY were recruited using commercial mailing lists for a larger study of risk for emotional disorders; children with significant medical or developmental disorders were excluded, and the child had to live with at least one biological parent [N = 559; (26)]. An additional 50 families were added in the second wave of assessments when children were 6 years old in order to increase the diversity of the sample. Only one child per family was included in the study. The sample was re-assessed when children were ∼9, 12, and 15 years old. Retention rates in waves 2–5 were 84.4, 81.3, 80.0, and 76.7%, respectively.

The current analysis sample included 577 children and mothers. Participants were included if the child's mother completed a diagnostic interview about her own history of psychopathology as part of her initial assessment. The mean ages of the children in the analysis sample at each wave were 3.56 years (SD = 0.26; range: 2.92–4.17), 6.08 years (SD = 0.41; range: 4.83–7.57), 9.18 years (SD = 0.39; range: 8.33–10.92), 12.66 years (SD = 0.46; range: 11.50–14.17), and 15.25 years (SD = 0.40; range: 14.43–17.64), respectively. Of the children in the analytic sample, 265 (45.8%) were female, 522 (90.5%) were white, 37 (6.4%) were Black, 14 (2.4%) were Asian, 1 (0.2%) were Native American, and 3 (0.5%) were other. Sixty seven (11.6%) offspring were Hispanic. Due to the small Ns, we coded race/ethnicity as white and non-Hispanic (N = 469; 81.3%) or as non-white and/or Hispanic (N = 108; 18.7%). More than half of children (379 [69.7%]) had at least one parent who had graduated from college at the initial

assessment. The demographic characteristics of the sample were representative of the surrounding county (27).

Measures

Maternal Depression

The Structured Clinical Interview for DSM–IV non-patient version (SCID) was used to assess maternal history of depression (28) at the age 3 (or age 6 for the 50 additional families) wave. As part of the interview, we obtained a detailed follow-back timeline of the course of depression from the DSM-IV Mood Disorders Field Trials (29, 30). The SCID was administered by telephone to 577 mothers by a highly experienced masters-level clinician. Based on audiotapes of 30 randomly selected interviews, interrater reliability (kappa) for lifetime depressive disorders was 0.93. In previous studies, our interviewer demonstrated high interrater reliability for distinguishing DSM-IV chronic and non-chronic depression and rating clinical course using the timeline (31, 32).

For the present study, we defined chronic and non-chronic (or episodic) depression in mothers in two different ways: using the DSM-IV (22) and applying a life course perspective (24). Using DSM-IV, 386 (66.9%) mothers were never depressed, 112 (19.4%) mothers had lifetime non-chronic (or episodic) major depressive epiosde, and 79 (13.7%) mothers had chronic depression (chronic major depressive episode and/or dysthymic disorder).

Using the DSM approach, 48 (60.8%) mothers with chronic depression had co-morbid anxiety and 64 (57.1%) mothers with non-chronic depression had co-morbid anxiety. Twenty six (32.9%) mothers with chronic depression had co-morbid substance abuse and 37 (33.0%) mothers with non-chronic depression had co-morbid substance abuse. Finally, 1 (1.3%) mothers with chronic depression and 1 (0.9%) mother with non-chronic depression had co-morbid bipolar disorder. The two groups did not significantly differ on co-morbid anxiety ($X^2 = 0.250$, $p = 0.617$), substance abuse ($X^2 = 0.000$, $p = 0.986$), or bipolar disorder ($X^2 = 0.062$, $p = 0.803$).

Using a life course perspective, mothers' depression was categorized based on course from the initial episode of depression to the time of the SCID assessment. Non-chronic depression was defined as: (1) a single episode of depression lasting up to 2 years ($N = 68$; 35.6%), (2) recurrent episodes of depression lasting up to 2 years with significant (>6 mos) periods of interepisode recovery ($N = 26$, 13.6%), (3) recurrent episodes of depression lasting up to 2 years with brief periods (≤6 mos) of interepisode recovery ($N = 1$; 0.05%), or (4) one or more episodes of chronic (>2 years) depression but with total time in remission longer than total time depressed since onset ($N = 44$; 23.0%). Chronic depression was defined as: (1) chronic (>2 years) depression with total time in remission shorter than total time depressed since onset ($N = 27$; 14.1%) or (2) mostly or virtually always depressed and never well for >2 consecutive months ($N = 25$; 13.1%). In sum, our life course criteria classified 386 (66.9%) mothers as never depressed, 139 (24.1%) mothers as having a history of non-chronic depression, and 52 (9.0%) mothers as having a history of chronic depression.

With regard to the life course approach, 29 (55.8%) mothers with chronic depression had co-morbid anxiety and 83 (59.7%) mothers with non-chronic depression had co-morbid anxiety. Nineteen (36.5%) mothers with chronic depression had co-morbid substance abuse and 44 (31.7%) mothers with non-chronic depression had co-morbid substance abuse. Finally, no mothers with chronic depression and 2 (1.4%) mothers with non-chronic depression had co-morbid bipolar disorder. The two groups did not significantly differ on co-morbid anxiety ($X^2 = 0.243$, $p = 0.622$), substance abuse ($X^2 = 0.408$, $p = 0.523$), or bipolar disorder ($X^2 = 0.756$, $p = 0.385$).

Early Childhood, Middle Childhood and Adolescent Symptoms

At the age 6, 9, 12, and 15 waves, children, and at the age 9, 12, and 15 waves, mothers and fathers, completed the child- and parent-report versions of the Children's Depression Inventory [CDI; (33)], a measure of depressive symptoms during the past 2 weeks that is designed for youth aged 7–17. At age 6, items were read aloud to the children. Cronbach's alpha across the waves ranged from 0.74–0.82 for child reports, 0.78–0.80 for mother reports, and 0.76–0.79 for father reports.

At the age 9, 12, and 15 waves, children, mothers, and fathers also completed the 41-item child- and parent-report versions, respectively, of the Screen for Childhood Anxiety Related Disorders [SCARED; (34)], a measure of anxiety symptoms over the past 3 months designed for youth aged 9–18. The SCARED is made up of five factor-analytically derived subscales: panic/somatic, generalized anxiety, separation anxiety, social phobia, and school phobia. In the current sample, Cronbach's alpha across the waves ranged from 0.89 to 0.93 for child reports, 0.90 to 0.91 for mother reports, and 0.88 to 0.89 for father reports.

Finally, at the age 6, 9, 12, and 15 waves, mothers and fathers completed the CBCL 6–18 (35). In the present paper, we examine the broadband internalizing (32 items) and externalizing (35 items) scales. For the internalizing scale, Cronbach's alpha across the waves ranged from 0.86 to 0.87 for mothers and 0.78 to 0.90 for fathers. Alphas for the externalizing scale ranged from 0.87 to 0.88 for mothers and 0.87 to 0.91 for fathers.

Data Analyses

Multilevel models were used to test the associations between maternal depression and CDI depression, SCARED anxiety, and CBCL internalizing and externalizing symptoms across assessment waves. In these models, time was centered at the final assessment, so the intercept reflects the level of the dependent variable at age 15. The models included both random intercept and random slope components. Time was coded as wave number, and missing data were estimated using Maximum Likliehood Estimation (ML). Multilevel models were conducted using Mplus (36); all other statistical analyses were performed using SPSS 25 (37).

RESULTS

Using DSM-IV, offspring of chronically, non-chronically, and never depressed mothers did not differ on race/ethnicity, $X^2(2, N = 577) = 2.86$, $p = 0.24$, sex, X^2 $(2, N = 577) = 2.69$, p

TABLE 1 | N, Means, and SDs of offspring symptom variables across assessment waves.

	Age 6		Age 9		Age 12		Age 15	
Measure	***N***	***M* (SD)**	***N***	***M* (SD)**	***N***	***M* (SD)**	***N***	***M* (SD)**
Child CDI	485	7.42 (5.27)	467	4.80 (4.16)	456	4.82 (5.33)	442	5.66 (5.30)
Mother CDI	-	-	471	7.20 (4.83)	461	7.09 (5.00)	447	8.02 (5.46)
Father CDI	-	-	414	7.35 (4.42)	374	7.50 (5.02)	370	8.03 (5.05)
Child SCARED	-	-	466	19.46 (11.02)	458	16.66 (10.57)	440	17.10 (12.08)
Mother SCARED	-	-	470	7.92 (8.03)	455	7.91 (7.90)	447	6.65 (7.60)
Father SCARED	-	-	412	6.72 (6.56)	372	7.02 (6.85)	369	6.04 (6.66)
Mother CBCL internalizing	455	3.54 (4.58)	471	4.06 (4.87)	460	3.63 (4.87)	447	3.78 (5.13)
Father CBCL internalizing	363	3.69 (3.81)	413	3.74 (4.96)	374	4.03 (5.09)	370	3.91 (5.80)
Mother CBCL externalizing	455	5.14 (5.69)	471	4.56 (5.27)	460	3.51 (4.75)	447	3.16 (4.50)
Father CBCL externalizing	363	5.44 (5.66)	413	4.45 (5.55)	374	4.40 (5.14)	447	3.16 (4.50)

CDI, Children's Depression Inventory; SCARED, Screen for Childhood Anxiety Related Disorders; CBCL, Children's Behavior Checklist.

TABLE 2 | Multi-level models using maternal depression at age 3 to predict symptom outcomes across subsequent waves using the DSM approach.

	Non-chronic vs. Never depressed		Chronic vs. Never depressed		Chronic vs. Non-chronic	
	Intercept	**Slope**	**Intercept**	**Slope**	**Intercept**	**Slope**
Measure	***B* (SE)**	***B* (SE)**	***B* (SE)**	***B* (SE)**	***B* (SE)**	***B* (SE)**
Child CDI	0.03 (0.62)	−0.02 (0.28)	2.45 (0.69)**	0.45 (0.32)	2.41 (0.84)**	0.48 (0.38)
Mother CDI	1.62 (0.62)**	0.18 (0.30)	3.19 (0.69)**	0.15 (0.34)	1.56 (0.83)	−0.03 (0.40)
Father CDI	0.63 (0.65)	0.01 (0.33)	1.09 (0.75)	−0.05 (0.38)	0.45 (0.89)	−0.07 (0.46)
Child SCARED	1.65 (1.46)	0.79 (0.88)	3.40 (1.61)*	0.71 (0.98)	1.74 (1.95)	−0.07 (1.18)
Mother SCARED	2.46 (0.91)**	−0.43 (0.44)	3.87 (1.01)**	0.33 (0.49)	1.40 (1.25)	0.76 (0.59)
Father SCARED	−0.50 (1.15)	−1.05 (0.42)*	−0.18 (1.31)	−0.35 (0.48)	−0.38 (1.18)	0.70 (0.59)
Mother CBCL internalizing	1.78 (0.60)**	0.01 (0.22)	2.98 (0.67)**	−0.05 (0.22)	1.23 (0.81)	−0.06 (0.30)
Father CBCL internalizing	2.04 (0.72)**	0.26 (0.25)	−0.85 (0.99)	−0.46 (0.34)	1.19 (0.82)	−0.20 (0.28)
Mother CBCL externalizing	0.57 (0.52)	−0.02 (0.21)	1.53 (0.58)**	−0.57 (0.23)*	0.95 (0.70)	−0.54 (0.28)
Father CBCL externalizing	1.34 (0.70)	0.28 (0.27)	0.89 (0.79)	−0.38 (0.30)	−0.45 (0.95)	−0.66 (0.37)

***p < 0.01, *p < 0.05.*
CDI, Children's Depression Inventory; SCARED, Screen for Childhood Anxiety Related Disorders; CBCL, Children's Behavior Checklist.

$= 0.26$, age at baseline, $F_{(2,538)} = 0.66$, $p = 0.52$, or having at least one parent who had graduated from college, X^2 (2, $N = 577$) $= 1.59$, $p = 0.45$. Similarly, using the life-course approach, children of chronically, non-chronically, and never depressed mothers did not differ on race/ethnicity, X^2 (2, $N = 577$) $= 4.02$, $p = 0.13$, sex, X^2 (2, $N = 577$) $= 1.41$, $p = 0.49$, age at baseline, $F_{(2,538)} = 0.42$, $p = 0.65$, or having at least one parent who had graduated from college, X^2 (2, $N = 577$) $= 3.14$, $p = 0.20$.

The life-course approach to defining chronicity was narrower than the approach in DSM-IV. Of the 112 mothers with non-chronic major depression using DSM-IV, 107 (95.5%) had non-chronic depression and 5 (4.5%) had chronic depression using the life-course approach. Of the 79 mothers with chronic depression using DSM-IV, 48 (60.8%) had chronic depression and 31 (39.2%) had non-chronic depression using the life-course perspective.

Associations of DSM-IV Maternal Chronic Depression With Child Symptoms

Means of each symptom measure at each wave can be seen in **Table 1**. Correlations between measures are presented in **Supplementary Table 1**; in line with the literature, these correlations are generally moderate in magnitude.

The first set of analyses used DSM-IV to define chronic and non-chronic depression. First, multilevel models were run to estimate the associations of maternal depression with the linear effect of time (i.e., assessment wave) on child, mother, and father-reports of child depressive symptoms on the CDI (see **Table 2**). Compared to mothers who had never been depressed, maternal non-chronic major depression predicted the intercept of mother-reported depressive symptoms in offspring. Offspring of non-chronically depressed mothers exhibited significantly higher estimated levels of mother-reported depressive symptoms at the final wave than offspring of never-depressed mothers. Similarly, offspring of chronically depressed mothers exhibited significantly

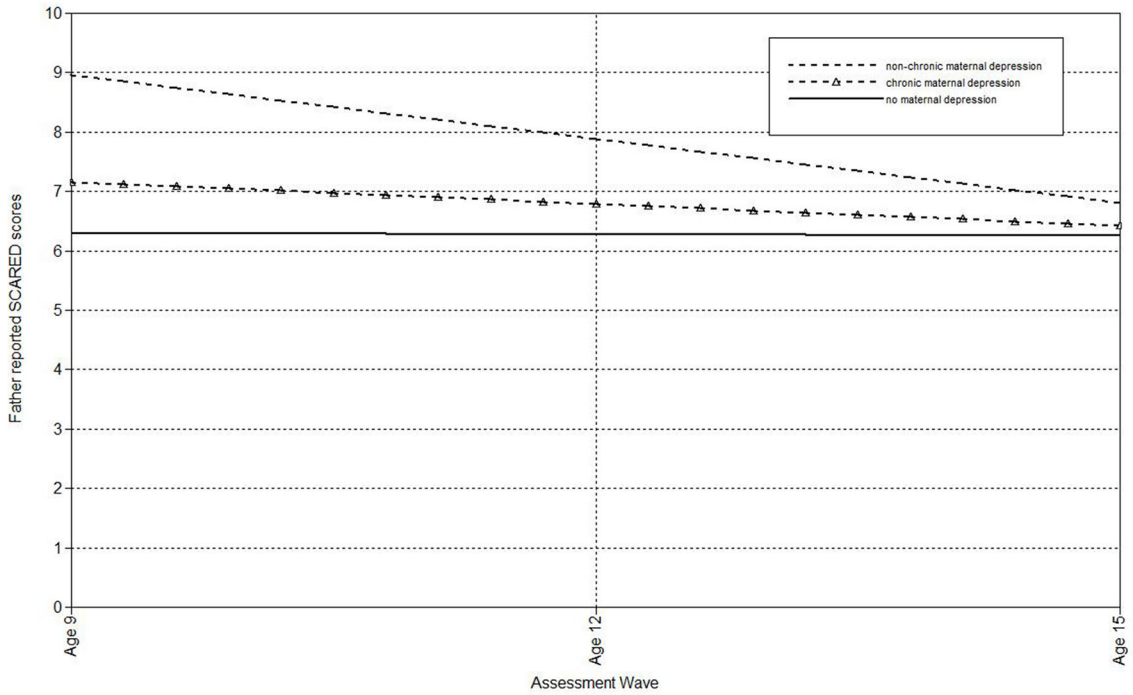

FIGURE 1 | Effect of non-chronic maternal depression (DSM approach) on the slope of father-reported SCARED scores in offspring.

higher estimated levels of both mother- and child-reported depressive symptoms at the age 15 wave than offspring of never-depressed mothers. Finally, compared to mothers with non-chronic depression, offspring of chronically depressed mothers exhibited significantly higher estimated levels of mother-reported depressive symptoms at the final wave.

Next, multilevel models were run to estimate the associations of maternal depression with the linear effect of time on child, mother, and father-reports on the SCARED (see **Table 2**). Compared to mothers who had never been depressed, offspring of non-chronically depressed mothers exhibited higher estimated levels of mother-reported anxiety symptoms at the final wave. Additionally, maternal non-chronic depression predicted the slope of father-reported anxiety symptoms in offspring. **Figure 1** shows the trajectory of change in father-reported SCARED scores in offspring of mothers with no depression, non-chronic major depression, and chronic depression. In this figure, maternal non-chronic depression was associated with more rapid declines in father-reported anxiety symptoms over time. Compared to mothers who had never been depressed, offspring of mothers with chronic depression exhibited higher estimated levels of both child- and mother-reported anxiety symptoms at the age 15 assessment. Offspring of mothers with chronic and non-chronic depression did not differ on the intercepts or slopes of SCARED scores regardless of informant.

Multilevel models were also run to estimate the associations of maternal depression with the linear effect of time on mother- and father-reported CBCL internalizing scores in offspring (**Table 2**). Offspring of non-chronically depressed mothers exhibited significantly higher estimated levels of both mother- and father-reported internalizing symptoms at the final wave than offspring of never-depressed mothers. Similarly, offspring of mothers with chronic depression exhibited higher estimated levels of mother-reported internalizing symptoms at the age 15 assessment than offspring of never-depressed mothers. Offspring of chronically and non-chronically depressed mothers did not differ on the intercept or slope of mother- or father-reported CBCL internalizing scores.

Finally, multilevel models were run to estimate the associations of maternal depression with the linear effect of time on mother- and father-reported CBCL externalizing scores in offspring (**Table 2**). Offspring of non-chronically and never depressed mothers did not differ on the intercepts or slopes of mother- or father-reported externalizing symptoms. Compared to mothers who had never been depressed, maternal chronic depression predicted both the intercept and slope of mother-reported CBCL externalizing scores. As shown in **Figure 2**, children of mothers with chronic depression exhibited more rapid declines in externalizing symptoms over time, but still continued to have higher estimated externalizing scores at the final wave than offspring of never-depressed mothers. Offspring of chronically and non-chronically depressed mothers did not differ on intercepts or slopes of mother- or father-reported CBCL externalizing scores.

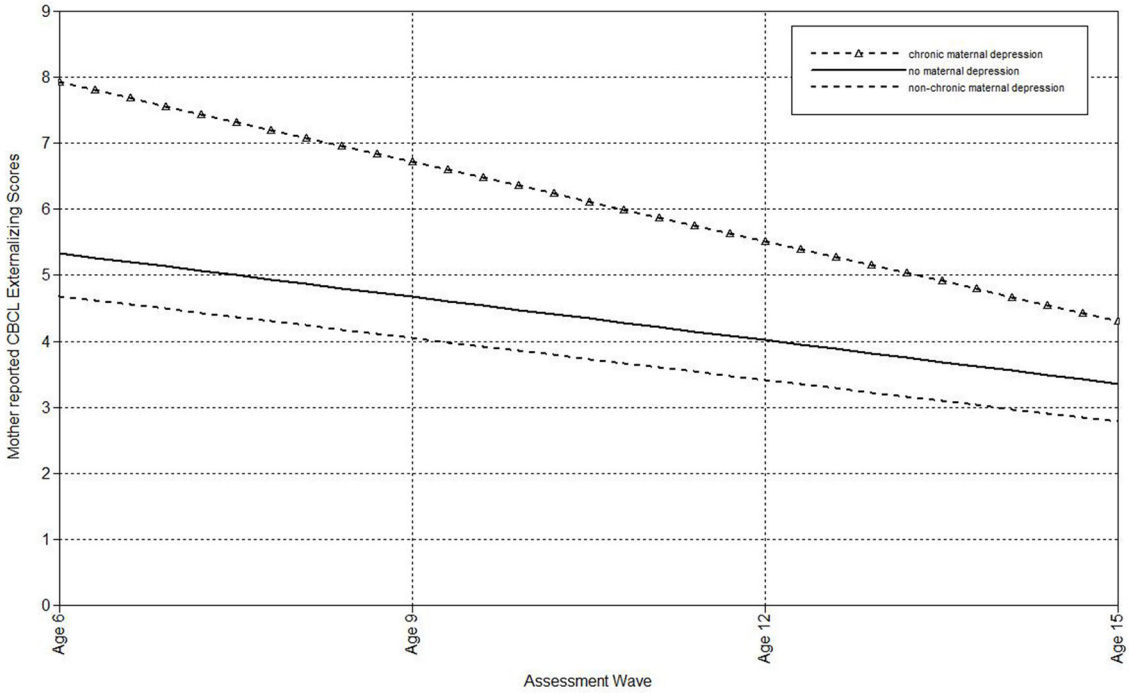

FIGURE 2 | Effect of chronic maternal depression (DSM approach) on the slope of mother-reported CBCL Externalizing scores in offspring.

Associations of Life-Course Maternal Chronic Depression With Child Symptoms

The second set of analyses used the life-course approach to classifying chronic and non-chronic depression. First, multilevel models were run to estimate the associations of maternal depression with the linear effect of time (i.e., assessment wave) on child-, mother-, and father-reports on the CDI (see **Table 3**). Offspring of non-chronically depressed mothers exhibited significantly higher estimated levels of mother-reported depressive symptoms at the final wave than offspring of never-depressed mothers. Compared both to mothers who had never been depressed and to mothers with non-chronic depression, maternal chronic depression predicted the intercepts of child-, mother-, and father-reported depressive symptoms in offspring, as well as the slopes of child-reported CDI scores. In addition, compared to mothers with non-chronic depression, maternal chronic depression predicted the slopes of father-reported depressive symptoms (**Table 3**). In each of these comparisons, the intercept effects indicated that offspring of mothers with chronic depression exhibited significantly higher estimated levels of depressive symptoms at the final assessment. In addition, offspring of mothers with chronic depression exhibited a more rapid increase in child-reported depression symptoms over time compared to offspring of both mothers with non-chronic depression and those with no history of depression (**Figure 3**), as well as a more rapid increase in father-reported CDI scores than offspring of mothers with non-chronic depression (**Figure 4**).

Next, multilevel models were run to estimate the associations of maternal depression with the linear effect of time on child-, mother-, and father-reports on the SCARED (**Table 3**). Offspring of non-chronically depressed mothers exhibited significantly higher estimated levels of mother reported anxiety symptoms at the last wave than offspring of never-depressed mothers. Non-chronic depression in mothers also predicted the slope of father-reported SCARED scores. Offspring of mothers with non-chronic depression exhibited more rapid declines in father-reported anxiety symptoms over time (**Figure 5**). Compared both to mothers who had never been depressed and mothers with a history of non-chronic depression, maternal chronic depression predicted higher estimated levels of child-, mother-, and father-reported SCARED scores in offspring at the age 15 wave (**Table 3**). Moreover, maternal chronic depression also predicted the slope of child-reported SCARED scores (**Figure 6**). Offspring of mothers with chronic depression exhibited more rapid increases in child-reported anxiety symptoms over time than offspring of both mothers with non-chronic depression and mothers with no history of depression.

Multilevel models were also run to estimate the associations of maternal depression with the linear effect of time on mother- and father-reported CBCL internalizing scores (**Table 3**). Offspring of non-chronically depressed mothers exhibited significantly higher

TABLE 3 | Multi-level models using maternal depression at age 3 to predict symptom outcomes across subsequent waves using the life course approach.

	Non–chronic vs. Never depressed		Chronic vs. Never depressed		Chronic vs. Non-chronic	
	Intercept	Slope	Intercept	Slope	Intercept	Slope
Measure	***B* (SE)**	***B* (SE)**	***B* (SE)**	***B* (SE)**	***B* (SE)**	***B* (SE)**
Child CDI	0.12 (0.56)	0.10 (0.26)	4.17 (0.82)**	0.94 (0.38)*	4.29 (0.91)**	1.04 (0.42)*
Mother CDI	−1.22 (0.55)*	−0.01 (0.27)	5.08 (0.82)**	0.56 (0.41)	3.85 (0.90)**	0.54 (0.45)
Father CDI	0.07 (0.58)	0.27 (0.30)	3.3 (0.91)**	0.79 (0.48)	3.50 (1.00)**	0.10 (0.52)*
Child SCARED	−0.40 (1.32)	0.03 (0.80)	7.51 (1.92)**	2.81 (1.20)*	7.10 (2.12)**	2.84 (1.31)*
Mother SCARED	−1.70 (0.82)*	0.43 (0.40)	6.65 (1.21)**	0.74 (0.60)	4.95 (1.33)**	1.17 (0.65)
Father SCARED	0.32 (0.78)	1.02 (0.38)**	2.45 (1.21)*	0.03 (0.61)	2.78 (1.32)*	1.05 (0.66)
Mother CBCL internalizing	−1.36 (0.54)*	0.05 (0.20)	4.63 (0.80)**	0.08 (0.30)	3.26 (0.88)**	0.14 (0.34)
Father CBCL internalizing	−0.93 (0.66)	0.02 (0.23)	3.76 (1.01)**	0.30 (0.36)	2.82 (1.11)*	0.33 (0.40)
Mother CBCL externalizing	−0.24 (0.45)	0.27 (0.19)	2.83 (0.69)**	−0.20 (0.28)	2.58 (0.77)**	0.07 (0.31)
Father CBCL externalizing	−0.56 (0.63)	−0.05 (0.24)	2.74 (0.98)**	−0.17 (0.39)	2.18 (1.08)*	−0.22 (0.42)

$^{**}p < 0.01$, $^{*}p < 0.05$.

CDI, Children's Depression Inventory; SCARED, Screen for Childhood Anxiety Related Disorders; CBCL, Children's Behavior Checklist.

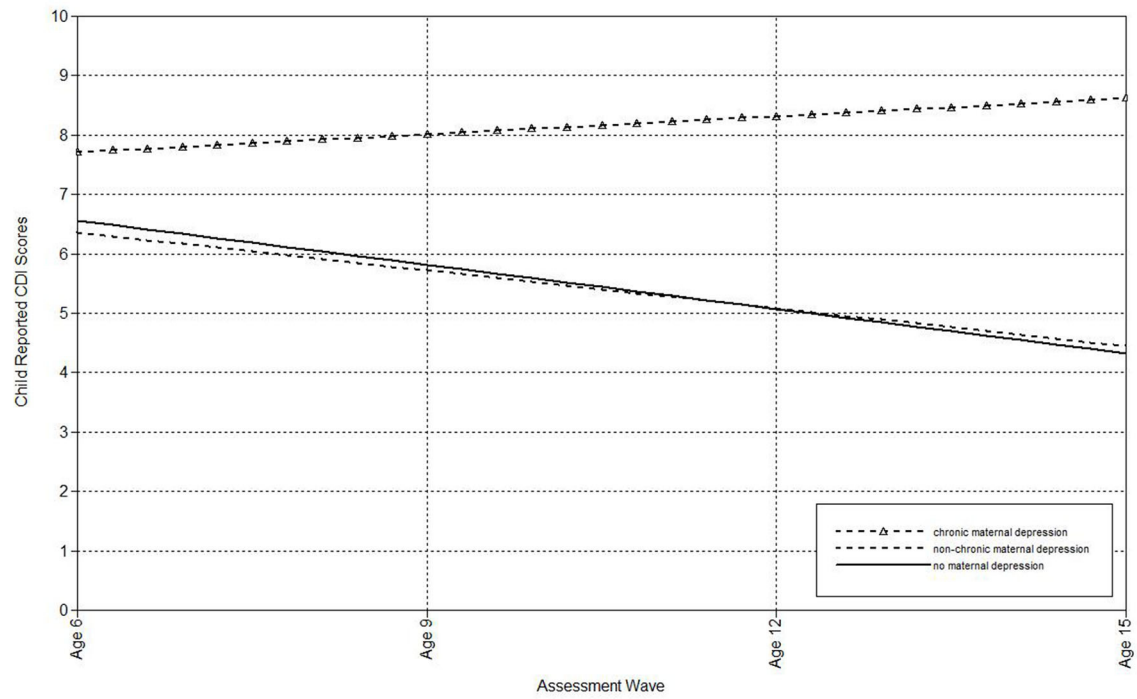

FIGURE 3 | Effect of chronic maternal depression (life-course perspective) on the slope of child-reported CDI scores in offspring.

estimated levels of mother-reported internalizing symptoms at the final assessment than offspring of never-depressed mothers. In addition, offspring of mothers with chronic depression exhibited higher estimated levels of internalizing symptoms, as reported by both parents, at the final assessment than children of both never-depressed and non-chronically depressed mothers.

Finally, multilevel models were run to estimate the associations of maternal depression with the linear effect of time on mother- and father-reported CBCL externalizing symptoms (**Table 3**). Children of mothers with chronic depression exhibited significantly higher estimated levels of externalizing problems at the final assessment, according to reports from both parents, than

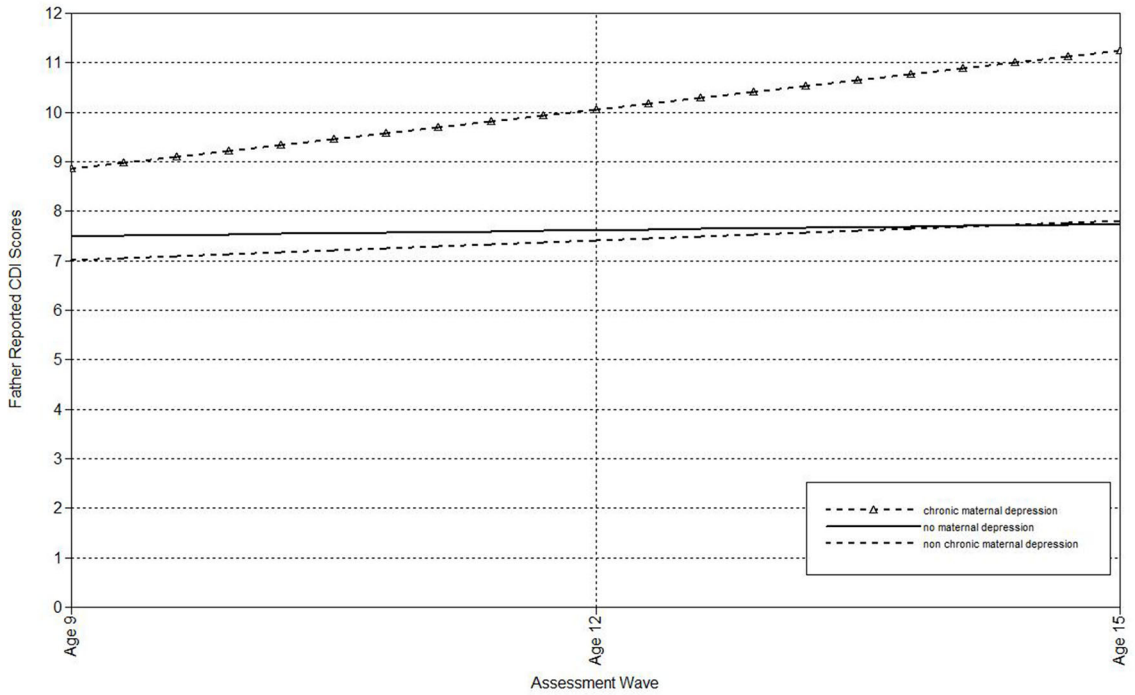

FIGURE 4 | Effect of chronic maternal depression (life-course perspective) on the slope of father-reported CDI scores in offspring.

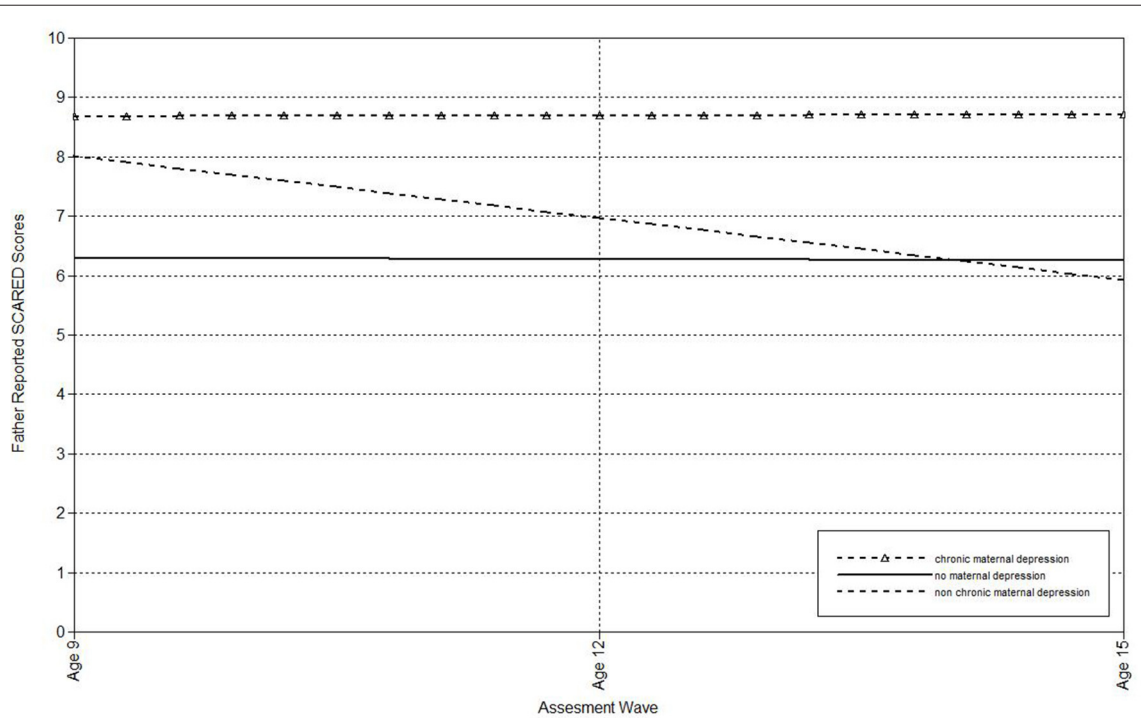

FIGURE 5 | Effect of non-chronic maternal depression (life-course perspective) on the slope of father-reported SCARED scores in offspring.

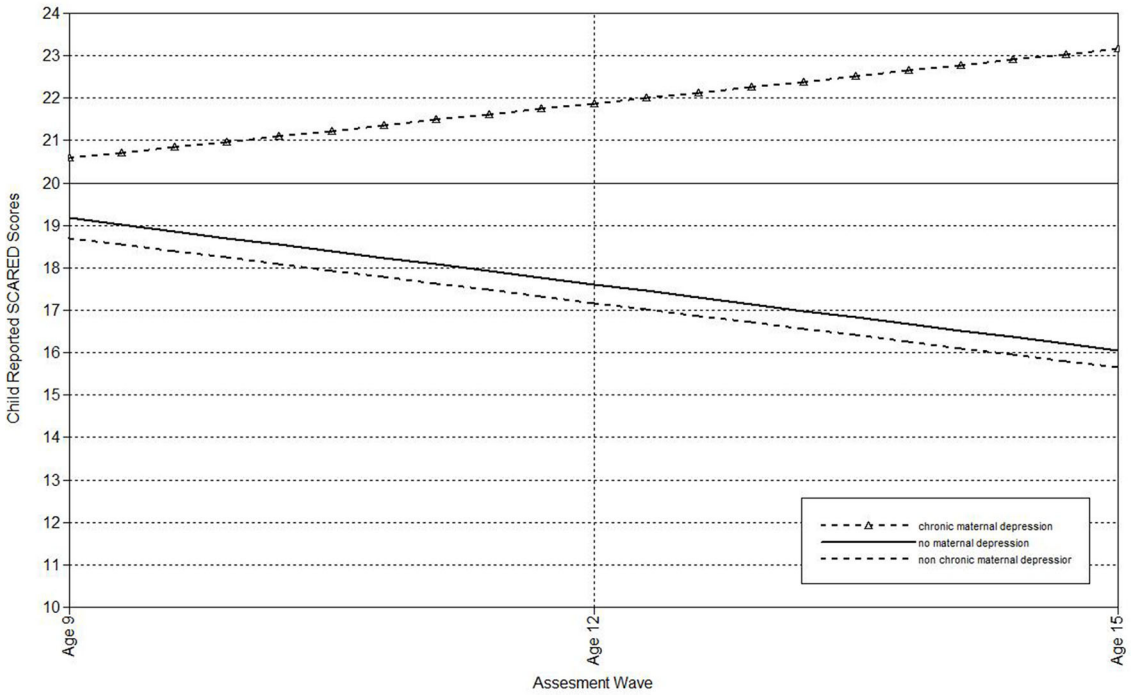

FIGURE 6 | Effect of chronic maternal depression (life-course perspective) on the slope of child-reported SCARED scores in offspring.

offspring of both non-depressed and non-chronically depressed mothers.

DISCUSSION

The present study examined the trajectories of depressive, anxiety, and externalizing symptoms in a community sample of offspring of mothers with histories of chronic depression, non-chronic (or episodic) major depression, and no depression using prospective, multi-informant assessments conducted every 3 years from age 6 to age 15. In addition to defining chronic and non-chronic depression using DSM-IV, we conducted parallel analyses using a life-course approach to classify chronic and non-chronic depression.

As expected, offspring of mothers with a history of depression generally exhibited higher estimated levels of depression, anxiety, and externalizing symptoms at the final assessment, a period when the increase in depression begins a rapid ascent (38). These findings echo the large literature documenting the familial aggregation (1) and intergenerational transmission of depressive disorders (9–12), as well as the many previous studies reporting that children of mothers with depressive disorders are also at increased risk for anxiety and behavioral disorders (2, 11, 14, 15).

However, a more nuanced picture emerged when the distinction between chronic and non-chronic depression in mothers was considered, and particularly when the DSM-IV and life-course approaches to defining chronicity were examined. Our findings generally supported the hypothesis that the effects of maternal depression on offspring are more pronounced for mothers with histories of chronic than non-chronic depression, although these effects were considerably stronger using the life-course approach to classifying chronicity.

Using the DSM-IV approach to classifying chronicity, comparisons of offspring of chronically depressed and never depressed mothers revealed a somewhat greater number of significant intercept effects (on 6 of 10 measures) than comparisons of offspring of non-chronically depressed and never depressed mothers (on 4 of 10 measures). In all cases, offspring of depressed mothers had significantly higher estimated levels of symptoms in the final assessment. In the only significant slope effects, offspring of non-chronically depressed mothers exhibited significantly faster decreases in father-reported anxiety symptoms and offspring of chronically depressed mothers exhibited significantly faster decreases in mother-reported externalizing symptoms than offspring of never-depressed mothers, suggesting that the effects of maternal depression on anxiety and externalizing symptoms faded over time. In direct comparisons of offspring of mothers with chronic vs. non-chronic depression, the children of mothers with chronic depression reported significantly higher estimated levels of depressive symptoms at the final assessment but did not differ on other 9 intercept and 10 slope comparisons.

However, when chronicity was classified using a life-course approach, offspring of mothers with chronic depression differed from offspring of never-depressed mothers on the intercepts for each of the ten symptom measures examined (reflecting higher estimated levels of depression, anxiety, and externalizing symptoms, as reported by offspring, mothers, and fathers, at

the final assessment). In addition, there were two significant slope effects, with offspring of chronically depressed mothers reporting significantly greater increases in depression and anxiety symptoms over time. In contrast, when offspring of non-chronically depressed and never depressed mothers were compared using the life-course approach there were only two significant intercept effects, and one significant slope effect reflecting a faster decrease in father-reported anxiety. Most telling were the direct comparisons between the offspring of mothers with histories of chronic and non-chronic depression. In contrast to the single significant intercept effect observed with DSM-IV-defined groups, when the life-course approach was used, the offspring of chronically depressed mothers exhibited significantly higher intercepts for all ten symptom measures (across three domains of symptoms and three informants) examined, as well as three significant slope effects. The slope effects revealed that offspring of chronically, compared to non-chronically, depressed mothers exhibited significantly greater increases in child- and father-reported depression and child-reported anxiety symptoms over time. Notably, these were the only instances in which a group of offspring showed progressively increasing levels of symptoms over the course of the four follow-up waves and suggest that these youth are already exhibiting signs of chronicity.

Taken together, these findings support the limited prior literature suggesting that the offspring of chronically depressed mothers are at even greater risk for depression and other forms of psychopathology than offspring of non-chronically depressed mothers (4, 10, 17), as well as evidence of the specificity of familial aggregation of chronic depression (4–6, 8). These data are also consistent with previous suggestions that a life-course approach to defining chronic depression may have greater validity than the approach currently adopted in the DSM (24).

In our community sample, the life-course approach to defining chronic depression was considerably narrower than the DSM-IV approach. Almost all participants (96%) who met DSM-IV criteria for non-chronic major depression were also classified as having non-chronic depression with the life-course approach. The few exceptions were cases that exhibited persistent depressive symptoms for more than half the time since the onset of depression, but did not quite meet full DSM-IV criteria for chronic major depressive episode or dysthymia (e.g., occasional periods of remission of >2 months that precluded the latter diagnosis). However, only 61% of those classified as having chronic depression by DSM-IV were also classified as having chronic depression using the life-course approach. The discrepant cases almost always involved lengthy (>2 years) but time-limited depressive episodes in the context of a largely depression-free course since onset. Thus, from a life-course perspective, a significant number of cases of DSM-IV chronic depression are actually episodic conditions, albeit with prolonged episodes. As the DSM-5 category of persistent depression places the DSM-IV chronic depressive conditions under a single rubric, the results using DSM-5 would probably be quite similar. However, we suspect that the DSM and life-course approaches to defining chronic depression would show much greater concordance in clinical samples, as most cases will be presenting with chronic depression and their future course is unknown.

The present study did not address which factors are responsible for the greater psychopathology in the offspring of mothers with chronic, compared to non-chronic, depression. A number of factors have been implicated in the intergenerational transmission of depression (2), some or all of which may account for the greater risk to offspring of mothers with chronic depression, including greater or different genetic liability, a higher rate of parental personality disorder, more problematic parenting, and higher levels of familial and peer stress (39).

The findings from the present study have a number of important implications. First, consistent with prior work [e.g., (18, 32)], these data suggest that the predominant approach to research on depressive disorders, which ignores the course of depression and combines chronic and episodic cases, includes significant heterogeneity that may hinder understanding of etiology and pathophysiology and reduce the likelihood of developing a cumulative and replicable literature. In addition, these findings have significant implications for nosology and assessment. The DSM has given increasingly greater recognition to the importance of longitudinal course in classifying depressive disorders in the last two editions (18, 29), but the present findings suggest that further efforts are needed. They also highlight the challenge faced by alternative nosological systems, such as the Hierarchical Taxonomy of Psychopathology (40), which has the virtue of being empirically-derived, but as of yet has not been able to incorporate a longitudinal perspective into its cross-sectional taxonomy (18). One approach, proposed by Klein (23), is to classify depression using two orthogonal axes representing symptom severity and longitudinal course. This approach has the advantage of capturing the primary depression diagnoses, but incorporating them within a dimensional framework.

The present findings also underscore the need for greater attention to longitudinal course in designing structured and semi-structured diagnostic interviews and rating scales (18, 30). Furthermore, our findings have implications for prevention and early intervention, as they suggest that it may be more efficient to target chronically depressed parents and their offspring, rather than depressed parents more generally. Finally, these results highlight the potential value of developing treatments specifically designed to target chronic, as opposed to all, forms of depression [e.g., (41)].

Strengths and Limitations

This study had a number of strengths. The sample was relatively large; we compared two different approaches to defining chronicity of maternal depression; offspring's trajectories were assessed on 4 occasions at 3-year intervals from age 6 to age 15; and we collected data on offspring's symptoms from multiple informants. We chose to use multiple informants due to the known limitations of single informants in general, and of self-reports and parent reports, specifically (42). Use of multiple informants who vary in their access to different types of symptoms and the specific contexts in which they observe behavior provides a more comprehensive perspective and reduces the effects of rater biases. Notably, in the present study few

results differed by informant, providing greater confidence in the robustness of the effects.

However, a number of limitations must be acknowledged. First, the study relied on mothers' retrospective reports of their histories of depression, and the reliability of such reports may be modest. Second, we used DSM-IV, rather than DSM-5 criteria for mothers' diagnoses. However, the criteria for non-chronic major depression were not altered in DSM-5, and, as noted above, the major change in classifying chronic depression involved grouping the several forms of DSM-IV chronic depression under the rubric of persistent depressive disorder (18). Third, interrater reliability of lifetime chronicity in our study is not available, although Mondimore et al. (24) reported good reliability.

Fourth, we focused on offspring's symptoms, rather than diagnoses, as by age 15 offspring were just entering the period when rates of depressive disorders begin to increase, and there were not yet a large enough number of diagnosable cases to allow for robust analyses. While dimensional approaches are often preferable to categorical diagnoses because of their greater reliability and statistical power (23, 40), our results are likely capturing the early development of depression, and analyses of diagnosable cases must await the next wave of follow-ups. In addition, future research that includes functional outcomes would be useful.

Fifth, it is also important to acknowledge that many of the same youth who experienced elevated levels of depression symptoms also had elevated levels of anxiety and externalizing symptoms. Hence, our findings on outcomes are not independent of one another.

Sixth, we examined mothers' histories of depression only prior to the baseline assessment. Thus, children's outcomes may reflect exposure to their mothers' continued depression, rather than simply the effects of maternal depression prior to the initial assessment. More specifically, we cannot determine whether the persisting or increasing symptoms in offspring of chronically depressed mothers (particularly when defined according to the life-course approach) are associated with the continued persistence of their mothers' depression, or whether offspring's symptoms persist even when mothers recover from chronic depression. In future studies it will be important to examine the association between the course of maternal depression and the trajectories of symptoms in their offspring.

Seventh, the sample was largely Caucasian and middle class, and as such, results should be replicated in more diverse populations. Finally, we focused exclusively on depressed mothers given evidence that maternal depression has stronger effects on offspring than paternal depression (13). However, it would be worthwhile for future studies to extend this work by including depressed fathers.

CONCLUSIONS

Overall, this study provides support for the effects of maternal depression, and more specifically, maternal chronic depression, on offspring's risk for depression, anxiety, and externalizing symptoms. Given the potential long-term effects of maternal chronic depression on offspring, early identification, appropriate treatment, and follow-up of depressed women and their children should be a key priority. Finally, the fact that effects were more pronounced when depression was classified using a life-course perspective has critical implications for the larger literature on depression and underscores an important source of heterogeneity that may be better captured from a life-course, rather than the traditional DSM, approach (23, 24).

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Stony Brook University Committee on Research Involving Human Subjects. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

JS helped conceptualize the study, conducted the analyses, and wrote the initial drafts of the manuscript. TO helped design and interpret the analyses and contributed to revising the manuscript. GC helped interpret the findings and contributed to revising the manuscript. DK helped conceptualize the study and design the analyses, designed and obtained finding for the larger project that the data are derived from, and contributed to revising the manuscript. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2020.601779/full#supplementary-material

REFERENCES

1. Sullivan PF, Neale MC, Kendler KS. Genetic epidemiology of major depression: review and meta-analysis. *Am J Psychiatry.* (2000) 157:1552–62. doi: 10.1176/appi.ajp.157.10.1552
2. Goodman SH. Intergenerational transmission of depression. *Annu Rev Clin Psychol.* (2020) 16:213–38. doi: 10.1146/annurev-clinpsy-071519-113915
3. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders,* 5th ed. Washington, DC: Author (2013). doi: 10.1176/appi.books.9780890425596
4. Klein DN, Clark DC, Dansky L, Margolis ET. Dysthymia in the offspring of parents with primary unipolar affective disorder. *J Abnorm Psychol.* (1988) 97:265–74. doi: 10.1037/0021-843X.97.3.265
5. Klein DN, Riso LP, Donaldson SK, Schwartz JE, Anderson RL, Ouimette PC, et al. Family study of early-onset dysthymia: mood and personality disorders in relatives of outpatients with dysthymia and episodic major depression and normal controls. *Arch Gen Psychiatry.* (1995) 52:487–96. doi: 10.1001/archpsyc.1995.03950180073010
6. Klein DN, Shankman SA, Lewinsohn PM, Rohde P, Seeley JR. Family study of chronic depression in a community sample of young adults. *Am J Psychiatry.* (2004) 161:646–53. doi: 10.1176/appi.ajp.161.4.646
7. Sang W, Li Y, Su L, Yang F, Wu W, Shang X, et al. A comparison of the clinical characteristics of Chinese patients with recurrent major depressive disorder with and without dysthymia. *J Affect Disord.* (2011) 135:106–10. doi: 10.1016/j.jad.2011.06.051
8. Mondimore FM, Zandi PP, Mackinnon DF, Mcinnis MG, Miller EB, Crowe RP, et al. Familial aggregation of illness chronicity in recurrent, early-onset major depression pedigrees. *Am J Psychiatry.* (2006) 163:1554–60. doi: 10.1176/ajp.2006.163.9.1554
9. Lieb R, Isensee B, Höfler M, Pfister H, Wittchen H. Parental major depression and the risk of depression and other mental disorders in offspring. *Arch Gen Psychiatry.* (2002) 59:365. doi: 10.1001/archpsyc.59.4.365
10. Hammen C, Brennan PA. Severity, chronicity, and timing of maternal depression and risk for adolescent offspring diagnoses in a community sample. *Arch Gen Psychiatry.* (2003) 60:253. doi: 10.1001/archpsyc0.60.3.253
11. Klein DN, Lewinsohn PM, Rohde P, Seeley JR, Olino TM. Psychopathology in the adolescent and young adult offspring of a community sample of mothers and fathers with major depression. *Psychol Med.* (2005) 35, 353–365. doi: 10.1017/S0033291704003587
12. Weissman MM, Wickramaratne P, Gameroff MJ, Warner V, Pilowsky D, Kohad RG, et al. Offspring of depressed parents: 30 years later. *Am J Psychiatry.* (2016) 173:1024–32. doi: 10.1176/appi.ajp.2016.15101327
13. Connell AM, Goodman SH. The association between psychopathology in fathers versus mothers and children's internalizing and externalizing behavior problems: a meta-analysis. *Psychol Bull.* (2002) 128:746–73. doi: 10.1037/0033-2909.128.5.746
14. Weissman MM, Warner V, Wickramaratne P, Moreau D, Olfson N. Offspring of depressed parents. *Arch Gen Psychiatry.* (1997) 54:932. doi: 10.1001/archpsyc.1997.01830220054009
15. Halligan SL, Murray L, Martins C, Cooper PJ. Maternal depression and psychiatric outcomes in adolescent offspring: a 13-year longitudinal study. *J Affect Disord.* (2007) 97:145–54. doi: 10.1016/j.jad.2006.06.010
16. NICHD early child care research network. Chronicity of maternal depressive symptoms, maternal sensitivity, and child functioning at 36 months. *Dev. Psychol.* (1999) 35:1297–310. doi: 10.1037/0012-1649.35.5.1297
17. Brennan PA, Hammen C, Andersen MJ, Bor W, Najman JM, Williams GM. Chronicity, severity, and timing of maternal depressive symptoms: relationships with child outcomes at age 5. *Dev Psychol.* (2000) 36:759–66. doi: 10.1037/0012-1649.36.6.759
18. Schramm E, Klein DN, Elsaesser M, Furukawa T, Domschke K. Review of persistent depressive disorder: history, correlates, and clinical implications. *Lancet Psychiatry.* (2020) 7:801–12. doi: 10.1016/S2215-0366(20)30099-7
19. Seifer R, Dickstein S, Sameroff AJ, Magee KD, Hayden LC. Infant mental health and variability of parental depression symptoms. *J Am Acad Child Adolesc Psychiatry.* (2001) 40:1375–82. doi: 10.1097/00004583-200112000-00007
20. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders.* 3rd ed. Arlington, VA: Author (1980).
21. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders.* 3rd ed. Arlington, VA: American Psychiatric Association (1987).
22. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders.* 4th ed. Arlington, VA: American Psychiatric Association (1994).
23. Klein DN. Classification of depressive disorders in the DSM-V: proposal for a two-dimension system. *J Abnorm Psychol.* (2008) 117:552–60. doi: 10.1037/0021-843X.117.3.552
24. Mondimore FM, Zandi PP, MacKinnon DF, McInnis MG, Miller EB, Schweizer B, et al. A comparison of the familiality of chronic depression in recurrent early-onset depression pedigrees using different definitions of chronicity. *J Affect Disord.* (2007) 100:171–7. doi: 10.1016/j.jad.2006.10.011
25. Robins E, Guze SB. Establishment of diagnostic validity in psychiatric illness: its application to schizophrenia. *Am J Psychiatry.* (1970) 126:983–7. doi: 10.1176/ajp.126.7.983
26. Klein DN, Finsaas MC. The stony brook temperament study: early antecedents and pathways to emotional disorders. *Child Dev Perspect.* (2017) 11:257–63. doi: 10.1111/cdep.12242
27. Bufferd S, Dougherty L, Carlson G, Klein D. Parent-reported mental health in preschoolers: findings using a diagnostic interview. *Compr Psychiatry.* (2011) 52:359–69. doi: 10.1016/j.comppsych.2010.08.006
28. First MB, Spitzer RL, Gibbon M, Williams JBW. *Structured Clinical Interview for DSM-IV Axis I Disorders, Clinician Version (SCID-CV).* Washington, DC: American Psychiatric Press (1996). doi: 10.1037/t07827-000
29. Keller MB, Klein DN, Hirschfeld RMA, Kocsis JH, McCullough JP, Miller I, et al. Results of the DSM-IV mood disorders field trial. *Am J Psychiatry.* (1995) 152:843–9. doi: 10.1176/ajp.152.6.843
30. McCullough JP, Jr, Clark SW, Klein DN, First MB. Introducing a clinical course graphing scale for DSM-5 disorders. *Am. J. Psychother.* (2016) 70:383–92. doi: 10.1176/appi.psychotherapy.2016.70.4.383
31. Klein DN, Shankman SA, Rose S. Ten-year prospective follow-up study of the naturalistic course of dysthymic disorder and double depression. *Am J Psychiatry.* (2006) 163:872–80. doi: 10.1176/ajp.2006.163.5.872
32. Klein DN, Kotov R. Persistence of depression in a 10-year prospective study: evidence for a qualitatively distinct subtype. *J Abnorm Psychol.* (2016) 125:337–48. doi: 10.1037/abn0000147
33. Kovacs M. *Children's Depression Inventory: Manual.* North Tonawanda, NY: Multi-Health Systems (1992).
34. Birmaher B, Khetarpal S, Brent D, Cully M, Balach L, Kaufman J, et al. The screen for child anxiety related emotional disorders (SCARED): scale construction and psychometric characteristics. *J Am Acad Child Adolesc Psychiatry.* (1997) 36:545–53. doi: 10.1097/00004583-199704000-00018
35. Achenbach TM, Rescorla L. *ASEBA School-Age Forms and Profiles.* ASEBA, University of Vermont (2001).
36. Muthén LK, Muthén BO. Mplus User's Guide. 8th ed. Los Angeles, CA: Muthén and Muthén (1998–2017).
37. IBM Corp (2017). *IBM SPSS Statistics for Windows, Version 25.0.* Armonk, NY: IBM Corp.
38. Thapar A, Collishaw S, Pine DS, Thapar AK. Depression in adolescence. *Lancet.* (2012) 379:1056–67. doi: 10.1016/S0140-6736(11)60871-4
39. Klein DN, Black SR. Persistent depressive disorder. In: DeRubeis RJ, Strunk DR, editors. *Oxford Handbook of Mood Disorders.* New York, NY: Oxford University Press (2017). p. 227–37.
40. Kotov R, Krueger RF, Watson D, Achenbach TM, Althoff RR, Bagby RM, et al. The hierarchical taxonomy of psychopathology (HiTOP): a dimensional alternative to traditional nosologies. *J Abnorm Psychol.* (2017) 126:454–77. doi: 10.1037/abn0000258
41. McCullough JP. *Treatment for Chronic Depression: Cognitive Behavioral Analysis System of Psychotherapy.* New York, NY: Guilford Press (2000).

42. Dougherty LR, Klein DN, Olino TM. Depression in children and adolescents. In: Hunsley J, Mash E, editors. *A Guide to Assessments that Work*. 2nd ed. New York, NY: Oxford University Press (2018). p. 99–130. doi: 10.1093/med-psych/9780190492243.003.0006

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Loneliness, Social Isolation and Their Difference: A Cross-Diagnostic Study in Persistent Depressive Disorder and Borderline Personality Disorder

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Background: Interpersonal difficulties are a key feature of persistent depressive disorder (PDD) and borderline personality disorder (BPD). Caught in a vicious circle of dysfunctional interpersonal transaction, PDD and BPD patients are at great risk of experiencing prolonged loneliness. Loneliness, in turn, has been associated with the development of mental disorders and chronic illness trajectories. Besides, several factors may contribute to the experience of loneliness across the lifespan, such as social network characteristics, a history of childhood maltreatment (CM), and cognitive-affective biases such as rejection sensitivity (RS). This cross-diagnostic study approached the topic of perceived loneliness by comparing PDD and BPD patients with healthy controls (HC) in its interplay with symptom burden, social network characteristics, RS as well as CM.

Method: Thirty-four PDD patients (DSM-5; 15 female, $M_{age} = 38.2$, $SD = 12.3$), 36 BPD patients (DSM-5; 19 female, $M_{age} = 28.8$, $SD = 9.2$), and 70 age- and gender-matched HC were assessed cross-sectionally using the following self-report measures: UCLA Loneliness Scale, Social Network Index (SNI; size, diversity, and embeddedness), Beck Depression Inventory (BDI-II), Borderline Symptom List (BSL-23), Childhood Trauma Questionnaire (CTQ), and Rejection Sensitivity Questionnaire (RSQ).

Results: Both patient groups reported significantly higher levels of perceived loneliness, symptom severity, and smaller social network characteristics compared to HC. Loneliness was significantly correlated with severity of self-reported clinical symptoms in PDD and at trend level in BPD. Besides, loneliness tended to be related to social network characteristics for all groups except PDD patients. Both PDD and BPD patients showed higher RS as well as CTQ scores than HC. A history of emotional abuse and emotional neglect was associated with loneliness, and this association was mediated by RS as demonstrated by an exploratory mediation analysis.

Discussion: Loneliness is highly prevalent in PDD and BPD patients and contributes to the overall symptom burden. Interestingly, loneliness showed an association with

prior experiences of CM as well as current RS. We therefore propose a comprehensive model on how intra- und interpersonal aspects may interplay in the dynamics of loneliness in light of CM. Finally, this model may have further implications for psychotherapeutic interventions.

Keywords: loneliness, social isolation, childhood maltreatment, rejection sensitivity, persistent depressive disorder, borderline personality disorder

INTRODUCTION

Interpersonal difficulties are highly prevalent in several complex psychiatric disorders, e.g., persistent depressive disorder (PDD) and borderline personality disorder (BPD). These are reflected in dysfunctional social interactions, low social integration, and insufficient social support (1–3). Regarding interpersonal styles, for instance, individuals with PDD tend to have more hostile, hostile-submissive, and hostile-dominant interpersonal behaviors than normative and other clinical samples (4–6). Regarding BPD, the first two diagnostic criteria directly refer to difficulties in making and maintaining interpersonal relationships (7). Over time, these interpersonal difficulties can elicit rejection from others, ultimately leading to poor-quality relationships and social withdrawal (8). The strain of PDD and BPD patients' relationships can be assumed to increase the likelihood and severity of experiencing loneliness: caught in this vicious circle of dysfunctional interpersonal transaction, PDD and BPD patients are likely at great risk of experiencing prolonged loneliness (9, 10). Loneliness, defined as a perceived mismatch between existing social relationships and subjective social ideals (11), develops when our needs for social belongingness are not sufficiently met (12). It is different from its positive counterpart called solitude and the formal criterion of social isolation (13). As loneliness influences affective, cognitive, and behavioral processes (14), it can in turn lead to a range of interpersonal problems and result in social isolation (15). It has even been suggested that the dysfunctional interpersonal processes of lonely individuals contribute to mental health problems [e.g., (16)]. Therefore, a vicious circle can be assumed with loneliness being both a causal as well as a maintaining factor of PDD and BPD.

Different theories aim at explaining the phenomenon of loneliness. Psychodynamic models of loneliness suggest that several factors across the lifespan may contribute to the experience of loneliness with early experiences during childhood, i.e., childhood maltreatment (CM), being of major importance (17, 18). As outlined in the attachment hypothesis on loneliness (19), adult interpersonal difficulties may result from non-secure attachment representations as well as a history of early interpersonal trauma (20). In line with this, CM experiences (e.g., emotional maltreatment, physical abuse and neglect, sexual abuse) have been found to predict adult loneliness (21–23) and lonely adolescents report higher levels of parental rejection during childhood compared to non-lonely adolescents (24). Taken together, prior studies suggest that loneliness later in life may be related to early experiences of CM.

Based on cognitive-behavioral models, cognitive-affective biases such as rejection sensitivity (RS) may also contribute to the development and maintenance of loneliness (25, 26). RS is defined as a personality disposition to anxiously expect, readily perceive, and overreact to rejection (27). As loneliness threatens the need for social belongingness, it is argued to serve as an aversive, yet adaptive, signal to promote social reconnection in a regulatory loop (28). Thus, short-term loneliness activates a series of social-cognitive processes that aim to provide a behavioral response to re-establish social contact (25, 29). However, prolonged loneliness may lead to a self-preservation bias in cognitive processes (such as RS) to protect the lonely individual in socially threatening environments (30). In line with this, previous research suggests that biased social cognitions are key characteristics of prolonged loneliness (31). These social-cognitive biases are assumed to affect attention, interpretation, and memory of social stimuli to increase attention toward socially relevant information (32). They may ultimately affect behavioral processes, resulting in a self-reinforcing loop in which lonely individuals actively distance themselves and elicit behaviors from others that validate their rejection expectations (25, 33).

Based on the assumption that loneliness arises from deficits in social relationships, prior research has investigated whether perceived loneliness may be associated with social network characteristics (34). According to the cognitive discrepancy perspective on loneliness, the decisive criterion for loneliness is subjective preference or expectation, making social isolation neither a necessary nor sufficient requirement for loneliness (11). Lonely and non-lonely individuals engage in similar activities with equivalent time alone during the day (35). Neither a high number of social contacts protects one from feeling lonely (36), nor is loneliness necessarily associated with a small number of social contacts (37). However, previous findings were heterogeneous, as other studies found individuals with less frequent participation in social activities at greatest risk of being lonely (38–40). Therefore, other aspects of the social network, i.e., its composition and functioning, may be more important than the network size. Jones (41) showed that while the total amount of social contact does not vary between lonely and non-lonely individuals, the type of contact does: as non-lonely individuals engage in more interactions with friends and family, lonely people engage in fewer interactions with intimates and more interactions with strangers and acquaintances. This implies that human beings need to feel connected to significant others and that the mere physical presence of others is not sufficient (42).

Considering the interplay of loneliness, depressive symptoms, and pervasive interpersonal difficulties, as well as their similar

roots in trauma history, it appears fruitful to further investigate the role of loneliness in patients with PDD and BPD. In terms of loneliness and related factors, however, PDD and BPD patients may share characteristic features but have not been directly compared to date.

As outlined above, loneliness is argued to arise when people perceive their social relationships as somehow deficient. As PDD and BPD have been linked to severe interpersonal disturbances, both patient groups are likely to perceive the quality and/or quantity of their social bonds to be unsatisfactory. Affective, cognitive, and interpersonal characteristics of PDD and BPD patients may hinder social reconnection and thus maintain loneliness, as a diminished capacity for pro-social behavior and interpersonal understanding is often related to increased feelings of loneliness (43). Enduring feelings of loneliness can thus be assumed highly prevalent in PDD and BPD patients, negatively impacting illness severity and course.

More specific findings regarding loneliness have been observed in BPD patients. Besides increased levels of loneliness, BPD patients have smaller social networks compared to HC (9, 44). Furthermore, the networks of BPD patients include a great number of former romantic partners (45). As BPD patients show a comparable trauma load, chronicity, and treatment resistance as PDD patients, comparing these two patient groups is especially valuable. Furthermore, depression is highly prevalent in BPD patients (46).

In summary, this study aimed to contribute to a better understanding of loneliness and its association with symptom burden, social network characteristics, potential cognitive-affective biases (e.g., RS), and CM in PDD patients in comparison with BPD patients and HC. Clarifying the psychological and interpersonal correlates of PDD and BPD as well as their relative influence on the development and maintenance of the disorder is particularly important given the limited effectiveness of current treatments. A deeper understanding of loneliness in PDD and BPD may guide clinical decision making and intervention efforts.

MATERIALS AND METHODS

Participants

Data were derived from 140 individuals who participated in a study assessing the response to social exclusion and rejection at the Department of Psychiatry and Psychotherapy of the LMU University Hospital, Munich. The study followed the Declaration of Helsinki and was approved by the Research Ethics Board of the Ludwig Maximilians University, Faculty of Medicine, Munich (#281-11). Participants provided written informed consent prior to study participation.

Both PDD patients and BPD patients were recruited at the Department of Psychiatry and Psychotherapy of the LMU University Hospital, Munich and by advertisements. Patients were included if they fulfilled the diagnoses PDD or BPD following DSM-5 criteria (7). General exclusion criteria included acute suicidality, mania, psychosis, substance use disorders as a primary diagnosis, taking sedative medication regularly, pregnancy, or current breastfeeding. Comorbid psychiatric disorders were assessed according to DSM-IV by experienced clinical psychologists who were trained in conducting interviews using the German version of the Structured Clinical Interview for DSM-IV [SCID-I, (47, 48); SCID-II, (49, 50)].

Two groups of HC were recruited by advertisements to age and gender-match both patient groups (HC_{PDD} and HC_{BPD}). Besides the mentioned general exclusion criteria, additional exclusion criteria for HC were any current or lifetime psychiatric diagnosis, BDI-II > 11, psychiatric medication, or psychotherapy within the past 10 years.

Loneliness

Loneliness was assessed using the German adaption of the UCLA Loneliness Scale (UCLA-LS) based on a revised version of the original UCLA-LS (51, 52). It consists of 20 items examining the frequency and intensity of loneliness-related experiences, both positively worded (e.g., "There are people I feel close to."), as well as negatively worded (e.g., "People are around me but not with me."). Responses range from 1 (not at all) to 5 (totally). A total score is formed by reversing items where needed and adding responses. The total score is divided by the number of valid items, with a mean score ranging from 1 to 5. Higher scores indicate more intense feelings of loneliness. The internal consistency in our sample was high (Cronbach's alpha: PDD:0.91; BPD:0.93; HC_{PDD}:0.90; HC_{BPD}:0.91).

Social Network Characteristics

Social network characteristics were assessed using the German version of the Social Network Index [SNI, (53)]. The SNI is a self-administered instrument with 12 items assessing 12 different types of social relationships (e.g., spouse, parents, children, friends, workmates). For each type of relationship, respondents are asked how many people he/she knows and talks to at least once every 2 weeks. These questions are answered with a number between 0 and 6 or "7 or more," except for parents, who are naturally restricted to two, and for the items on romantic partnership, where only a yes or no answer is permitted. The SNI quantifies (a) the size of the social network, (b) network diversity, and (c) the number of embedded networks. The size of the social network is defined as the total number of people with whom the respondent has regular contact (i.e., speaks at least once every 2 weeks). Social network diversity quantifies the number of social roles, i.e., the number of social relationship domains in which the respondent has regular contact with at least one person. The number of embedded networks is a measurement reflecting the number of different network domains within which the respondent has at least four high-contact people. The family roles are collapsed into a single domain for this measure. High scores indicate large size, diversity, or a high number of embedded networks.

Severity of Depressive and Borderline Symptoms

Severity of depressive symptoms was evaluated using the German version of the Beck Depression Inventory, revised version [BDI-II, (54, 55)] as a 21-item self-report measure. The total score ranges from 0 to 63 with higher scores indicating greater severity.

The BDI-II has a high internal consistency (Cronbach's alpha > 0.84) and a good test-retest reliability ($r > 0.75$) (56).

The Montgomery–Åsberg Depression Rating Scale [MADRS, (57)] is an observer-based interview that assesses the severity of 10 depressive symptoms with a total score between 0 and 60. Internal consistency is high (Cronbach's alpha = 0.85) (58).

BPD severity was measured using the short version of the Borderline Symptom List [BSL-23, (59)]. The BSL-23 assesses self-reported severity of borderline-specific symptomatology during the past week. It contains 23 items rated on a 5-point Likert scale that are summarized and divided by the number of items to form a total score from 0 to 92. The BSL-23 has a high internal consistency (Cronbach's alpha = 0.94–0.97), high test-retest reliability ($r = 0.82$) and is very reliable in the diagnosis of BPD (60).

Rejection Sensitivity

RS was measured with the German version of the Rejection Sensitivity Questionnaire for adults [RSQ, (61)]. Respondents are presented with 20 scenarios in which they have to make a request of a significant other (e.g., parent, friend, romantic partner). They are then asked to rate both their anxiety and their expectation to be rejected in the particular scenario on a 6-point Likert scale. Scores for each scenario are multiplied and then divided by the number of scenarios. Total scores range from 1 to 36, with higher scores indicating greater RS. The RSQ has a high internal consistency (Cronbach's alpha = 0.88) and a high test-retest reliability ($r = 0.90$) (61).

Childhood Maltreatment

CM was assessed using the German version of the Childhood Trauma Questionnaire, short-form [CTQ, (62–64)]. The CTQ is a 28-item self-report measure consisting of statements about experiences of sexual, physical, and emotional abuse as well as physical and emotional neglect during childhood and adolescence. Respondents are asked to indicate to which extent these statements describe their experiences, rating items on a 5-point Likert scale from 1 (never true) to 5 (very often true). Item scores are added to several subscales ranging from 5 to 25, with higher scores indicating more frequent childhood abuse and/or neglect. For the German version of the CTQ the internal consistency of all scales (apart from physical neglect) is high (Cronbach's alpha > 0.80). The psychometric properties of the German version are similar to the American original, making it a reliable and valid screen for the retrospective assessment of CM (65).

Data Analysis

Statistical analyses were conducted with SPSS version 25 (https://www.ibm.com/de-de/products/spss-statistics). One-way ANOVAs with four planned contrasts were applied to analyze group differences for the different measures: (1) PDD patients vs. matched HC_{PDD}, (2) BPD patients vs. matched HC_{BPD}, (3) PDD patients vs. BPD patients, (4) HC_{PDD} vs. HC_{BPD}. As age and sex were not correlated with loneliness, these variables were not included as covariates. In the next step, correlations of loneliness with different variables were calculated within each subgroup using parametric and non-parametric methods (Pearson, Spearman) as appropriate. Due to the high number of correlations, *p*-values were adjusted according to Benjamini and Hochberg (66) for all calculated correlations. As loneliness was found to be associated with emotional abuse, emotional neglect, and RS in patients as well as in HC though in varying strength, two exploratory mediation analyses were conducted using a robust bootstrapping approach (10.000 bootstraps, PROCESS macro version 3.5) with loneliness as dependent variable, emotional abuse or emotional neglect as independent variable, and RS as mediating variable. Analyses were restricted to either the patient or to the HC subgroup due to the observed group differences in these variables.

RESULTS

Sample

Thirty-four PDD patients (DSM-5; 15 female, $M_{age} = 38.2$, SD = 12.3), 36 BPD patients (DSM-5; 19 female, $M_{age} = 28.8$, SD = 9.2) and two groups of age- and gender-matched HC (in total 70 HC) were assessed cross-sectionally. Groups differed significantly regarding age [$F_{(3, 136)} = 8.6$, $p < 0.001$]: PDD patients were significantly older than BPD patients ($p = 0.002$) as were HC_{PDD} compared to HC_{BPD}, respectively. Furthermore, groups differed regarding years of education [$F_{(3, 135)} = 7.9$, $p < 0.001$], i.e., BPD patients had significantly less years of education than their matched HC ($p = 0.02$), than PDD patients ($p = 0.004$) and than HC_{PDD} ($p < 0.001$).

Patients showed a variety of comorbid disorders: 47.2% of BPD patients met criteria for a current major depressive episode with 38.9% meeting criteria for comorbid PDD. Further, 41.7% of BPD patients had a comorbid PTSD, 36.1% a comorbid social anxiety disorder, and 19.4% of BPD patients an eating disorder. 47.1% of PDD patients met criteria for current major depressive episode, 17.6% for social anxiety disorder, and 14.7% for PTSD.

Loneliness and Social Network Characteristics

Both PDD and BPD patients reported significantly higher levels of perceived loneliness than the matched HC group (see **Tables 1**, **2**). BPD patients reported even more feelings of loneliness than PDD patients. Besides, HC groups differed regarding loneliness, with higher loneliness scores in HC_{PDD} compared to HC_{BPD}. Social network characteristics (i.e., size, diversity, and number of embedded networks) differed between both patient groups and the matched HC groups, but neither between PDD and BPD patients nor between HC groups.

Severity of Depressive and Borderline Symptoms

Depressive symptoms were more prevalent in both patient groups than in their matched HC, and BPD patients had higher BDI-II scores than PDD patients but did not differ in the observer-rated measure (MADRS, see **Tables 1**, **2**). Similarly, both patient groups reported higher borderline symptom scores than their matched HC (BSL-23), with a significant difference

TABLE 1 | Loneliness, social network characteristics, clinical symptoms, and childhood maltreatment: mean scores and standard deviation together with results of univariate ANOVA.

Measure	PDD	BPD	HC_{PDD}	HC_{BPD}	ANOVA	
					Global F	*p*
UCLA-Loneliness	2.7 (0.7)	3.0 (0.7)	1.7 (0.5)	1.4 (0.4)	57.7	< 0.001***
SNI-Size	8.8 (5.3)	9.6 (7.0)	20.4 (8.4)	21.9 (10.8)	25.3	< 0.001***
SNI-Diversity	3.7 (1.6)	3.4 (1.6)	5.9 (1.9)	5.6 (1.8)	19.2	< 0.001***
SNI-Embeddedness	0.8 (0.8)	1.0 (1.1)	2.4 (1.2)	2.4 (1.5)	18.0	< 0.001***
BDI-II	25.5 (11.3)	31.4 (10.7)	1.8 (2.7)	2.4 (2.9)	128.8	< 0.001***
MADRS	18.0 (7.5)	15.9 (7.0)	0.6 (1.2)	0.5 (1.0)	96.1	< 0.001***
BSL-23	1.0 (0.7)	2.0 (0.9)	0.2 (0.2)	0.2 (0.2)	85.8	< 0.001***
RSQ	12.8 (4.1)	16.6 (5.7)	6.3 (2.9)	5.9 (3.0)	57.3	< 0.001***
CTQ-Emotional abuse	13.3 (5.5)	14.7 (4.9)	7.0 (3.5)	6.8 (2.4)	33.5	< 0.001***
CTQ-Physical abuse	6.7 (2.5)	8.9 (5.3)	5.7 (2.0)	5.4 (1.1)	8.6	< 0.001***
CTQ-Sexual abuse	6.6 (4.2)	8.0 (5.2)	5.6 (1.6)	5.2 (0.7)	4.8	0.003**
CTQ-Emotional neglect	15.4 (5.0)	16.5 (4.9)	8.3 (3.1)	7.7 (3.0)	45.0	< 0.001***
CTQ-Physical neglect	7.9 (2.5)	10.1 (3.7)	6.5 (2.6)	6.4 (1.6)	14.8	< 0.001***

*PDD, persistent depressive disorder; BPD, borderline personality disorder; HC, healthy controls; SNI, social network index; BDI-II, Beck depression inventory; MADRS, Montgomery-Åsberg Depression Rating Scale; BSL-23, borderline symptom list; RSQ, rejection sensitivity questionnaire; CTQ, childhood trauma questionnaire; **p < 0.01, ***p < 0.001.*

TABLE 2 | Loneliness, social network characteristics, clinical symptoms, and childhood maltreatment: results and effect size (Cohen's *d*) of planned contrasts between patient groups and their matched healthy controls.

Measure	Contrast PDD vs. HC_{PDD}			Contrast BPD vs. HC_{BPD}			Contrast PDD vs. BPD			Contrast HC_{PDD} vs. HC_{BPD}		
	t	*p*	*d*	*t*	*p*	*d*	*t*	*p*	*d*	*t*	*p*	*d*
UCLA-Loneliness	6.8	< 0.001***	1.8	11.2	< 0.001***	2.8	2.1	0.04*	−0.4	2.1	0.04*	0.7
SNI-Size	5.8	< 0.001***	−1.7	6.4	< 0.001***	−1.4	0.4	0.68	−0.1	0.8	0.43	−0.2
SNI-Diversity	5.2	< 0.001***	−1.3	5.4	< 0.001***	−1.3	0.9	0.45	0.2	0.7	0.47	0.2
SNI-Embeddedness	5.3	< 0.001***	−1.5	5.0	< 0.001***	−0.9	0.6	0.53	−0.2	0.1	0.90	−0.0
BDI-II	12.2	< 0.001***	2.9	15.2	< 0.001***	3.7	3.0	0.003**	−0.5	0.3	0.75	−0.2
MADRS	12.2	< 0.001***	3.2	11.6	< 0.001***	3.1	1.6	0.11	0.3	0.1	0.93	0.1
BSL-23	6.3	< 0.001***	1.6	13.8	< 0.001***	2.8	7.3	< 0.001***	−1.2	0.1	0.96	−0.0
RSQ	6.6	< 0.001***	1.8	11.1	< 0.001***	2.3	3.8	< 0.001***	−0.8	0.4	0.71	0.1
CTQ-Emotional abuse	6.1	< 0.001***	1.4	7.9	< 0.001***	2.0	1.4	0.16	−0.3	0.2	0.80	0.1
CTQ-Physical abuse	1.3	0.20	0.4	4.6	< 0.001***	0.9	2.9	0.005**	−0.5	0.4	0.68	0.2
CTQ-Sexual abuse	1.2	0.22	0.3	3.5	0.001**	0.8	1.7	0.09	−0.3	0.5	0.64	0.3
CTQ-Emotional neglect	7.2	< 0.001***	1.7	9.14	< 0.001***	2.2	1.1	0.25	−0.2	0.6	0.56	0.2
CTQ-Physical neglect	2.1	0.03*	0.5	5.9	< 0.001***	1.3	3.4	0.001**	−0.7	0.1	0.88	0.0

*PDD, persistent depressive disorder; BPD, borderline personality disorder; HC, healthy controls; SNI, social network index; BDI-II, Beck depression inventory; MADRS, Montgomery-Åsberg Depression Rating Scale; BSL-23, borderline symptom list; RSQ, rejection sensitivity questionnaire; CTQ, childhood trauma questionnaire; *p < 0.05, **p < 0.01, ***p < 0.001.*

between PDD and BPD patients, i.e., moderate scores in PDD and high scores in BPD (67).

Rejection Sensitivity and Childhood Maltreatment

Both patient groups showed significantly higher RS scores than their HC group, and BPD patients had significantly higher RS scores than PDD patients. Regarding CM, PDD patients reported more often emotional abuse, emotional neglect, and physical neglect than their matched HC. In contrast, BPD patients reported a higher CM load on all CTQ subscales than their matched HC. BPD patients showed higher levels of physical abuse and physical neglect compared to PDD patients (see **Tables 1**, **2**).

Associations Between Loneliness, Social Network, Clinical Symptoms, and Childhood Maltreatment

Loneliness and social network features correlated significantly negatively within HC_{PDD} and at trend level within HC_{BPD} after FDR correction (size: HC_{PDD}: $r = -0.42$, $p_{FDR} = 0.04$;

TABLE 3 | Correlation coefficients of loneliness with social network characteristics, clinical symptoms, and childhood maltreatment.

	PDD			BPD			HC_{PDD}			HC_{BPD}		
UCLA-Loneliness	***r***	***p***	p_{FDR}	***r***	***p***	p_{FDR}	***r***	***p***	p_{FDR}	***r***	***p***	p_{FDR}
SNI-Size	−0.15	0.41	0.46	−0.34	0.04	0.08	-0.42	0.01	0.04*	−0.35	0.04	0.07
SNI-Diversity	−0.19	0.28	0.34	−0.37	0.02	0.06	-0.43	0.01	0.04*	−0.24	0.16	0.21
SNI-Embeddedness	−0.07	0.69	0.73	−0.25	0.14	0.20	-0.42	0.01	0.04*	−0.40	0.02	0.05
BDI-II	0.55	0.001	0.008**	0.38	0.02	0.06	0.08	0.67	0.73	0.34	0.04	0.08
MADRS	0.41	0.02	0.05	0.22	0.19	0.23	-0.08	0.71	0.73	0.31	0.08	0.12
BSL-23	0.44	0.009	0.04*	0.32	0.06	0.09	0.38	0.03	0.06	0.37	0.03	0.06
RSQ	0.54	0.001	0.008**	0.42	0.01	0.04*	0.74	< 0.001	< 0.001***	0.54	0.001	0.008**
CTQ-Emotional abuse	0.44	0.009	0.04*	0.46	0.004	0.02*	0.30	0.08	0.12	0.30	0.08	0.12
CTQ-Physical abuse	0.17	0.35	0.40	0.35	0.04	0.08	0.19	0.27	0.06	0.16	0.34	0.40
CTQ-Sexual abuse	0.00	0.99	0.99	0.34	0.04	0.08	0.32	0.07	0.11	0.24	0.17	0.21
CTQ-Emotional neglect	0.25	0.16	0.21	0.53	0.001	0.008**	0.61	< 0.001	0.003**	0.49	0.003	0.02*
CTQ-Physical neglect	0.23	0.19	0.23	0.38	0.02	0.06	0.52	0.002	0.01*	−0.07	0.70	0.73

*PDD, persistent depressive disorder; BPD, borderline personality disorder; SNI, social network index; BDI-II, Beck depression inventory; MADRS, Montgomery-Åsberg Depression Rating Scale; BSL-23, borderline symptom list; RSQ, rejection sensitivity questionnaire; CTQ, childhood trauma questionnaire; *p < 0.05, **p < 0.01, ***p < 0.001 before and after false discovery rate (FDR) correction according to Benjamini Hochberg.*

HC_{BPD}: $r = -0.35$, $p_{FDR} = 0.07$; diversity: HC_{PDD}: $r = -0.43$, $p_{FDR} = 0.04$; embeddedness: HC_{PDD}: $r = -0.42$, $p_{FDR} = 0.04$; HC_{BPD}: $r = -0.40$, $p_{FDR} = 0.05$; see **Table 3**). Furthermore, loneliness showed an inverse correlation at trend level within the BPD group with social network size ($r = -0.34$, $p_{FDR} = 0.08$) and diversity ($r = -0.37$, $p_{FDR} = 0.06$). In contrast, PDD patients showed no inter-correlation of social network features and loneliness at all. Loneliness and severity of self-reported depressive symptoms correlated significantly in PDD patients ($r = 0.55$, $p_{FDR} = 0.008$) and at trend level in BPD patients ($r = 0.38$, $p_{FDR} = 0.06$) and their matched HC_{BPD} ($r = 0.34$, $p_{FDR} = 0.08$). Loneliness was significantly correlated with the BSL-23 scores (after removing the BSL-23 loneliness item) in the PDD sample ($r = 0.44$, $p_{FDR} = 0.04$) and at trend level in the other groups (BPD: $r = 0.32$, $p_{FDR} = 0.09$; HC_{PDD}: $r = 0.38$, $p_{FDR} = 0.06$; HC_{BPD}: $r = 0.37$, $p_{FDR} = 0.06$). Additionally, loneliness showed a significant positive correlation with RS in both patient groups and HC (PDD: $r = 0.54$, $p_{FDR} = 0.008$; BPD: r = 0.42, $p_{FDR} = 0.04$; HC_{PDD}: $r = 0.74$, $p_{FDR} < 0.001$; HC_{BPD}: $r = 0.54$, $p_{FDR} = 0.008$). Regarding loneliness and CM, only the correlation with emotional abuse reached significance in the PDD sample ($r = 0.44$, $p_{FDR} = 0.04$), whereas correlations with emotional abuse and emotional neglect were significant in BPD patients (emotional abuse: $r = 0.46$, $p_{FDR} = 0.02$; emotional neglect: $r = 0.53$, $p_{FDR} = 0.008$). In the HC group, loneliness was significantly correlated with emotional neglect in both HC groups (HC_{PDD}: $r = 0.61$, $p_{FDR} = 0.003$; HC_{BPD}: $r = 0.49$, $p_{FDR} = 0.02$) and with physical neglect in HC_{PDD} ($r = 0.52$, $p_{FDR} = 0.01$).

When comparing the strengths of the correlation coefficients between groups, analyses revealed that BDI-II and MADRS showed a significantly stronger correlation with loneliness in PDD patients compared to HC_{PDD} (BDI-II: $Z = 2.11$, $p = 0.03$; MADRS: $Z = 2.03$, $p = 0.04$). Furthermore, there was a trend that emotional neglect correlated stronger with loneliness in HC_{PDD} compared to PDD patients ($Z = 1.79$, $p = 0.07$). Finally, physical neglect was significantly less associated with loneliness in HC_{BPD} compared to HC_{PDD} ($Z = 2.58$, $p = 0.01$) and to BPD patients ($Z = 1.91$, $p = 0.06$). No other significant differences between correlation coefficients were detected.

Mediation Analyses

In the patient sample, we found that the total effect of emotional abuse on loneliness when not including RS was positive and significant ($b = 0.07$, SE = 0.02, $p < 0.001$). Second, the path from emotional abuse to RS was positive and statistically significant ($b = 0.46$, SE = 0.11, $p < 0.001$). Third, when predicting loneliness from emotional abuse and RS, the effect of RS on loneliness was positive and significant ($b = 0.05$, SE = 0.02, $p < 0.001$) as was the path from emotional abuse to loneliness ($b = 0.04$, SE = 0.02, $p < 0.001$). Finally, the indirect effect of emotional abuse on loneliness was found to be statistically significant [indirect effect $b = 0.02$, 95% C.I. (0.01, 0.04)], indicating a significant mediation effect of RS (see **Figure 1A**).

When using emotional neglect as independent variable, the total effect of emotional neglect on loneliness (when not including RS) was positive and significant ($b = 0.06$, SE = 0.02, $p < 0.001$). Second, the path from emotional neglect to RS was positive and statistically significant ($b = 0.44$, SE = 0.12, $p < 0.001$). Third, when predicting loneliness from emotional neglect and RS, the effect of RS on loneliness was positive and significant (b = 0.05, SE =.02, p =.001) as was the path from emotional neglect to loneliness ($b = 0.04$, SE = 0.02, $p = 0.03$). Finally, the indirect effect of emotional neglect on loneliness was found to be statistically significant [indirect effect $b = 0.02$, 95% C.I. (0.01, 0.05)], indicating a significant mediation effect of RS (see **Figure 1B**).

In contrast, when repeating the analyses for the HC group, no significant mediation effect of RS could be found for the association of emotional abuse with loneliness [indirect effect: $b = 0.01$, 95% C.I. (−0.02, 0.05), see **Figure 1C**]. With emotional

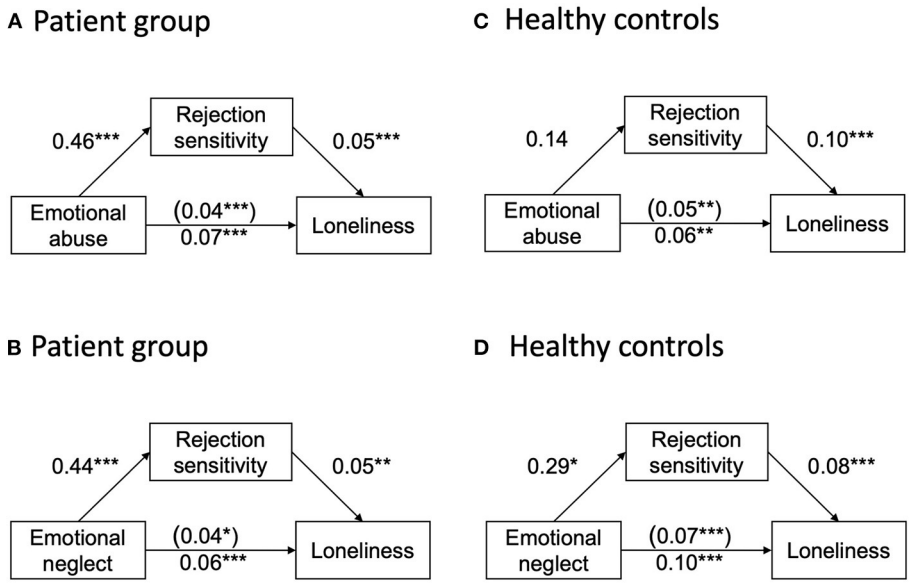

FIGURE 1 | (A) and **(C)**: Unstandardized regression coefficients for the relationship between emotional abuse and loneliness as mediated by rejection sensitivity for the patient **(A)** and healthy control sample **(C)**. The regression coefficient between emotional abuse and loneliness, controlling for rejection sensitivity, is in parentheses; **(B)** and **(D)**: Unstandardized regression coefficients for the relationship between emotional neglect and loneliness as mediated by rejection sensitivity for the patient **(B)** and healthy control sample **(D)**. The regression coefficient between emotional neglect and loneliness, controlling for rejection sensitivity, is in parentheses, $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$.

neglect as independent variable, however, the total effect of emotional neglect on loneliness (when not including RS) was positive and significant ($b = 0.10$, SE $= 0.02$, $p < 0.001$). Second, the path from emotional neglect to RS was positive and statistically significant ($b = 0.29$, SE $= 0.11$, $p = 0.01$). Third, when predicting loneliness from emotional neglect and RS, the effect of RS on loneliness was positive and significant ($b = 0.08$, SE $= 0.01$, $p < 0.001$) as was the path from emotional neglect to loneliness ($b = 0.07$, SE $= 0.01$, $p < 0.001$). Finally, the indirect effect of emotional neglect on loneliness was found to be statistically significant [indirect effect $b = 0.02$, 95% C.I. (0.01, 0.05)] indicating a significant mediation effect of RS (see **Figure 1D**).

DISCUSSION

To our knowledge, the present study investigated loneliness and its underpinnings in terms of symptom burden, social network characteristics, RS, and patients' history (i.e., CM) in a cross-diagnostic approach comparing PDD and BPD patients and HC for the first time. We aimed at understanding the impact of the common phenomenon of loneliness on the development and maintenance of PDD and BPD to derive possible implications for intervention efforts.

Loneliness is of high societal interest and appears to be a major risk factor in mental health (68). Our findings confirmed that both PDD and BPD patients report higher levels of loneliness than HC. Besides, PDD and BPD patients reported significantly more depressive symptoms and borderline symptoms than their respective matched HC group. BPD patients reported even higher depression and borderline scores than PDD patients, consistent with prior research showing that BPD patients rate their depressive symptoms higher (69). High levels of loneliness were associated with greater symptom severity of depression and BPD in both patient groups, again confirming previous findings (44, 70). This indicates that the subjective perception and evaluation of social relationships might play an important role in the development and maintenance of mental disorders. While loneliness is known as a specific risk factor for depression (71, 72), loneliness and depression are discussed as two distinct phenomena that are associated with each other (73). Evidence holds that loneliness might impact illness trajectory and treatment outcome in depression (74). Further, loneliness has been discussed as a core experience of BPD patients (44) as it is closely linked to the feeling of inner emptiness which is a diagnostic criterion in BPD [i.e., diagnostic criterion 7; (7)]. As expected, SNI scores were significantly lower in both patient groups when compared to HC. To date, knowledge about social networks in PDD and BPD is still limited; however, our results are consistent with previous research regarding patients with PDD (75) and BPD (9). Social isolation has been discussed as a risk for depression (76, 77), e.g., people with PDD appear to have smaller social networks than the general population and patients with other mental disorders (75). Similarly, BPD patients are found to have smaller networks (9) and less satisfactory social integration (78) compared to HC.

In our study, loneliness and social network size were negatively correlated in BPD patients and both HC groups (at least at trend level after FDR correction), but not in PDD patients. One possible explanation could be that PDD is considered

to be maintained by a longstanding and pervasive pattern of interpersonal avoidance, fueled by interpersonal fears such as RS. PDD patients are considered to have a "wall" around them that hinders them to perceive their interactions with others (8). Hence, the perceived loneliness of PDD patients may not depend on objective social indices, as PDD patients are perceptually disconnected from others. Furthermore, although interacting with others might end loneliness on the one hand, the potential risk of rejection might promote anxiety and hyperarousal on the other, which might be considered even worse than loneliness (79). Consistent with this, prior research has found that social interactions (16) and even the simple exposure to pleasant depictions of people (80) are more rewarding for individuals low than high in loneliness. After feeling lonely, social company was judged more negatively, predicting the frequency with which company was avoided (72). This suggests that the negative appraisal of social relationships and subsequent social withdrawal may play a role in the development of psychopathology. The dynamics between feeling lonely, being socially isolated, and negatively appraising social company may therefore represent a self-reinforcing loop. Whereas a bigger social network may be helpful in BPD patients and HC to protect from loneliness, this may not be the case in PDD. The self-protective behavior of social withdrawal prompted by fearful sensations may rather produce a self-fulfilling prophecy in which actual rejection is elicited from others (81, 82), moving lonely individuals further toward the periphery of their social networks (83, 84). Simply increasing social contact, networks, or social roles in PDD may therefore not be sufficient to mitigate loneliness. Consistent with previous research, BPD patients' loneliness correlated negatively at trend level with social network size and diversity (after FDR correction) (9). BPD patients are considered to be more ambivalent and may switch between social withdrawal and clinging behavior (61). As BPD patients may not show the perceptual disconnection from others compared to PDD patients, regular contact with a high number of people seems relevant in regard to loneliness.

Another individual factor closely related to both previous experiences in relationships as well as personality features is RS. As expected, both patient groups showed higher RS scores than HC. These results are in line with previous research that found both BPD (61, 78, 85) and PDD patients (86) to experience increased RS. Further, loneliness was correlated with RS in both patient groups and HC suggesting that RS may be an unspecific factor for the experience of loneliness. These findings are in line with previous research linking loneliness to higher self-reported anticipation of rejection (33, 86).

Finally, we analyzed the interaction between loneliness and CTQ subscales to investigate a potential origin of loneliness in CM. In line with previous research, both patient groups reported higher CTQ scores compared to their matched HC group (87). PDD patients reported more often emotional neglect and emotional abuse than their matched HC as previously reported (88–90), whereas patients with BPD reported a higher trauma load on all CTQ subscales compared to their matched HC (87). Our results are in line with previous research showing that CM has far-reaching effects on adult physical and mental health (91, 92). After correcting for multiple comparisons, loneliness correlated with emotional abuse in PDD, and with both emotional abuse and emotional neglect in BPD. To date, little is known about the association of loneliness with CM in patients with PDD and BPD. Etiological models of PDD propose experiences of abuse and neglect during childhood as possible causal factors for interpersonal problems, which may contribute to aversive feelings of loneliness (93). For BPD, Gunderson (94) suggests that loneliness might develop as a consequence of abusive primary caretakers. Consistently, loneliness was found to mediate the association between CM and adult mental disorders (22). Our findings suggest that feelings of loneliness may be related to a history of CM, i.e., particularly emotional abuse and neglect, in both PDD and BPD patients. Furthermore, we observed loneliness to be associated with RS in both patient groups and HC. Thus, we further explored the interactions of these factors in mediation analyses for emotional abuse and emotional neglect which suggested a mediating role of RS in the association of loneliness and emotional abuse/neglect in the patient group and of emotional neglect in HC. However, the divergent findings between groups have to be interpreted with caution due to the decreased prevalence of CM in HC.

Combining our findings with previously reported models of loneliness [(25); current updates by (13, 29)], we propose an expanded hypothetical model of loneliness (see **Figure 2**). Loneliness is conceptualized as an unmet emotional need that arises from a history of CM (i.e., particularly emotional abuse and neglect) with cognitive-attentional, affective-feeling, sensory-perceptual, and motor-expressive aspects. Following the idea of a basic emotional need, the function of loneliness can be conceptualized in terms of evolution theory: As a social species, humans depend on a safe social surround to survive and therefore have an "innate need to belong" (12). Thus, the feeling of loneliness may serve as an alert when social connections are threatened (30). It motivates people to re-establish and maintain social contacts to increase the likelihood of survival and reproduction (30).

Horowitz et al. (95) suggested a "prototype," including affective, cognitive, and behavioral features to conceptualize the experience of loneliness. When the individual need for social belonging—determined by the subjective level of vulnerability to social disconnection—is not met, people experience emotional distress. This distress may be triggered by external events like the loss of a significant other or by internal thoughts (e.g., "I do not belong", "I am excluded"). Consistently, empirical research showed that lonely individuals experience predominantly negative affect (15). Weiss (19) described loneliness as a strong sense of social pain, emptiness, isolation, sadness for lack of confidants, unimportance, and worthlessness. Feeling unsafe or threatened in a social world sets off implicit hypervigilance for (additional) social threat and alters cognitive processes (25). Hypervigilance for social cues when feeling lonely could be functional in terms of choosing the most appropriate way to socially reconnect (26), as the heightened sensitivity to social verbal and non-verbal information enables the individual to react faster to perceived threats for further social isolation (25). In case maladaptive social-cognitive biases, e.g., RS, step in, and reconnection is not supported or even hampered by

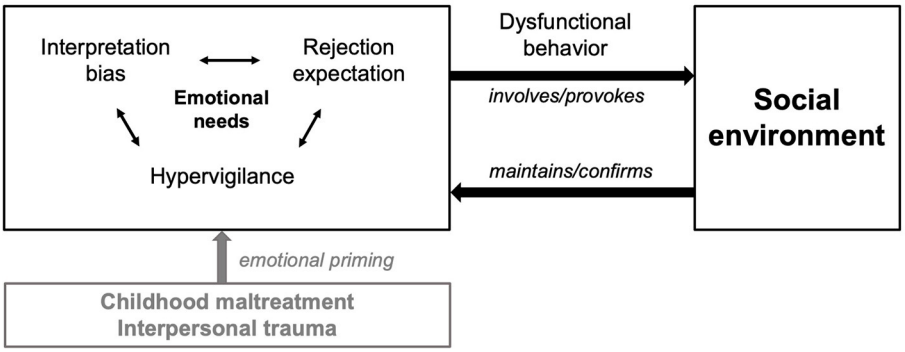

FIGURE 2 | Proposed model of loneliness in PDD and BPD. Loneliness is conceptualized as an unmet emotional need rooted in a history of childhood maltreatment, e.g., emotional abuse and neglect. The interplay of intraindividual cognitive-affective biases (esp. high rejection sensitivity, comprising hypervigilance to and expectation of rejection as well as interpretation biases) contributes to dysfunctional interaction patterns with the social environment maintaining a self-reinforcing loop.

the environment, this regulatory loop may become a vicious circle, resulting in frequently recurrent or persistent feelings of loneliness which may maintain the course of PDD or BPD (16). Previous research suggests that biased social cognitions are one of the most pronounced characteristics of loneliness (31). Predominantly, surveillance of social environment appears to be enhanced, with lonely individuals sensing socially threatening stimuli earlier than their non-lonely peers (96). The evidence for deficits in social cognition of PDD patients is scarce (6). Regarding BPD, previous research suggests that alterations may not only be caused by a hypersensitivity to negative social information, but also a hyposensitivity to positive social stimuli, combined with reduced confidence to judge particularly positive emotional states. Interestingly, reduced confidence was related to stronger feelings of loneliness and the expectation of social rejection (97). In line with this, loneliness has been linked to higher self- and peer-reported anticipation of rejection (33, 86). The relation between loneliness and RS appears hereby to be bidirectional, with RS representing both a risk factor and a consequence of loneliness (98). This loop may even reduce prosocial behavior (43, 99), as individuals high in RS are found to engage in more dysfunctional relationship behaviors (100). Ultimately, lonely individuals may engage in a self-fulfilling expectation regarding social rejection by others which validates their negative social expectations (82) and distance themselves further (33), as they believe that the cause of social distance is beyond their control (16). Prolonged social withdrawal in child- and adulthood may limit opportunities for social reconnection (101) and impede acquisition learning of skills when relationships rupture and repair is required (15, 102).

This model could have wider clinical implications, as loneliness may represent a cross-diagnostic risk factor in mental health. Accordingly, loneliness has been identified as a target for therapeutic interventions (103) which either address (1) social or (2) cognitive factors (104). The majority of loneliness interventions focus on social factors, e.g., improving social skills, increasing the social network, or enhancing interaction quality (105, 106). Consistently, facilitating meaningful social interaction has been reported to effectively prevent and reduce depressive symptoms and relapse rates (107, 108). Social interventions are therefore a promising research avenue for alleviating loneliness in PDD and BPD patients. However, loneliness and social network characteristics are often weakly associated as observed here and by others (109). Thus, merely enhancing the frequency of social contact does not necessarily alleviate loneliness and such interventions may miss the point that loneliness has rather to do with the perception of ourselves and the quality of social interactions than with social network sizes (109). Indeed, a very recent study suggests cognitive reappraisal interventions addressing time spent alone as an effective method to alleviate loneliness (104). Thus, psychotherapeutic approaches for reducing loneliness should focus on dysfunctional interpersonal processes and maladaptive social cognitions, stemming from early interpersonal trauma (CM). One example of such a therapeutic approach is the Cognitive Behavioral Analysis System of Psychotherapy (CBASP) that has been specifically designed for the treatment of PDD. In brief, CBASP encompasses techniques like the "situational analysis" that focuses on actual automatic thoughts, cognitive biases, and behavioral patterns, and largely aims at improving the quality of interpersonal situations (8). Regarding BPD, therapeutic approaches such as schema therapy (110) may address unmet emotional needs helping to cope with loneliness distress. Besides, analytic therapies, e.g., transference-focused psychotherapy [TFP, (111)] may analyze transference and countertransference processes to identify and integrate primary experiences in dyadic relationships to address loneliness.

Though our findings are valuable for generating a hypothetical model, we are aware that the study has clear limitations: first, due to limited sample sizes, particularly negative findings carry a large beta error. Despite FDR correction, we calculated a large number of correlation analyses. A lower variance in the HC sample (e.g., less CM), may explain the observed diverging results for correlation coefficients and mediation analyses that underline the need to replicate our results in larger samples. For instance, mediation analyses were not performed for each

patient group separately due to the small sample size. Similarly, larger sample sizes are needed to clarify whether RS is a general factor in the experience of loneliness or a rather characteristic feature in PDD and BPD patients. Second, as depression is a prevalent comorbidity in BPD patients, findings in both patient groups may rather be related to their depressive symptoms than represent specific characteristics in BPD. Thus, future studies need to disentangle this issue by comparing BPD patients with and without co-morbid depression. Third, as cross-sectional data were used to model longitudinal processes, we cannot draw any conclusions regarding causality. Further, cross-sectional analyses can produce biased estimates of longitudinal processes (112, 113) underlining the need to replicate our findings in a longitudinal design. Fourth, intervention studies could help to dismantle the direction of effect (i.e., do patients report lower levels of loneliness after psychotherapy in which cognitive-affective biases associated with loneliness and possible CM are targeted). In addition, our matched HC groups differed regarding loneliness, as HC_{PDD} reported higher loneliness levels than HC_{BPD}. This may explain different correlation patterns, however, HC groups did not differ in this respect for most measures. Finally, our data rely on self-reports, and the reliability of retrospective reports on CM could be questioned. Though subjective recall is an acceptable method as it more likely results in under-reporting of CM than over-reporting (114), a recent meta-analysis suggests that retrospectively self-reported CM might reflect a negative bias (115). In sum, our results should therefore be considered preliminary and interpreted with caution.

CONCLUSION

Feelings of loneliness are highly prevalent in PDD and BPD patients and contribute to symptom burden. Therefore, clinicians should pay attention to feelings of loneliness when treating patients with PDD or BPD. Of note, both objective and subjective measures of social isolation should be considered in a complementary way, as they are likely to have an independent effect on mental health. Our findings suggest that clinicians should assess the history of early interpersonal trauma and be aware of the possible presence of high RS when treating PDD or BPD patients. Psychotherapeutic approaches that focus on dysfunctional interpersonal processes and maladaptive social cognitions may be promising in reducing feelings of loneliness. Finally, future studies are needed to validate the hypothetical model of loneliness as proposed here.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethics committee Faculty of Medicine Ludwig Maximilian University Munich, Munich, Germany EK-No. 281-11. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

TN-M, BB, JD-K, FP, and MR designed research. TN-M, BB, SG, SR, KZ, RM, AJ, FP, and MR analyzed and interpreted data. TN-M, BB, and MR wrote first draft of manuscript. All authors revised the work critically, approved the final manuscript, and agree to be accountable for the content of the work.

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REFERENCES

1. Hölzel L, Härter M, Reese C, Kriston L. Risk factors for chronic depression—A systematic review. *J Affect Disord.* (2011) 129:1–13. doi: 10.1016/j.jad.2010.03.025
2. Santini ZI, Koyanagi A, Tyrovolas S, Mason C, Haro JM. The association between social relationships and depression: a systematic review. *J Affect Disord.* (2015) 175:53–65. doi: 10.1016/j.jad.2014.12.049
3. Schramm E, Klein DN, Elsaesser M, Furukawa TA, Domschke K. Review of dysthymia and persistent depressive disorder: history, correlates, and clinical implications. *Lancet Psychiatry.* (2020) 7:801–12. doi: 10.1016/S2215-0366(20)30099-7
4. Bird T, Tarsia M, Schwannauer M. Interpersonal styles in major and chronic depression: a systematic review and meta-analysis. *J Affect Disord.* (2018) 239:93–101. doi: 10.1016/j.jad.2018.05.057
5. Constantino MJ, Manber R, Degeorge J, McBride C, Ravitz P, Zuroff DC, et al. Interpersonal styles of chronically depressed outpatients: profiles and therapeutic change. *Psychotherapy (Chicago, Ill).* (2008) 45:491–506. doi: 10.1037/a0014335
6. Köhler S, Chrysanthou S, Guhn A, Sterzer P. Differences between chronic and nonchronic depression: systematic review and implications for treatment. *Depress Anxiety.* (2019) 36:18–30. doi: 10.1002/da.22835
7. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders (DSM-5®).* Washington, DC: American Psychiatric Pub (2013).
8. McCullough J. *Treatment for Chronic Depression: Cognitive Behavioral Analysis System of Psychotherapy (CBASP).* New York, NY: Guilford Press (2000).
9. Liebke L, Bungert M, Thome J, Hauschild S, Gescher DM, Schmahl C, et al. Loneliness, social networks, and social functioning in borderline

personality disorder. *Personal Disord.* (2017) 8:349–56. doi: 10.1037/per0000208
10. Achterbergh L, Pitman A, Birken M, Pearce M, Sno HN, Johnson S. The experience of loneliness among young people with depression: a qualitative meta-synthesis of the literature. *BMC Psychiatry.* (2020) 20:415. doi: 10.1186/s12888-020-02818-3
11. Peplau LA, Perlman D. *Loneliness: A sourcebook of Current Ttheory, Research and Therapy.* New York, NY: John Wiley & Sons Inc. (1982).
12. Baumeister RF, Leary MR. The need to belong: desire for interpersonal attachments as a fundamental human motivation. *Psychol Bull.* (1995) 117:497–529. doi: 10.1037/0033-2909.117.3.497
13. Quadt L, Esposito G, Critchley HD, Garfinkel SN. Brain-body interactions underlying the association of loneliness with mental and physical health. *Neurosci Biobehav Rev.* (2020) 116:283–300. doi: 10.1016/j.neubiorev.2020.06.015
14. Cacioppo JT, Patrick W. *Loneliness: Human Nature and the Need for Social Connection*. New York, NY: WW Norton & Company (2008).
15. Heinrich LM, Gullone E. The clinical significance of loneliness: a literature review. *Clin Psychol Rev.* (2006) 26:695–718. doi: 10.1016/j.cpr.2006.04.002
16. Hawkley LC, Cacioppo JT. Loneliness matters: a theoretical and empirical review of consequences and mechanisms. *Ann Behav Med.* (2010) 40:218–27. doi: 10.1007/s12160-010-9210-8
17. Sullivan HS. *The Interpersonal Theory of Psychiatry*. New York, NY: Norton (1953).
18. Reichmann FF. Loneliness. *Psychiatry.* (1959) 22:1–15. doi: 10.1080/00332747.1959.11023153
19. Weiss RS. *Loneliness: The Experience of Emotional and Social Isolation*. Cambridge, MA: The MIT Press (1973).
20. Wiersma JE, van Schaik DJ, Blom MB, Bakker L, van Oppen P, Beekman AT. Treatment for chronic depression: cognitive behavioral analysis system of psychotherapy (CBASP). *Tijdschr Psychiatr.* (2009) 51:727–36.
21. Merz E-M, Jak S. The long reach of childhood. Childhood experiences influence close relationships and loneliness across life. *Adv Live Course Res.* (2013) 18:212–22. doi: 10.1016/j.alcr.2013.05.002
22. Shevlin M, McElroy E, Murphy J. Loneliness mediates the relationship between childhood trauma and adult psychopathology: evidence from the adult psychiatric morbidity survey. *Soc Psychiatry Psychiatr Epidemiol.* (2015) 50:591–601. doi: 10.1007/s00127-014-0951-8
23. Nicolaisen M, Thorsen K. Loneliness among men and women–a five-year follow-up study. *Aging Ment Health.* (2014) 18:194–206. doi: 10.1080/13607863.2013.821457
24. Ferguson S, Zimmer-Gembeck MJ. Associations of parental and peer rejection with preadolescents' loneliness: emotional sensitivities as mediators. *J Relatsh Res.* (2014) 5:e9. doi: 10.1017/jrr.2014.9
25. Cacioppo JT, Hawkley LC. Perceived social isolation and cognition. *Trends Cogn Sci.* (2009) 13:447–54. doi: 10.1016/j.tics.2009.06.005
26. Qualter P, Vanhalst J, Harris R, Van Roekel E, Lodder G, Bangee M, et al. Loneliness Across the life span. *Pers Psychol Sci.* (2015) 10:250–64. doi: 10.1177/1745691615568999
27. Downey G, Feldman SI. Implications of rejection sensitivity for intimate relationships. *J Pers Soc Psychol.* (1996) 70:1327–43. doi: 10.1037/0022-3514.70.6.1327
28. Cacioppo JT, Hawkley LC, Ernst JM, Burleson M, Berntson GG, Nouriani B, et al. Loneliness within a nomological net: an evolutionary perspective. *J Res Pers.* (2006) 40:1054–85. doi: 10.1016/j.jrp.2005.11.007
29. Matthews GA, Tye KM. Neural mechanisms of social homeostasis. *Ann N Y Acad Sci.* (2019) 1457:5–25. doi: 10.1111/nyas.14016
30. Cacioppo JT, Cacioppo S, Boomsma DI. Evolutionary mechanisms for loneliness. *Cogn Emot.* (2014) 28:3–21. doi: 10.1080/02699931.2013.837379
31. Spithoven AWM, Bijttebier P, Goossens L. It is all in their mind: a review on information processing bias in lonely individuals. *Clin Psychol Rev.* (2017) 58:97–114. doi: 10.1016/j.cpr.2017.10.003
32. Gardner WL, Pickett CL, Jefferis V, Knowles M. On the outside looking in: loneliness and social monitoring. *Pers Soc Psychol Bull.* (2005) 31:1549–60. doi: 10.1177/0146167205277208
33. Watson J, Nesdale D. Rejection sensitivity, social withdrawal, and loneliness in young adults. *J Appl Soc Psychol.* (2012) 42:1984–2005. doi: 10.1111/j.1559-1816.2012.00927.x
34. Wang J, Lloyd-Evans B, Giacco D, Forsyth R, Nebo C, Mann F, et al. Social isolation in mental health: a conceptual and methodological review. *Soc Psychiatry Psychiatr Epidemiol.* (2017) 52:1451–61. doi: 10.1007/s00127-017-1446-1
35. Hawkley LC, Burleson MH, Berntson GG, Cacioppo JT. Loneliness in everyday life: cardiovascular activity, psychosocial context, and health behaviors. *J Pers Soc Psychol.* (2003) 85:105–20. doi: 10.1037/0022-3514.85.1.105
36. Child ST, Lawton L. Loneliness and social isolation among young and late middle-age adults: associations with personal networks and social participation. *Aging Ment Health.* (2019) 23:196–204. doi: 10.1080/13607863.2017.1399345
37. Cacioppo JT, Cacioppo S, Capitanio JP, Cole SW. The neuroendocrinology of social isolation. *Annu Rev Psychol.* (2015) 66:733–67. doi: 10.1146/annurev-psych-010814-015240
38. Böger A, Wetzel M, Huxhold O. Allein unter vielen oder zusammen ausgeschlossen: Einsamkeit und wahrgenommene soziale Exklusion in der zweiten Lebenshälfte. In: Mahne K, Wolff J, Simonson J, Tesch-Römer C, editors. *Altern im Wandel*. Wiesbaden: Springer (2017). p. 273–85. doi: 10.1007/978-3-658-12502-8_18
39. Drennan J, Treacy M, Butler M, Byrne A, Fealy G, Frazer K, et al. The experience of social and emotional loneliness among older people in Ireland. *Ageing Soc.* (2008) 28:1113–32. doi: 10.1017/S0144686X08007526
40. Hawkley LC, Hughes ME, Waite LJ, Masi CM, Thisted RA, Cacioppo JT. From social structural factors to perceptions of relationship quality and loneliness: the Chicago health, aging, and social relations study. *J Gerontol B-Psychol.* (2008) 63:S375–84. doi: 10.1093/geronb/63.6.s375
41. Jones WH. Loneliness and social contact. *J Soc Psychol.* (1981) 113:295–6. doi: 10.1080/00224545.1981.9924386
42. Cacioppo JT, Ernst JM, Burleson MH, McClintock MK, Malarkey WB, Hawkley LC, et al. Lonely traits and concomitant physiological processes: the MacArthur social neuroscience studies. *Int J Psychophysiol.* (2000) 35:143–54. doi: 10.1016/s0167-8760(99)00049-5
43. Twenge JM, Baumeister RF, DeWall CN, Ciarocco NJ, Bartels JM. Social exclusion decreases prosocial behavior. *J Pers Soc Psychol.* (2007) 92:56–66. doi: 10.1037/0022-3514.92.1.56
44. Lieb K, Zanarini MC, Schmahl C, Linehan MM, Bohus M. Borderline personality disorder. *Lancet.* (2004) 364:453–61. doi: 10.1016/s0140-6736(04)16770-6
45. Clifton A, Pilkonis PA, McCarty C. Social networks in borderline personality disorder. *J Pers Disord.* (2007) 21:434–41. doi: 10.1521/pedi.2007.21.4.434
46. Yoshimatsu K, Palmer B. Depression in patients with borderline personality disorder. *Harv Rev Psychiatry.* (2014) 22:266–73. doi: 10.1097/hrp.0000000000000045
47. First MB, Spitzer RL, Gibbon M, Williams JB. *User's Guide for the Structured Clinical Interview for DSM-IV Axis I Disorders SCID-I: Clinician Version*. Washington, DC: American Psychiatric Pub (1997).
48. Wittchen H-U, Wunderlich U, Gruschwitz S, Zaudig M. *SKID I. Strukturiertes Klinisches Interview für DSM-IV. Achse I: Psychische Störungen. Interviewheft und Beurteilungsheft. Eine deutschsprachige, erweiterte Bearb. d. amerikanischen Originalversion des SKID I.* Göttingen: Hogrefe (1997).
49. Fydrich T, Renneberg B, Schmitz B, Wittchen H-U. *SKID II. Strukturiertes Klinisches Interview für DSM-IV, Achse II: Persönlichkeitsstörungen. Interviewheft. Eine deutschsprachige, erw. Bearb. d. amerikanischen Originalversion d. SKID-II von: MB First, RL Spitzer, M. Gibbon, JBW Williams, L. Benjamin (Version 3/96).* Göttingen: Hogrefe (1997).
50. First MB, Gibbon M, Spitzer RL, Benjamin LS, Williams JB, Benjamin LS. *Structured Clinical Interview for DSM-IV Axis II Personality Disorders, (SCID-II).* Washington, DC: American Psychiatric Association (1997).
51. Döring N, Bortz J. Psychometric research on loneliness: a new German version of the University of California at Los Angeles (UCLA) Loneliness Scale. *Diagnostica.* (1993) 39:224–39.
52. Russell D, Peplau LA, Cutrona CE. The revised UCLA loneliness scale: concurrent and discriminant validity evidence. *J Pers Soc Psychol.* (1980) 39:472–80. doi: 10.1037//0022-3514.39.3.472
53. Cohen S, Doyle WJ, Skoner DP, Rabin BS, Gwaltney JM, Jr. Social ties and susceptibility to the common cold. *JAMA.* (1997) 277:1940–4. doi: 10.1001/jama.1997.03540480040036

54. Beck AT, Steer RA, Brown G. *Beck Depression Inventory–II*. Washington, DC: APA PsycTests (1996).
55. Hautzinger M, Keller F, Kühner C, Bürger C. *Beck Depression Inventar II (BDI-II)*. Frankfurt/Main: Harcourt Test Services (2006).
56. Kühner C, Bürger C, Keller F, Hautzinger M. Reliability and validity of the revised beck depression inventory (BDI-II). Results from German samples. *Nervenarzt.* (2007) 78:651–6. doi: 10.1007/s00115-006-2098-7
57. Montgomery S, Åsberg M. A new depression scale designed to be sensitive to change. *Br J Psychiatry.* (1979) 134:382–9. doi: 10.1192/bjp.134.4.382
58. Smalbrugge M, Jongenelis L, Pot AM, Beekman AT, Eefsting JA. Screening for depression and assessing change in severity of depression. Is the geriatric depression scale (30-, 15- and 8-item versions) useful for both purposes in nursing home patients? *Aging Ment Health.* (2008) 12:244–8. doi: 10.1080/13607860801987238
59. Bohus M, Kleindienst N, Limberger MF, Stieglitz RD, Domsalla M, Chapman AL, et al. The short version of the borderline symptom list (BSL-23): development and initial data on psychometric properties. *Psychopathology.* (2009) 42:32–9. doi: 10.1159/000173701
60. Wolf M, Limberger MF, Kleindienst N, Stieglitz RD, Domsalla M, Philipsen A, et al. Short version of the borderline symptom list (BSL-23): development and psychometric evaluation. *Psychother Psychosom Med Psychol.* (2009) 59:321–4. doi: 10.1055/s-0028-1104598
61. Staebler K, Helbing E, Rosenbach C, Renneberg B. Rejection sensitivity and borderline personality disorder. *Clin Psychol Psychother.* (2011) 18:275–83. doi: 10.1002/cpp.705
62. Bernstein D, Fink L. *Manual for the Childhood Trauma Questionnaire.* New York, NY: The Psychological Corporation (1998).
63. Bernstein DP, Stein JA, Newcomb MD, Walker E, Pogge D, Ahluvalia T, et al. Development and validation of a brief screening version of the childhood trauma questionnaire. *Child Abuse Negl.* (2003) 27:169–90. doi: 10.1016/s0145-2134(02)00541-0
64. Wingenfeld K, Spitzer C, Mensebach C, Grabe HJ, Hill A, Gast U, et al. The German version of the childhood trauma questionnaire (CTQ): preliminary psychometric properties. *Psychother Psychosom Med Psychol.* (2010) 60:442–50. doi: 10.1055/s-0030-1247564
65. Klinitzke G, Romppel M, Häuser W, Brähler E, Glaesmer H. The German version of the childhood trauma questionnaire (CTQ): psychometric characteristics in a representative sample of the general population. *Psychother Psychosom Med Psychol.* (2012) 62:47–51. doi: 10.1055/s-0031-1295495
66. Benjamini Y, Hochberg Y. Controlling the false discovery rate: a practical and powerful approach to multiple testing. *J R Stat Soc Series B Stat Methodol.* (1995) 57:289–300. doi: 10.1111/j.2517-6161.1995.tb02031.x
67. Kleindienst N, Jungkunz M, Bohus M. A proposed severity classification of borderline symptoms using the borderline symptom list (BSL-23). *Borderline Personal Disord Emot Dysregul.* (2020) 7:11. doi: 10.1186/s40479-020-00126-6
68. Wang J, Mann F, Lloyd-Evans B, Ma R, Johnson S. Associations between loneliness and perceived social support and outcomes of mental health problems: a systematic review. *BMC Psychiatry.* (2018) 18:156. doi: 10.1186/s12888-018-1736-5
69. Stanley B, Wilson ST. Heightened subjective experience of depression in borderline personality disorder. *J Pers Disord.* (2006) 20:307–18. doi: 10.1521/pedi.2006.20.4.307
70. Matthews T, Odgers CL, Danese A, Fisher HL, Newbury JB, Caspi A, et al. Loneliness and neighborhood characteristics: a multi-informant, nationally representative study of young adults. *Psychol Sci.* (2019) 30:765–75. doi: 10.1177/0956797619836102
71. Domènech-Abella J, Mundó J, Haro JM, Rubio-Valera M. Anxiety, depression, loneliness and social network in the elderly: longitudinal associations from the Irish longitudinal study on ageing (TILDA). *J Affect Disord.* (2019) 246:82–8. doi: 10.1016/j.jad.2018.12.043
72. van Winkel M, Wichers M, Collip D, Jacobs N, Derom C, Thiery E, et al. Unraveling the role of loneliness in depression: the relationship between daily life experience and behavior. *Psychiatry.* (2017) 80:104–17. doi: 10.1080/00332747.2016.1256143
73. Cacioppo JT, Hawkley LC, Thisted RA. Perceived social isolation makes me sad: 5-year cross-lagged analyses of loneliness and depressive symptomatology in the Chicago health, aging, and social relations study. *Psychol Aging.* (2010) 25:453–63. doi: 10.1037/a0017216
74. Erzen E, Çikrikci Ö. The effect of loneliness on depression: a meta-analysis. *Int J Soc Psychiatry.* (2018) 64:427–35. doi: 10.1177/0020764018776349
75. Visentini C, Cassidy M, Bird VJ, Priebe S. Social networks of patients with chronic depression: a systematic review. *J Affect Disord.* (2018) 241:571–8. doi: 10.1016/j.jad.2018.08.022
76. Matthews T, Danese A, Wertz J, Odgers CL, Ambler A, Moffitt TE, et al. Social isolation, loneliness and depression in young adulthood: a behavioural genetic analysis. *Soc Psychiatry Psychiatr Epidemiol.* (2016) 51:339–48. doi: 10.1007/s00127-016-1178-7
77. Zebhauser A, Baumert J, Emeny RT, Ronel J, Peters A, Ladwig KH. What prevents old people living alone from feeling lonely? Findings from the KORA-Age-study. *Aging Ment Health.* (2015) 19:773–80. doi: 10.1080/13607863.2014.977769
78. De Panfilis C, Riva P, Preti E, Cabrino C, Marchesi C. When social inclusion is not enough: Implicit expectations of extreme inclusion in borderline personality disorder. *Personal Disord.* (2015) 6:301–9. doi: 10.1037/per0000132
79. Baumeister RF, Tice DM. Point-counterpoints: anxiety and social exclusion. *J Soc Clin Psychol.* (1990) 9:165–95. doi: 10.1521/jscp.1990.9.2.165
80. Cacioppo JT, Norris CJ, Decety J, Monteleone G, Nusbaum H. In the eye of the beholder: individual differences in perceived social isolation predict regional brain activation to social stimuli. *J Cogn Neurosci.* (2009) 21:83–92. doi: 10.1162/jocn.2009.21007
81. Murray SL, Bellavia GM, Rose P, Griffin DW. Once hurt, twice hurtful: how perceived regard regulates daily marital interactions. *J Pers Soc Psychol.* (2003) 84:126–47. doi: 10.1037/0022-3514.84.1.126
82. Romero-Canyas R, Downey G. Rejection sensitivity as a predictor of affective and behavioral responses to interpersonal stress. In: Williams KD, Forgas JP, von Hippel W, editors. *The Social Outcast: Ostracism, Social Exclusion, Rejection, and Bullying*. London: Psychology Press (2005). p. 131–54.
83. Cacioppo JT, Fowler JH, Christakis NA. Alone in the crowd: the structure and spread of loneliness in a large social network. *J Pers Soc Psychol.* (2009) 97:977–91. doi: 10.1037/a0016076
84. Platt B, Cohen Kadosh K, Lau JY. The role of peer rejection in adolescent depression. *Depress Anxiety.* (2013) 30:809–21. doi: 10.1002/da.22120
85. Renneberg B, Herm K, Hahn A, Staebler K, Lammers CH, Roepke S. Perception of social participation in borderline personality disorder. *Clin Psychol Psychother.* (2012) 19:473–80. doi: 10.1002/cpp.772
86. Gao S, Assink M, Cipriani A, Lin K. Associations between rejection sensitivity and mental health outcomes: a meta-analytic review. *Clin Psychol Rev.* (2017) 57:59–74. doi: 10.1016/j.cpr.2017.08.007
87. Brakemeier EL, Dobias J, Hertel J, Bohus M, Limberger MF, Schramm E, et al. Childhood maltreatment in women with borderline personality disorder, chronic depression, and episodic depression, and in healthy controls. *Psychother Psychosom.* (2018) 87:49–51. doi: 10.1159/000484481
88. Christ C, de Waal MM, Dekker JJM, van Kuijk I, van Schaik DJF, Kikkert MJ, et al. Linking childhood emotional abuse and depressive symptoms: the role of emotion dysregulation and interpersonal problems. *PLoS ONE.* (2019) 14:e0211882. doi: 10.1371/journal.pone.0211882
89. Nelson J, Klumparendt A, Doebler P, Ehring T. Childhood maltreatment and characteristics of adult depression: meta-analysis. *Br J Psychiatry.* (2017) 210:96–104. doi: 10.1192/bjp.bp.115.180752
90. Schramm E, Zobel I, Dykierek P, Kech S, Brakemeier EL, Külz A, et al. Cognitive behavioral analysis system of psychotherapy vs. interpersonal psychotherapy for early-onset chronic depression: a randomized pilot study. *J Affect Disord.* (2011) 129:109–16. doi: 10.1016/j.jad.2010.08.003
91. Gilbert R, Widom CS, Browne K, Fergusson D, Webb E, Janson S. Burden and consequences of child maltreatment in high-income countries. *Lancet.* (2009) 373:68–81. doi: 10.1016/s0140-6736(08)61706-7
92. Zanarini MC, Frankenburg FR, Reich DB, Marino MF, Lewis RE, Williams AA, et al. Biparental failure in the childhood experiences of borderline patients. *J Pers Disord.* (2000) 14:264–73. doi: 10.1521/pedi.2000.14.3.264

93. Riso LP, Miyatake RK, Thase ME. The search for determinants of chronic depression: a review of six factors. *J Affect Disord.* (2002) 70:103–15. doi: 10.1016/s0165-0327(01)00376-7
94. Gunderson JG. The borderline patient's intolerance of aloneness: insecure attachments and therapist availability. *Am J Psychiatry.* (1996) 153:752–8. doi: 10.1176/ajp.153.6.752
95. Horowitz LM, French RDS, Anderson CA. The prototype of a lonely person. In: Peplau LA, Perlman D, editors. Loneliness: a sourcebook of current theory, research and therapy. New York, NY: John Wiley & Sons Inc. (1982). p. 183–205.
96. Bangee M, Harris RA, Bridges N, Rotenberg KJ, Qualter P. Loneliness and attention to social threat in young adults: findings from an eye tracker study. *Pers Individ Differ.* (2014) 63:16–23. doi: 10.1016/j.paid.2014.01.039
97. Thome J, Liebke L, Bungert M, Schmahl C, Domes G, Bohus M, et al. Confidence in facial emotion recognition in borderline personality disorder. *J Pers Dis.* (2016) 7:159–68. doi: 10.1037/per0000142
98. London B, Downey G, Bonica C. Social causes and consequences of rejection sensitivity. *J Res Adolesc.* (2007) 17:481–506. doi: 10.1111/j.1532-7795.2007.00531.x
99. Twenge JM, Baumeister RF, Tice DM, Stucke TS. If you can't join them, beat them: effects of social exclusion on aggressive behavior. *J Pers Soc Psychol.* (2001) 81:1058–69. doi: 10.1037//0022-3514.81.6.1058
100. Downey G, Freitas AL, Michaelis B, Khouri H. The self-fulfilling prophecy in close relationships: rejection sensitivity and rejection by romantic partners. *J Pers Soc Psychol.* (1998) 75:545–60. doi: 10.1037//0022-3514.75.2.545
101. Jobe-Shields L, Cohen R, Parra GR. Patterns of change in children's loneliness: trajectories from third through fifth grades. *Merrill Palmer Q.* (2011) 57:25–47.
102. Schinka KC, van Dulmen MH, Mata AD, Bossarte R, Swahn M. Psychosocial predictors and outcomes of loneliness trajectories from childhood to early adolescence. *J Adolesc.* (2013) 36:1251–60. doi: 10.1016/j.adolescence.2013.08.002
103. Bessaha ML, Sabbath EL, Morris Z, Malik S, Scheinfeld L, Saragossi J. A systematic review of loneliness interventions among non-elderly adults. *Clin Soc Work J.* (2020) 48:110–25. doi: 10.1007/s10615-019-00724-0
104. Rodriguez M, Bellet BW, McNally RJ. Reframing time spent alone: reappraisal buffers the emotional effects of isolation. *Cognit Ther Res.* (2020) 4:1–16. doi: 10.1007/s10608-020-10128-x
105. Cacioppo S, Grippo AJ, London S, Goossens L, Cacioppo JT. Loneliness: clinical import and interventions. *Perspect Psychol Sci.* (2015) 10:238–49. doi: 10.1177/1745691615570616
106. Masi CM, Chen HY, Hawkley LC, Cacioppo JT. A meta-analysis of interventions to reduce loneliness. *Pers Soc Psychol Rev.* (2011) 15:219–66. doi: 10.1177/1088868310377394
107. Cruwys T, Dingle GA, Haslam C, Haslam SA, Jetten J, Morton TA. Social group memberships protect against future depression, alleviate depression symptoms and prevent depression relapse. *Soc Sci Med.* (2013) 98:179–86. doi: 10.1016/j.socscimed.2013.09.013
108. Cruwys T, Haslam SA, Dingle GA, Jetten J, Hornsey MJ, Desdemona Chong EM, et al. Feeling connected again: interventions that increase social identification reduce depression symptoms in community and clinical settings. *J Affect Disord.* (2014) 159:139–46. doi: 10.1016/j.jad.2014.02.019
109. Cornwell EY, Waite LJ. Social disconnectedness, perceived isolation, and health among older adults. *J Health Soc Behav.* (2009) 50:31–48. doi: 10.1177/002214650905000103
110. Young JE, Klosko JS, Weishaar ME. *Schema Therapy.* New York, NY: Guilford (2003).
111. Clarkin JF, Yeomans FE, Kernberg OF. *Psychotherapy for Borderline Personality.* New York, NY: John Wiley & Sons Inc. (1999).
112. Maxwell SE, Cole DA. Bias in cross-sectional analyses of longitudinal mediation. *Psychol Methods.* (2007) 12:23–44. doi: 10.1037/1082-989X.12.1.23
113. Maxwell SE, Cole DA, Mitchell MA. Bias in cross-sectional analyses of longitudinal mediation: Partial and complete mediation under an autoregressive model. *Multivariate Behav Res.* (2011) 46:816–41. doi: 10.1080/00273171.2011.606716
114. Hardt J, Rutter M. Validity of adult retrospective reports of adverse childhood experiences: review of the evidence. *J Child Psychol Psychiatry.* (2004) 45:260–73. doi: 10.1111/j.1469-7610.2004.00218.x
115. Baldwin JR, Reuben A, Newbury JB, Danese A. Agreement between prospective and retrospective measures of childhood maltreatment: a systematic review and meta-analysis. *JAMA Psychiatry.* (2019) 76:584–93. doi: 10.1001/jamapsychiatry.2019.0097

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Impact of Baseline Characteristics on the Effectiveness of Disorder-Specific Cognitive Behavioral Analysis System of Psychotherapy (CBASP) and Supportive Psychotherapy in Outpatient Treatment for Persistent Depressive Disorder

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Importance: In the treatment of persistent depressive disorder (PDD), disorder-specific Cognitive Behavioral Analysis System of Psychotherapy (CBASP) has been shown to be superior to Supportive Psychotherapy (SP) in outpatients. It remains to clear which subgroups of patients benefit equally and differentially from both psychotherapies.

Objective: To identify those patient-level baseline characteristics that predict a comparable treatment effectiveness of CBASP and SP and those that moderate the differential effectiveness of CBASP compared to SP.

Design, setting and participants: In this analysis of a 48-week multicenter randomized clinical trial comparing CBASP to SP in adult antidepressant-free outpatients with early-onset PDD, we evaluated baseline variables from the following domains as potential predictors and moderators of treatment effectiveness: socio-demography, clinical status, psychosocial and global functioning, life quality, interpersonal problems, childhood trauma, treatment history, preference for psychotherapy, and treatment expectancy.

Interventions: A 48-week treatment program with 32 sessions of either CBASP or SP.

Main outcomes and measures: Depression severity measured by the 24-item Hamilton Rating Scale for Depression (HRSD-24) at week 48.

Results: From $N = 268$ randomized outpatients, $N = 209$ completed the 48-week treatment program. CBASP completers had significantly lower post-treatment HRSD-24 scores than SP completers ($mean_{CBASP}$ =13.96, $sd_{CBASP} = 9.56$; $mean_{SP} = 16.69$, $sd_{SP} = 9.87$; $p = 0.04$). A poor response to both therapies was predicted by higher baseline levels of clinician-rated depression, elevated suicidality, comorbid anxiety, lower social functioning, higher social inhibition, moderate-to-severe early emotional or sexual abuse, no preference for psychotherapy, and the history of at least one previous inpatient treatment. Moderator analyses revealed that patients with higher baseline levels of self-rated depression, comorbidity of at least one Axis-I disorder, self-reported moderate-to-severe early emotional or physical neglect, or at least one previous antidepressant treatment, had a significantly lower post-treatment depression severity with CBASP compared to SP (all $p < 0.05$).

Conclusions and relevance: A complex multifactorial interaction between severe symptoms of depression, suicidality, and traumatic childhood experiences characterized by abuse, social inhibition, and anxiety may represent the basis of non-response to psychotherapy in patients with early onset PDD. Specific psychotherapy with CBASP might, however, be more effective and recommendable for a variety of particularly burdened patients compared to SP.

Keywords: persistent depressive disorder, CBASP, supportive psychotherapy, moderator analysis, predictor analysis, childhood trauma, personalized medicine

INTRODUCTION

Over 20% of the patients with major depressive disorder (MDD) develop a chronic course lasting two years or longer (1), called Persistent Depressive Disorder (PDD) (2, 3). Compared to single major depressive episodes, PDD is characterized by a longer illness duration with a more complicated treatment course, lower quality of life, concurrent generalized anxiety disorder, more frequent suicide attempts, comorbid psychiatric and personality disorders, dysfunctional interpersonal behavior and more complicated treatment courses (1, 4, 5). More than two-thirds of all patients with PDD report an early illness onset (before age 21) often associated with severe experiences of childhood maltreatment characterized by emotional, physical, and sexual abuse or by deprivation in form of emotional or physical neglect (1, 4, 6, 7). Importantly, a large majority of patients with PDD experience side effects, relapses or resistances in the treatment with antidepressant medication (1, 7, 8) and report to prefer psychological over pharmacological treatment (9). Thereby, psychotherapy is an indispensable tool in the treatment of PDD.

So far, the Cognitive Behavioral Analysis System of Psychotherapy (CBASP) (10) is the only psychotherapy-model especially designed to address the specific needs of patients with early-onset PDD. Its principle lies on treating early trauma related dysfunctionalities by focusing on the patient's interpersonal problems through systematic social problem solving and discriminative interpersonal learning (10, 11). Its effectiveness has been evidenced in a number of clinical trials that compared CBASP to other psychotherapies (7), antidepressant medication (12, 13), or to combined treatments (8, 12). The European Psychiatric Association has recommended CBASP as the first-line psychotherapy for PDD, which is largely justified by its superiority over alternative, non-specific psychotherapies (5).

Nevertheless, little progress has been achieved in understanding which PDD subpopulations may or may not profit from psychotherapy in general and which benefit from CBASP in particular, leaving the questions for whom and when exactly CBASP should be recommended largely unanswered (5, 14).

This is particularly problematic, as PDD is a heterogeneous disorder, and different PDD subpopulations may benefit to varying degrees from CBASP (15). Gaining evidence is crucial not only for further explaining its general effectiveness, but also for detecting specific subpopulations for which CBASP can be recommended as first-choice psychotherapy.

One possibility to examine its disorder-specific effectiveness is by comparing it to alternative forms of psychotherapy. In a multicenter randomized clinical trial, Schramm and colleagues (7) evaluated the effectiveness of CBASP by comparing it with non-specific supportive psychotherapy (SP) in $N = 268$ antidepressant-free, adult outpatients with early-onset PDD (ClinicalTrials.gov identifier NCT00970437). Overall, CBASP was found to be more effective and acceptable than SP. Patients treated with CBASP showed small, but significant advantages in most primary and secondary outcomes, as well as in response and remission rates.

So far, a number of secondary analyses of this trial have been performed in order to analyze if CBASP outperformed SP for patients with early trauma (16), comorbid personality

disorders (17), comorbid anxiety disorders (18), as well as various baseline characteristics combined to one single moderator (19). With regard to early trauma, only those patients reporting early severe-to-moderate emotional abuse seemed to benefit significantly more from CBASP than from SP at week 20 (16). The presence of comorbid personality disorders was neither a predictor nor a moderator of depression severity at week 20 (17). However, the CBASP was significantly more effective than SP in patients with comorbid anxiety disorders compared to those without anxiety disorders in terms of both depression severity and interpersonal problems as outcomes (18). In a more recent secondary analysis (19), the data of this trial was analyzed with a modern moderator approach combined with two machine learning algorithms. An optimal composite moderator (M*) was developed as a weighted combination of 13 preselected baseline variables and used for identifying and characterizing subgroups for which CABSP was more beneficial to SP and vice versa, focusing on the change in depression severity from baseline to week 48. Of the analyzed sample of patients, 58.65% experienced a better treatment outcome with CBASP, while 41.35% showed a better outcome with SP. In terms of baseline characteristics, patients responding more favorably to CBASP were more severely depressed, had more often a comorbid Axis-I disorder, were more often previously hospitalized, and were more likely affected by moderate-to-severe early emotional or physical neglect. In contrast, patients responding more favorably to SP had a higher pre-treatment global and social functioning level, a higher quality of life, and more often a recurrent MDD without complete remission between the episodes.

An important outstanding question which remains to be clarified is which subgroups of patients respond to both therapies. The main goal of this analysis will therefore be to identify *predictors*, i.e. baseline variables which predict treatment success regardless of treatment assignment. Discovering predictors is especially helpful for understanding which factors contribute to non-response to psychotherapy and consequently to the persistent course in chronically depressed patients. In contrast to the common practice of limiting analyses to a few characteristics and in order to gain a complex understanding, we investigated a large span of baseline characteristics including socio-demography, clinical status, psychosocial and global functioning, quality of life, interpersonal problems, childhood trauma, treatment history, preference for psychotherapy, and treatment expectancy.

Baseline characteristics which have been previously associated with a better treatment response for psychotherapy in patients with PDD and thus plausible to have contributed to a greater alleviation of depression severity in both arms are: lower baseline levels of depression and anxiety (20), having a preference for psychotherapy at the baseline (21, 22), as well as a positive treatment expectancy at baseline (23). We therefore expected an equally high effectiveness of both therapies in patients characterized by these features at baseline.

In addition, the present analysis will also examine the same baseline variables as moderators of differential treatment effectiveness of CBASP vs. SP at week 48. This will be done for statistical reasons (for determining if a variable is a predictor, one has to examine its interaction effect with the group variable), as well as for reasons of comparability with the previous moderator analysis (19) which was based on a more modern approach. Statistical models such as the one applied in the previous analysis (19), which are based on integrating several multi-domain baseline variables into one moderator to identify subpopulations with different treatment responses, are particularly useful for the prediction of treatment response in samples which are sufficiently statistically powered, and can be further validated as a prediction algorithm in new clinical populations. In comparison, the more classical approach of selecting and testing one baseline variable as predictor and moderator per model, which will be used in the analysis presented here, provides evidence about the individual impact of single baseline characteristics on the treatment outcome. These findings can further be used for selecting those clinical subpopulations which seem to respond particularly poorly to one or both therapies for testing new treatments or combination of treatments, which can be especially developed to target their needs (for instance, patients with childhood trauma, or comorbid anxiety). As for moderators, in view of its emphasis in treating cognitive-behavioral consequences of childhood trauma and previous moderator findings (19), we expected CBASP to outperform SP in reducing depression severity in patients marked by an elevated baseline depression severity, at least one comorbid Axis-I disorder, experiences of early emotional or physical neglect, lower quality of life, a longer illness duration, and those which were separated, divorced or widowed. Conversely, we expected to replicate those moderators of a higher effectiveness of SP vs. CBASP, which were: a recurrent MDD without remission between the episodes, having at least one comorbid Axis-II disorder, and a higher social and global functioning at baseline. Although these variables were not defined as moderators by testing for statistical significance in the previous approach (19), but by their moderator effect size, we expect many of them to significantly interact with the group variable in the present analysis.

METHODS

Participants

As described in (7), eligible outpatients were fluent in the German language, 18–65 years old and met *DSM-IV* criteria for a current episode of chronic major depressive disorder (MDD) with a total duration of at least two years, MDD superimposed on a preexisting dysthymic disorder ("double depression"), or a recurrent MDD with incomplete remission between two major depressive episodes (MDEs) with a current MDD and a total duration of at least 2 years. In addition, an early illness onset (i.e. before the age of 21) and a score of at least 20 on the 24-item version of the Hamilton Rating Scale for Depression (HRSD-24) (24) at screening as well as a 2-week medication-free period at baseline were required for inclusion. Patients were excluded from study participation if they had an acute risk for suicide and/or the need for hospitalization; a primary diagnosis of another Axis I disorder; a diagnosis of antisocial, schizotypal, or borderline personality disorder; a serious medical condition; severe cognitive impairment; a history of psychotic

symptoms, bipolar or organic brain disorder; an absence of a response to a previous adequate trial with CBASP and/or SP; or an ongoing psychotherapy or antidepressant medication. Intake of antidepressant medication during the trial was forbidden.

From the $N = 622$ patients assessed for eligibility, $N = 268$ met inclusion criteria and were randomized to receive CBASP ($N = 137$) or SP ($N = 131$). For further details on the inclusion process, refer to the chart flow of the main publication (7). The study was approved by the Ethics Committee of the following participating institutions: University of Freiburg, University of Bonn, University of Heidelberg, University of Tübingen, University Medical Center Hamburg-Eppendorf, University of Marburg, and University of Lübeck. Written informed consent was obtained from all participants.

Interventions

During the entire duration of the study, both CBASP and SP were each applied following a standardized treatment manual: The CBASP was applied based on a manual developed by James P McCullough (10), while SP was applied by a revised manual developed by John C Markowitz, which was translated into German by the trial coordinators. Eligible participants were allocated to one of the intervention groups by a 1:1 treatment ratio drawing on a computer-generated block randomization sequence with randomly varying block size, stratified for trial site.

The CBASP is a highly structured psychotherapy especially developed for treating patients with chronic depression. It builds on techniques such as situation analysis, interpersonal discrimination exercises, and behavioral skill training/rehearsal (25). It was designed to address the typical preoperational cognitive-emotive functioning of patients with chronic depression by demonstrating to patients that their behavior has (negative) consequences on their environment, leading to interpersonal difficulties. Predominantly relying on the administration of negative reinforcement, CBASP supports the patient in the process of recognizing and understanding the consequences of one's behavior on their environment, which, in turn, leads to a modification of one's behavior and, consequently, to an alleviation of chronic depression. In comparison to the widely used Cognitive Behavioral Therapy (CBT), the CBASP focuses primarily on the person's behavior and interaction with its environment, and not on the pure cognitive content, which is the case for CBT (26). There is strong evidence supporting the effectiveness of CBASP with or without antidepressant medication in early-onset chronic depression: For instance, one large study (27) demonstrated that CBASP was particularly effective for the subgroup of chronically depressed patients marked by early trauma when compared to Nefazodone as antidepressant medication (remission rates: 33% with Nefazodone, 48% with CBASP, and 54% with a combination of both). Moreover, in a trial (11) conducted in $N = 30$ chronically depressed outpatients with early onset, statistically significant differences were found between CBASP and Interpersonal Therapy (IPT) regarding remission rates (57% in CBASP vs. 20% in IPT) and the decrease of self-rated depressive symptoms in favor of CBASP.

In contrast, SP is a disorder non-specific, non-confrontational psychotherapy. The supportive therapist builds an emotional connection to the patient, follows his affect, encourages catharsis, inspires hopes, and emphasizes patient's strengths (28). The main effect of this approach is the enforcement of the patient's awareness of its self-efficacy in changing its own circumstances. In a 16-week study conducted in $N = 94$ patients with dysthymia, which is a milder form of PDD, SP equaled IPT in treatment effect (29).

In an earlier trial (8), CBASP did not prove to be superior to SP when applied as a short-term (12 sessions) augmentation strategy in chronically depressed patients who showed partial or non-response to a pharmacotherapy algorithm. The present study comparing CBASP to SP was designed in order to meet the need for more and larger trials in patients with early-onset PDD, controlling for medication, and including CBASP as a disorder-specific intervention with a more intensive (larger number of sessions) and a longer course of treatment to unfold beneficial and lasting effects in PDD. In this trial, during the acute treatment phase, patients received bi-weekly sessions of CBASP or SP in the first four weeks and weekly sessions for the next 16 weeks. For the following 28 weeks, eight further continuation sessions were delivered, resuming in a total of 32 sessions extended over 48 weeks.

Both the CBASP ($N = 42$ study therapists) and SP ($N = 39$ study therapists) sessions were conducted by psychotherapists or psychiatrists with experience in the treatment of depression (mean of 5.45 years for CBASP; mean of 4.00 years for SP). Age, gender, and experience of the therapists were similar in both study conditions. All study therapists had completed a 3-year, post-graduate psychotherapy training program or were in an advanced stage of their training. In addition, both groups of study therapists were trained in CBASP or SP during a 2-day training workshop. Before treatment start, study therapists' mastery of CBASP or SP methods was assessed by specific rating scales during two videotaped pilot cases (7).

The fidelity of the therapists to the therapy manuals was measured by adherence scales including standardized scales for disciplined personal involvement and situation analysis for the CBASP. Therapy sessions of both interventions were videotaped and reviewed by site supervisors regularly on a random basis to assess psychotherapists' fidelity to the treatment procedures. In addition, an independent team of trained expert raters randomly evaluated one video-taped session of each therapy. The evaluations revealed that of $N = 244$ evaluable sessions ($N = 123$ in CBASP and $N = 121$ in SP), $N = 227$ (93.0%; with $N = 112$ in CBASP and $N = 115$ in SP) met criteria for fidelity.

In order to ensure compliance with ethical principles and the study protocol, as well as to check data quality and accuracy, monthly telephone conferences, semi-annual Data and Safety Monitoring Board conferences, and annual monitoring visits at trial sites were conducted by the Principal Investigator in cooperation with all trial site coordinators (7).

Measurements

All ratings were performed by trained and experienced raters. Raters were furthermore blinded to patients' treatment allocation

in order to avoid their possible subjective influence on the rating. For ensuring the blinding of raters, they were separately located from the therapists. In addition, patients were instructed not to mention any information that could reveal their intervention to their rater. Furthermore, back-up raters were provided in case of unintentional unblinding (7).

The HRSD-24 was used to screen for participants' eligibility before randomization (approx. two weeks before treatment start), as a main outcome after 12 and 20 weeks of acute treatment, as well as at the end of the extended treatment phase, which was 48 weeks after randomization. The interrater reliability for the HRSD-24 scores was measured based on data from 21 evaluators who rated nine audio- or video-taped interviews (intra-class correlation coefficient, 0.973; 95% CI, 0.889–0.999). Further baseline variables which were rated and subject to the present secondary analysis are described in the following section.

Analyzed Baseline Characteristics

In the present secondary analysis of the trail by Schramm et al. (7), we tested the following baseline characteristics as potential predictors and moderators of depression severity measured by the HRSD-24 at week 48.

Socio-Demographic Characteristics

Gender (female/ male), age at the time point of randomization (years), marital status (single/ married or cohabiting/ separated, divorced or widowed), high educational level (corresponding to at least 12 years of education in the German school system with the possibility of university studies), employment status (employed/unemployed), working hours per week, and the presence of at least one physical illness (yes/no).

Clinical Characteristics

Illness subtype (chronic MDD, "double depression," or recurrent MDD with incomplete remission between episodes), age at illness onset (years), illness duration (years), baseline severity of depression by patients' self-rating using the Inventory of Depressive Symptomatology (IDS-SR) (30) and by clinicians' rating through the HRSD-24 (24), acute suicidality assessed by the Beck Scale for Suicide Ideation (BSSI) (31), a history of previous suicidal attempts (yes/no), generalized and phobic anxiety measured by the Brief Symptom Inventory (BSI) (32) and the Generalized Anxiety Disorder Scale (GAD-7) (33), as well as comorbidity of any Axis I or II disorder diagnosed by the Structured Clinical Interview for *DSM-IV-TR* Axis I Disorders (SCID-I) (34) and the Structured Clinical Interview for *DSM-IV* Axis II Personality Disorders (SCID-II) (35). For examining comorbid anxiety as a predictor and moderator, we decided to only use the BSI and GAD-7 as self-report questionnaires for several reasons: First, they are continuous scales representing the current expression of anxiety, thereby providing more variance for the statistical analyses compared to diagnoses made by the SCID-I, which are of binary character, thus containing less variance. Second, we assessed all forms of anxiety disorders by the SCID-I (both lifetime and current diagnoses), and to test all these variables as predictors and moderators would needlessly increase the number of statistical tests.Third, we have less missing cases for the BSI and GAD-7 compared to the SCID-I.

Global, Psycho-Social Functioning, and Quality of Life

Baseline degree of global functioning and overall psychiatric burden assessed by the Global Assessment Functioning Scale (GAF) (36), dysfunctional social attitudes assessed by the Social Adaptation Self-Evaluation Scale (SASS) (37) and impairment of life quality through depression assessed by the Quality of Life in Depression Scale (QLDS) (38).

Interpersonal Problems

Self-reported, repeatedly occurring difficulties in interpersonal relationships assessed on the eight scales of the Inventory of Interpersonal Problems (IIP-64) (39); these are: domineering, suspicious/ distrustful, cold, socially inhibited, non-assertive, overly accommodating, self-sacrificing, and intrusive.

Childhood Trauma

Retrospective, self-reported forms of childhood trauma before the age of 18 assessed on the five scales of the Childhood Trauma Questionnaire (CTQ) (40). In this analysis, we defined the presence of the different types of childhood maltreatment as at least moderate-to-severe, corresponding to a pre-defined, specific cut-off of the respective scale set by Bernstein and Fink (41): emotional abuse ($\geq$ 13 points), emotional neglect ($\geq$ 15 points), physical abuse ($\geq$ 10 points), physical neglect ($\geq$ 10 points), and sexual abuse ($\geq$ 8 points).

Treatment History

Previous underwent antidepressant medication received for a minimum of 4 weeks, psychotherapy underwent for at least eight sessions, a combination of both, as well as any form of previous inpatient treatment (yes/no).

Treatment Preference for Psychotherapy

All patients were asked to indicate which treatment option they generally prefer: antidepressant medication alone; psychotherapy alone; combined treatment of antidepressant medication and psychotherapy; or no preference. In the present analysis, we classified the answers in preferring psychotherapy (=1) or not (=0; all other options).

Treatment Expectancy

Self-ratings of the expected depression severity at week 48 assessed by the e-IDS-SR, which is an unpublished adaptation of the IDS-SR, used in this trial.

There is a large overlap with those baseline variables tested in the previous analysis relying on the combined moderator (19); however, due to an insufficient moderator effect size, not all tested baseline variables were entered as moderators into the final regression analysis there. In this analysis, we tested all enumerated variables as both individual predictor *and* moderator, enabling to discuss the roles of each one of these variables in conclusion.

Treatment Outcome

The main outcome variable for all predictor/ moderator analyses was the HRSD-24 total score at week 48. Both groups did not differ in their baseline HRSD-24 scores (CBASP: mean=24.50, sd=7.60; SP: mean=25.18, sd=6.63; p=0.50).

Statistical Analyses

All statistical analyses were performed on treatment completers, i.e patients who completed the whole therapy program of 32 sessions of CBASP or SP and presented valid HRSD-24 ratings at week 48. Between-group analyses were conducted to compare general differences in post-treatment scores (*Student's t*-test). We tested differences in demographic variables between patients allocated to CBASP and those allocated to SP, as well as between completers and non-completers (i.e., patients who dropped out from the trial before week 48).

With regard to the predictor and moderator analyses, linear regression models were built as depression severity was a continuous outcome. By following the recommendations of Kraemer et al. (42), we first z-standardized all continuous baseline variables in order to facilitate the interpretation of their effects. Predictors were defined as those baseline variables that showed a significant main effect in predicting the outcome without demonstrating an interaction with the treatment group variable, while moderators were defined as baseline variables that interacted with the treatment group variable in predicting the outcome, independently of the significance of the main effect (42). Models were built for each candidate baseline variable separately and were adjusted for study site and baseline depression severity, which were implemented as covariates into the models. Models testing predictors thus contained the main effects of study site, standardized baseline HRSD-24 scores, treatment group and the respective candidate baseline variable. For identifying moderators, separate models were built by adding the interaction term of the candidate variable and the treatment assignment to the main effects of the predictor model accordingly. Results are presented by regression coefficients and reported as significant at the conventional threshold of $p < 0.05$, two-sided. Analyses were performed with STATA 15.1 (Stata Corp, College Station, Texas).

RESULTS

From the $N = 268$ randomized outpatients, $N = 209$ completed the 48-week treatment program with 32 sessions of either CBASP ($N = 113$) or SP ($N = 96$). For a detailed description of the completer population, see **Table 1**. At baseline, the only significant difference between CBASP and SP completers was a higher percentage of employment in the group treated with CBASP. We found no significant differences in baseline variables between completers and non-completers (see **Table 2** for descriptive statistics).

The between-group comparisons at week 48 revealed that CBASP completers had significantly lower HRSD-24 scores (CBASP: mean = 13.96, sd = 9.56; SP: mean = 16.69, sd = 9.87; $p = 0.044$).

TABLE 1 | Sociodemographic and clinical characteristics of the completers subdivided by treatment arm.

Variable	CBASP	SP
	(*N* = 113)	(*N* = 96)
Age at randomization, mean (SD), y	45.20 (11.98)	45.78 (11.98)
Female sex, No. (%)	81 (71.7)	57 (59.4)
Single, No. (%)	47 (41.6)	43 (44.8)
Married or cohabiting, No. (%)	45 (39.8)	40 (41.7)
Separated, divorced or widowed, No. (%)	21 (18.6)	13 (13.5)
High level of education, No. (%)	73 (64.6)	56 (58.3)
Employed, No. (%)*	90 (79.6)	59 (61.5)
Working hours per week, mean (SD), h	24.46 (16.51)	21.36 (20.13)
Presence of at least one physical illness, No. (%)	8 (7.3)	5 (5.4)
Subtype, No. (%)		
Double depression	47 (42.3)	43 (46.7)
Chronic MDD	35 (31.5)	31 (33.7)
Recurrent MDD with incomplete remission between episodes	29 (26.1)	18 (19.6)
Age at illness onset, mean (SD), y	13.01 (4.41)	13.02 (4.49)
Illness duration, mean (SD), y	32.19 (13.80)	32.77 (13.18)
HRSD-24 baseline score, mean (SD)	24.50 (7.60)	25.18 (6.63)
Remitters, No. (%)	41 (36.3)	24 (25.0)

HRSD-24, 24-Item Hamilton Rating Scale for Depression; MDD, major depressive disorder; SD, standard deviation; y, years.
**Significant between-group difference at p = 0.004.*

Predictors of Depression Severity at Week 48

In total, our analyses identified 10 predictors (all main effects with $p < 0.05$): Higher HRSD-24 scores at week 48 were predicted by higher baseline scores on the HRSD-24 scale, BSSI scale, BSI anxiety scale, GAD-7 scale, and IIP-64 social inhibition scale. In addition, higher HRSD-24 scores at week 48 were also predicted by the presence of early emotional or sexual abuse at baseline, as well as by the presence of at least one previous inpatient treatment. In contrast, lower HRSD-24 scores at week 48 were predicted by higher baseline scores on the SASS scale, as well as by the presence of preference for psychotherapy rated as baseline (for more details, please see **Table 3**).

Moderators of Depression Severity at Week 48

Baseline variables identified as moderators of lower post-treatment HRSD-24 scores for patients treated with CBASP were: Higher levels of self-rated depression severity (IDS-SR scores), comorbidity of at least one Axis I disorder, a history of childhood moderate-to-severe emotional or physical neglect (CTQ scales), and a history of at least one previous treatment with antidepressant medication. This means that CBASP patients showing these features at baseline had lower post-treatment scores at week 48 than those with similar features treated with SP. Concerning the PDD subtype, we found a crossover-effect in that patients with chronic MDD and Double Depression treated

TABLE 2 | Differences in baseline variables between completers and non-completers.

Baseline variable	Completers	Non-completers	
Continous variables	**Mean (SD)**	**Mean (SD)**	***p***
Age at randomization	45.47 (11.96)	42.93 (11.18)	0.15
Age at illness onset	13.01 (4.44)	12.95 (4.36)	0.92
Illness duration (y)	32.45 (13.49)	29.98 (12.51)	0.21
IDS-SR score	38.90 (9.82)	38.83 (8.33)	0.96
HRSD-24 score	24.81 (7.16)	24.70 (6.41)	0.91
BSSI score	6.30 (7.19)	7.49 (7.95)	0.30
GAD-7 score	10.86 (4.65)	11.02 (4.20)	0.83
BSI anxiety score	6.14 (3.78)	6.58 (3.82)	0.45
BSI phobia score	2.62 (2.48)	3.17 (2.76)	0.16
GAF score	54.38 (9.25)	54.09 (8.87)	0.84
SASS score	30.22 (6.55)	29.39 (6.19)	0.41
QLDS score	18.91 (7.70)	19.98 (7.72)	0.37
IIP-64 total score	14.89 (3.63)	14.77 (3.83)	0.83
Binary variables	**N**	**N**	***p***
Female gender	138	39	0.99
Single	90	27	0.71
Married or cohabiting	85	21	0.48
Separated, divorced or widowed	34	11	0.67
High level of education	129	43	0.11
Employed	149	41	0.79
Presence of morbidities (≥1 physical illness)	13	2	0.37
Chronic MDD	66	16	0.52
Double depression	90	29	0.38
Recurrent MDD with incomplete remission between episodes	47	12	0.74
History of suicidal attempts	58	18	0.47
Any Axis I disorder[a]	87	26	0.74
Any Axis II disorder[a]	82	21	0.61
Early physical abuse[b]	42	13	0.55
Early physical neglect[b]	61	21	0.18
Early emotional abuse[b]	119	32	0.82
Early sexual abuse[b]	48	9	0.99
Early emotional neglect[b]	132	35	0.76
Prior medication[c]	117	31	0.64
Prior psychotherapy[d]	117	36	0.49
Prior combination therapy[e]	39	14	0.39
Prior inpatient treatment[f]	105	33	0.44
Preference for psychotherapy	157	41	0.47

BSI, Brief Symptom Inventory; BSSI, Beck Scale for Suicidal Ideation; CTQ, Childhood Trauma Questionnaire; GAD-7, Generalized Anxiety Disorder Scale-7; GAF, Global Assessment Functioning Scale; HRSD-24, 24-Item Hamilton Rating Scale for Depression; IDS-SR, self-rated Inventory of Depressive Symptomatology; IIP-64, Inventory of Interpersonal Problems; MDD, major depressive disorder; QLDS, Quality of Life in Depression Scale; SASS, Social Adaptation Self-Evaluation Scale; y, years.

[a] *Diagnosed by the SKID-I or SKID-II according to DSM-IV classification.*

[b] *Presence indicates a clinical severity of at least moderate to severe on the CTQ.*

[c] *History of ≥ 4 weeks of treatment with antidepressant medication.*

[d] *History of ≥ 8 sessions of psychotherapy.*

[e] *History of combination treatment with antidepressant medication (≥ 4 weeks) and psychotherapy (≥ 8 sessions).*

[f] *History of any kind of psychiatric inpatient treatment.*

with CBASP had lower post-treatment scores at week 48 than those with these features treated with SP. In line with this, those classified to have a recurrent MDE without complete remission between the episodes benefited more from SP than from CBASP (**Table 3**). **Figure 1** illustrates all six identified moderators by plots of their interaction effects with the treatment group. All other baseline variables lacked statistical significance for being declared as predictors or moderators (all $p > 0.05$).

DISCUSSION

In a large randomized clinical trial conducted in adult, antidepressant-free outpatients with early-onset PDD, CBASP has been shown to outperform SP with response rates of 38,7% compared to 24,3% at the end of the extended treatment phase after 48 weeks (7). In this secondary-analysis conducted in patients who completed the interventions of this randomized clinical trial, we examined the roles of a wide range of baseline variables as predictors and moderators of the effectiveness of CBASP and SP on depression severity at the end of the extended treatment phase at week 48.

In terms of predictors, we found that a poor response to both psychotherapies was predicted by a higher baseline severity of depression (higher HRSD-24 baseline scores), more pronounced suicidality (higher BSSI baseline scores), more intense anxiety (higher BSI anxiety and GAD-7 baseline scores), stronger social inhibition (higher IIP-64 baseline scores), a self-reported history of moderate-to-severe emotional or sexual abuse, as well as at least one inpatient treatment. Patients who had higher baseline levels of social functioning (higher SASS baseline scores) and a preference for psychotherapy had, contrarily, lower levels of depression severity at week 48 independent of the assigned treatment form.

The findings of the performed predictor analyses largely confirmed our hypotheses and are in line with previous research confirming that those patients who were initially more mentally stable (i.e less depressed, less anxious, less suicidal), higher socially functioning and preferring psychotherapy, responded better to both treatments when compared to patients on the other side of the respective continuum or category. It is reasonable that a less pathological and higher functioning baseline status has facilitated the psychotherapeutic learning and enabled a better recovery process in both groups. Moreover, the confirmed positive impact of having a preference for psychotherapy on the outcomes of both psychotherapies is in line with previous results (21, 22) and supports the conclusion that psychotherapy is more effective and recommendable than other treatments options for PDD patients who prefer psychotherapy over other alternative treatments for depression (9).

From the opposite perspective, we can also conclude that patients who were initially more pathologic benefitted less from both therapies. Thus, for more severely affected patients, both psychotherapies might be insufficient for achieving significant symptom reductions when delivered as monotherapies, as was the case in this trial. These subpopulations might respond better to a combined approach between antidepressant medication and

TABLE 3 | Predictors and moderators of depression severity at week 48.

Baseline variable	Variable main effect		Variable x Group		Role
	B (95% CI)	*p*	B (95% CI)	*p*	
SOCIO-DEMOGRAPHY					
Female gender[a]	0.50 (−2.14; 3.15)	0.71	−1.05 (−6.34; 4.23)	0.69	
Age at randomization[b]	0.72 (−0.53; 1.98)	0.26	−2.03 (−4.45; 0.39)	0.10	
Single[a]	0.44 (−2.11; 3.00)	0.73	1.91 (−3.12; 6.95)	0.45	
Married or cohabiting[a]	−1.07 (−3.61; 1.47)	0.41	0.97 (−4.17; 6.11)	0.71	
Separated, divorced or widowed[a]	1.11 (−2.28; 4.51)	0.52	−5.61 (−2.42; 1.20)	0.17	
High level of education[a]	−0.11 (−2.70; 2.48)	0.93	−0.83 (−5.94; 4.29)	0.75	
Employed[a]	−1.65 (−4.47; 1.17)	0.25	2.68 (−2.90; 8.27)	0.34	
Working hours per week[b]	−0.27 (−1.64; 1.09)	0.69	−0.75 (−3.57; 2.07)	0.60	
Presence of morbidities (≥1 physical illness)[a]	1.53 (−3.57; 6.63)	0.55	−2.50 (−12.97; 7.97)	0.64	
CLINICAL CHARACTERISTICS					
Double depression[a]	0.11 (−2.53; 2.76)	0.93	−1.09 (−6.25; 4.07)	0.68	
Chronic MDD[a]	0.94 (−1.92; 3.81)	0.52	−3.51 (−8.98; 2.96)	0.21	
Recurrent MDD with incomplete remission between episodes[a]	−1.32 (−4.49; 1.84)	0.41	6.18 (0.16; 12.20)	0.044*	M
Age at illness onset[b]	0.36 (−0.91; 1.63)	0.57	1.55 (−0.92; 4.03)	0.22	
Illness duration[b]	0.53 (−0.73; 1.79)	0.41	−2.39 (−4.82; 0.04)	0.054	
HRSD-24 score[b]	2.43 (1.17; 3.70)	<0.001*	−1.10 (−3.62; 1.41)	0.39	P
IDS-SR score[b]	1.50 (−0.11; 3.11)	0.069	−3.68 (−6.14; −1.21)	0.004*	M
BSSI score[b]	2.32 (0.93; 3.71)	0.001*	1.13 (−1.45; 3.72)	0.39	P
History of suicidal attempts[a]	0.28 (−2.58; 3.14)	0.85	−4.33 (−10.00; 1.33)	0.13	
BSI anxiety score[b]	1.80 (0.38; 3.23)	0.014*	−1.83 (−4.31; 0.66)	0.15	P
BSI phobia score[b]	1.10 (−0.36; 2.56)	0.14	−0.35 (−2.96; 2.27)	0.79	
GAD-7 score[b]	1.57 (0.14; 2.99)	0.031*	−2.13 (−4.59; 0.32)	0.09	P
Any Axis I disorder[a,c]	1.43 (−1.21; 4.08)	0.29	−6.02 (−11.04; −0.99)	0.019*	M
Any Axis II disorder[a,c]	2.25 (−0.51; 5.01)	0.11	0.03 (−5.14; 5.21)	0.99	
FUNCTIONALITY AND QUALITY OF LIFE[b]					
GAF score	0.25 (−1.49; 1.99)	0.78	2.12 (−0.45; 4.70)	0.11	
SASS score	−2.05 (−3.39; −0.72)	0.003*	1.06 (−1.42; 3.54)	0.40	P
QLDS score	0.85 (−0.63; 2.33)	0.26	−1.19 (−3.80; 1.41)	0.37	
INTERPERSONAL PROBLEMS[b,d]					
Domineering	−0.46 (−1.80; 0.88)	0.50	−2.33 (−4.93; 0.28)	0.08	
Suspicious/distrustful	0.92 (−0.42; 2.26)	0.18	−1.31 (−3.99; 1.38)	0.34	
Cold	1.06 (−0.24; 2.37)	0.11	−1.32 (−3.91; 1.27)	0.32	
Socially inhibited	2.34 (1.04; 3.65)	0.001*	−1.35 (−3.86; 1.15)	0.29	P
Non-assertive	1.04 (−0.29; 2.38)	0.13	−1.14 (−3.70; 1.41)	0.38	
Overly accommodating	1.00 (−0.33; 2.33)	0.14	−1.45 (−3.95; 1.06)	0.26	
Self-sacrificing	0.76 (−0.56; 2.07)	0.26	−2.02 (−4.52; 0.48)	0.11	
Intrusive	−0.15 (−1.43; 1.13)	0.82	−0.67 (−3.24; 1.89)	0.60	
EARLY TRAUMA[a,e]					
Emotional abuse	3.40 (0.79; 6.01)	0.011*	−3.93 (−9.00; 1.14)	0.13	P
Emotional neglect	2.81 (0.08; 5.53)	0.043*	−6.72 (−12.04; −1.41)	0.013*	M
Physical abuse	−0.91 (−4.14; 2.33)	0.58	−4.09 (−10.39; 2.20)	0.20	
Physical neglect	1.44 (−1.37; 4.26)	0.31	−7.06 (−12.51; −1.61)	0.011*	M
Sexual abuse	6.03 (3.17; 8.88)	<0.001*	0.81 (−4.89; 6.52)	0.78	P
PREVIOUS TREATMENTS[a]					
Medication[f]	1.27 (−1.33; 3.87)	0.34	−5.58 (−10.50; −0.65)	0.027*	M
Psychotherapy[g]	1.80 (−0.71; 4.30)	0.16	0.95 (−4.11; 6.02)	0.71	
Combination[h]	1.94 (−1.26; 5.14)	0.23	−2.79 (−9.14; 3.55)	0.39	
Inpatient[i]	4.52 (2.00; 7.04)	0.001*	−4.41 (−9.24; 0.40)	0.07	P

(Continued)

TABLE 3 | Continued

Baseline variable	Variable main effect		Variable x Group		Role
	B (95% CI)	*p*	B (95% CI)	*p*	
Preference for psychotherapy[a]	−3.01 (−6.00; −0.01)	0.049*	−2.64 (−8.56; 3.28)	0.38	P
Therapy expectancy[b]	0.64 (−0.60; 1.88)	0.31	−2.08 (−4.53; 0.36)	0.09	

BSI, Brief Symptom Inventory; BSSI, Beck Scale for Suicidal Ideation; CI, confidence interval; CTQ, Childhood Trauma Questionnaire; GAD-7, Generalized Anxiety Disorder Scale-7; GAF, Global Assessment Functioning Scale; HRSD-24, 24-Item Hamilton Rating Scale for Depression; IDS-SR, self-rated Inventory of Depressive Symptomatology; IIP-64, Inventory of Interpersonal Problems; M, moderator; MDD, major depressive disorder; P, predictor; QLDS, Quality of Life in Depression Scale; SASS, Social Adaptation Self-Evaluation Scale.

[a] *Categorical variable (0=no; 1=yes).*

[b] *Z-standardized continuous variable (0=mean; 1=mean + 1SD).*

[c] *Diagnosed by the SKID-I or SKID-II according to DSM-IV classification.*

[d] *As assessed by the IIP-64.*

[e] *Presence indicates a clinical severity of at least moderate to severe on the CTQ.*

[f] *History of ≥ 4 weeks of treatment with antidepressant medication.*

[g] *History of ≥ 8 sessions of psychotherapy.*

[h] *History of combination treatment with antidepressant medication (≥ 4 weeks) and psychotherapy (≥ 8 sessions).*

[i] *History of any kind of psychiatric inpatient treatment.*

**significant at $p < 0.05$.*

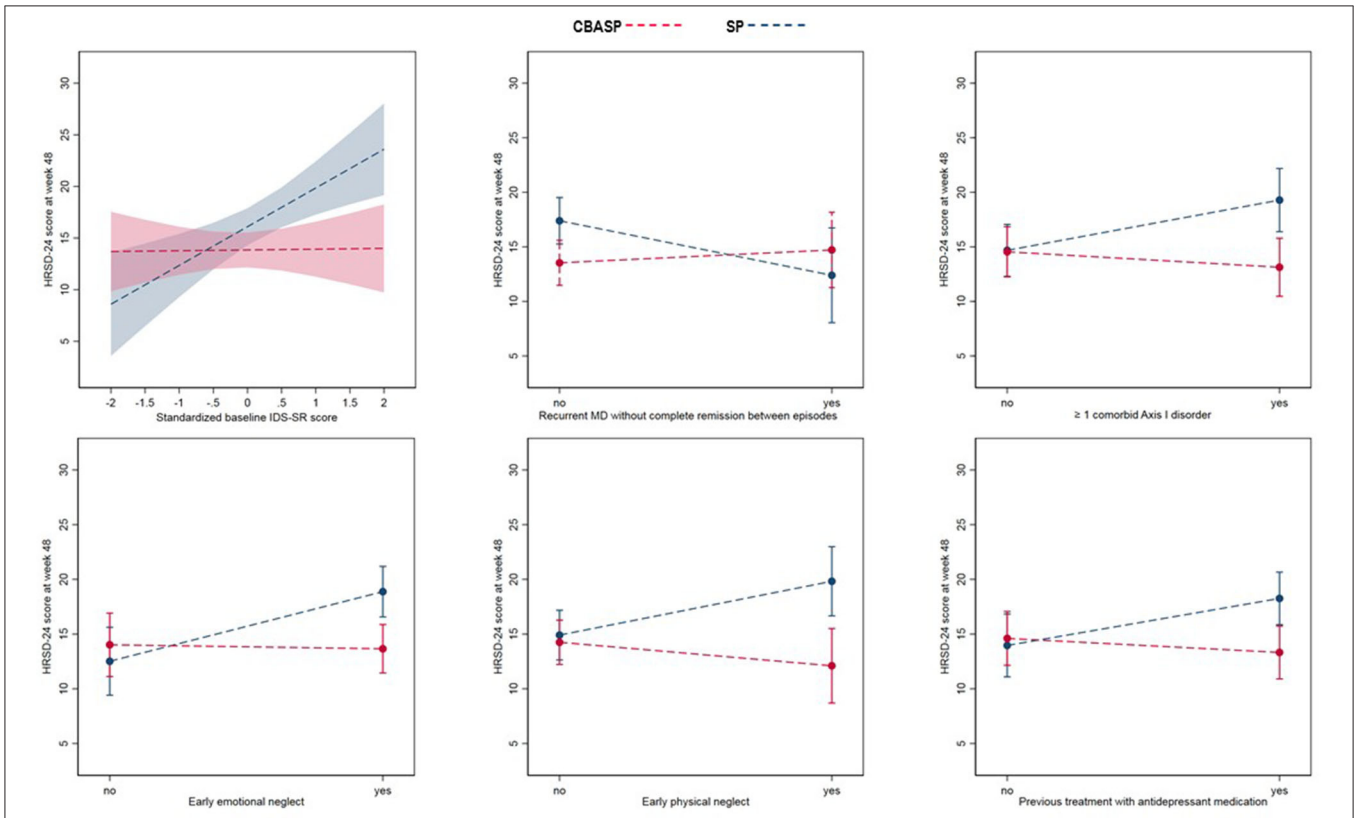

FIGURE 1 | Moderators of depression severity at week 48. IDS, self-rated Inventory of Depressive Symptomatology; HRSD-24, 24-Item Hamilton Rating Scale for Depression; MDD, major depressive disorder.

person-centered psychotherapy which flexibly and adaptively combines unspecific, transdiagnostic, and disorder-specific interventions. For example, it has been shown that the combination of CBASP and an antidepressant medication was more effective for PDD patients with a higher baseline symptom severity and pronounced anxiety (43, 44) than monotherapy with CBASP, indicating that an augmentation with pharmacotherapy is more recommendable for these patients than treatment with CBASP alone (7). This conclusion has also been supported in a participant data network meta-analysis which compared the effectiveness of CBASP as monotherapy to that of antidepressant medication and their combination (20). In a 2-year follow-up study of this trial, Schramm et al. (45) evaluated the effects of CBASP and SP one and two years after treatment termination.

CBASP outperformed SP in the number of well weeks with no/minimal symptoms, self-rated depressive symptoms, and depression-related quality of life one year after treatment termination, but not after two years. This result could be strongly attributed to a worsening of symptoms in the subgroups marked by baseline characteristics here identified as predictors, who benefitted less favorable from both interventions, and indicates the necessity of maintenance treatment for PDD patients.

Interestingly, we detected a lower effectiveness of both interventions for patients reporting a history of moderate-to-severe early emotional or sexual abuse, while CBASP was found to be more effective than SP for patients reporting early emotional or physical neglect. These results suggest that early-life trauma in form of abuse might be an important factor that contributes to non-response to psychotherapy in chronically depressed patients, while cognitive-behavioral consequences of early neglect might be modifiable by disorder-specific psychotherapy with CBASP. If different types of early trauma are associated with different responses to psychotherapy, then this information may prove crucial in designing and selecting optimal treatments for chronically depressed patients.

Finally, treatment expectancy had no influence on the post-treatment depression severity in our trial. We did not identify predictors or moderators from the socio-demographic domain, which could be attributable to the relatively homogeneous population of this trial (7).

In terms of moderators, CBASP displayed a multifaceted superiority over SP, meaning that patients with an elevated self-perceived depression severity (higher IDS-SR baseline scores), no recurrent MDE without complete remission between the episodes, comorbidity of Axis-I disorders, a history of at least one previous antidepressant treatment, and, as mentioned before, early trauma in form of moderate-to-severe emotional or physical neglect, had a lower depression severity at week 48 when treated with CBASP than those who were treated with SP. These results are in line with the previous moderator analysis (19) based on the data of this trial, which applied a modern machine learning method in order to identify subgroups of patients who respond better to CBASP than to SP and vice versa. With except of previous antidepressant medication, all here identified moderators had a moderator effect size large enough to be entered into the final regression model used in the analysis by Serbanescu et al. (19) to combine the most relevant moderators in order to exploratory identify the subgroups. The fact that the moderating role of these variables could be replicated in this more classical analysis underlines its robustness and validity in this trial. A more detailed interpretation of the moderating role of these variables is provided in the previous article (19). As emphasized there, these promising findings are in need of additional detailed investigations in order to be understood, as well as replication in future trials for enabling reliable treatment choice recommendations for the clinical practice.

This study has a number of important strengths: First, the antidepressant-free status of the patients allows ascribing the findings to the two tested psychotherapies alone. Second, we tested a relatively wide range of baseline characteristics. Third, the here performed analysis provides evidence for predictors as well as for moderators of two widely used therapies. We tested a relatively high number of variables, yielding many interesting results that open new questions which remain to be further investigated. However, some limitations must be also considered: Possible undesired, side-effects including transient worsening of symptoms and transient risk of suicidality at the beginning of therapy or in the context of unexpected psychosocial stress might have occurred in both treatment groups, and were not subject of this analysis. As a further limitation, our sample included only medication-free patients who were evaluated as enough mentally stable to be able to participate in the study. It can be assumed that the effectiveness of both therapies would have been smaller in more severely depressed patients. The exclusion criteria of the trial therefore may limit the generalizability of the findings to the general PDD population. Furthermore, the therapy duration of 48 weeks has revealed numerous clinically relevant predictors and moderators, but may be very resource-intensive for implementation in clinical practice. Finally, given the exploratory approach and large number of performed tests, the possibility of false positive findings has to be taken into account when considering the results. Thereby, our results need replication in future trials in order to permit valid treatment choice recommendations.

CONCLUSION

A multifactorial combination between elevated depression severity, suicidality, traumatic childhood experiences characterized by abuse, social inhibition and anxiety may represent the basis of non-response to psychotherapy in patients with PDD and consequently contribute to the persistence of the illness and its refractoriness. Nevertheless, disorder-specific psychotherapy with CBASP might be more effective and recommendable for a variety of particularly burdened patients with PDD than Supportive Psychotherapy. Further personalized clinical research is needed in order to understand and develop the (combination of) treatments that meet the needs of the most affected patients with PDD.

DATA AVAILABILITY STATEMENT

The data analyzed in this study is subject to the following licenses/restrictions: The dataset of the initial clinical randomized trial is not available to the public. Requests to access these datasets should be directed to elisabeth.schramm@uniklinik-freiburg.de.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethics Committee of the University of Freiburg, University of Bonn, University of Heidelberg, University of Tübingen, University Medical Center Hamburg-Eppendorf, University of Marburg, and University of Lübeck. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

IS and DS: had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis and drafting of the manuscript. IS: was responsible for statistical data analysis. IS, HW, SD, and DS: study concept and design. IS, HW, SD, JK, IZ, MB, MHa, RM, MHä, ES, and DS: acquisition, analysis, or interpretation of data. IS, BW, IZ, RM, MHa, MHä, DS, and ES: administrative, technical, or material support. All authors gave critical revision of the manuscript for important intellectual content.

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REFERENCES

1. Arnow BA, Constantino MJ. Effectiveness of psychotherapy and combination treatment for chronic depression. *J Clin Psychol.* (2003) 59:893–905. doi: 10.1002/jclp.10181
2. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition. Arlington, VA: American Psychiatric Association (2013). doi: 10.1176/appi.books.9780890425596
3. Schramm E, Klein DN, Elsaesser M, Furukawa TA, Domschke K. Review of dysthymia and persistent depressive disorder: history, correlates, and clinical implications. *Lancet Psychiatry*. (2020) 7:801–12. doi: 10.1016/S2215-0366(20)30099-7
4. Berndt ER, Koran LM, Finkelstein SN, Gelenberg AJ, Kornstein SG, Miller IM, et al. Lost human capital from early-onset chronic depression. *Am J Psychiatry*. (2000) 157:940–7. doi: 10.1176/appi.ajp.157.6.940
5. Jobst A, Brakemeier E-L, Buchheim A, Caspar F, Cuijpers P, Ebmeier KP, et al. European psychiatric association guidance on psychotherapy in chronic depression across Europe. *Eur Psychiatry*. (2016) 33:18–36. doi: 10.1016/j.eurpsy.2015.12.003
6. Klein DN, Schatzberg AF, McCullough JP, Dowling F, Goodman D, Howland RH, et al. Age of onset in chronic major depression: relation to demographic and clinical variables, family history, and treatment response. *J Affect Disord.* (1999) 55:149–57. doi: 10.1016/S0165-0327(99)00020-8
7. Schramm E, Kriston L, Zobel I, Bailer J, Wambach K, Backenstrass M, et al. Effect of disorder-specific vs nonspecific psychotherapy for chronic depression: a randomized clinical trial. *JAMA Psychiatry*. (2017) 74:233–42. doi: 10.1001/jamapsychiatry.2016.3880
8. Kocsis JH, Gelenberg AJ, Rothbaum BO, Klein DN, Trivedi MH, Manber R, et al. Cognitive behavioral analysis system of psychotherapy and brief supportive psychotherapy for augmentation of antidepressant nonresponse in chronic depression: the REVAMP trial. *Arch Gen Psychiatry*. (2009) 66:1178–88. doi: 10.1001/archgenpsychiatry.2009.144
9. McHugh RK, Whitton SW, Peckham AD, Welge JA, Otto MW. Patient preference for psychological vs. pharmacological treatment of psychiatric disorders: a meta-analytic review. *J Clin Psychiatry*. (2013) 74:595–602. doi: 10.4088/JCP.12r07757
10. McCullough JP. *Treatment for Chronic Depression: Cognitive Behavioral Analysis System of Psychotherapy*. New York, NY: Guilford Press (2000).
11. Schramm E, Zobel I, Dykierek P, Kech S, Brakemeier EL, Külz A, et al. Cognitive behavioral analysis system of psychotherapy versus interpersonal psychotherapy for early-onset chronic depression: a randomized pilot study. *J Affect Disord.* (2011) 129:109–16. doi: 10.1016/j.jad.2010.08.003
12. Keller MB, McCullough JP, Klein DN, Arnow B, Dunner DL, Gelenberg AJ. A comparison of nefazodone, the cognitive behavioral analysis system of psychotherapy, and their combination for the treatment of chronic depression. *N Engl J Med.* (2000) 342:1462–70. doi: 10.1037/e492572004-001
13. Schramm E, Zobel I, Schoepf D, Fangmeier TKS, Walter H. Cognitive behavioral analysis system of psychotherapy versus escitalopram in chronic major depression. *Psychother Psychosom*. (2015) 84:227–40. doi: 10.1159/000381957
14. Cuijpers P, Huibers MJH, Furukawa TA. The need for research on treatments of chronic depression. *JAMA Psychiatry*. (2017) 74:242. doi: 10.1001/jamapsychiatry.2016.4070
15. Stulz N, Thase ME, Klein DN, Manber R, Crits-Christoph P. Differential effects of treatments for chronic depression: a latent growth model reanalysis. *J Consult Clin Psychol*. (2010) 78:409–19. doi: 10.1037/a0019267
16. Klein JP, Erkens N, Schweiger U, Kriston L, Bausch P, Zobel I, et al. Does childhood maltreatment moderate the effect of the cognitive behavioral analysis system of psychotherapy versus supportive psychotherapy in persistent depressive disorder? *Psychother Psychosom.* (2018) 87:46–8. doi: 10.1159/000484412
17. Erkens N, Schramm E, Kriston L, Hautzinger M, Härter M, Schweiger U, et al. Association of comorbid personality disorders with clinical characteristics and outcome in a randomized controlled trial comparing two psychotherapies for early-onset persistent depressive disorder. *J Affect Disord.* (2018) 229:262–8. doi: 10.1016/j.jad.2017.12.091
18. Assmann N, Schramm E, Kriston L, Hautzinger M, Härter M, Schweiger U, et al. Moderating effect of comorbid anxiety disorders on treatment outcome in a randomized controlled psychotherapy trial in early-onset persistently depressed outpatients. *Depress Anxiety*. (2018) 35:1001–8. doi: 10.1002/da.22839
19. Serbanescu I, Walter H, Schnell K, Kessler H, Weber B, Drost S, et al. Combining baseline characteristics to disentangle response differences to disorder-specific versus supportive psychotherapy in patients with persistent depressive disorder. *Behav Res Ther*. (2020) 124:103512. doi: 10.1016/j.brat.2019.103512
20. Furukawa TA, Efthimiou O, Weitz ES, Cipriani A, Keller MB, Kocsis JH, et al. Cognitive-behavioral analysis system of psychotherapy, drug, or their combination for persistent depressive disorder: personalizing the treatment choice using individual participant data network metaregression. *Psychother Psychosom*. (2018) 87:1–14. doi: 10.1159/000489227
21. Kocsis JH, Leon AC, Markowitz JC, Manber R, Arnow B, Klein DN, et al. Patient preference as a moderator of outcome for chronic forms of major depressive disorder treated with nefazodone, cognitive behavioral analysis aystem of psychotherapy, or their combination. *J Clin Psychiatry*. (2009) 70:354–61. doi: 10.4088/JCP.08m04371
22. Steidtmann D, Manber R, Arnow BA, Klein DN, Markowitz JC, Rothbaum BO, et al. Patient treatment preference as a predictor of response and attrition in treatment for chronic depression. *Depress Anxiety*. (2012) 29:896–905. doi: 10.1002/da.21977
23. Meyer B, Pilkonis PA, Krupnick JL, Egan MK, Simmens SJ, Sotsky SM. Treatment expectancies, patient alliance and outcome: further analyses from the National Institute of Mental Health treatment of depression collaborative research program. *J Consult Clin Psychol*. (2002) 70:1051–5. doi: 10.1037/0022-006X.70.4.1051
24. Hamilton M. Development of a rating scale for primary depressive illness. *Br J Soc Clin Psychol*. (1967) 6:278–96. doi: 10.1111/j.2044-8260.1967.tb00530.x
25. McCullough JP. Treatment for chronic depression: cognitive behavioral analysis system of psychotherapy (CBASP). *J Psychother Integr*. (2003) 13:241–63. doi: 10.1037/1053-0479.13.3-4.241
26. Schoepf D, Neudeck P. Cognitive Behavioural Analysis System of Psychotherapy (CBASP): a disorder-oriented, theory-driven psychotherapy

method from the "third generation" of behaviour therapy models, designed for the treatment of chronic depression. In: Uehara T, editor. *Psychiatric Disorders: Worldwide Advances INTECH*. (2011). p. 87–120. doi: 10.5772/26058
27. Nemeroff CB, Heim CM, Thase ME, Klein DN, Rush AJ, Schatzberg AF, et al. Differential responses to psychotherapy versus pharmacotherapy in patients with chronic forms of major depression and childhood trauma. *Proc Natl Acad Sci USA*. (2003) 100:14293–6. doi: 10.1073/pnas.2336126100
28. Markowitz JC. What is supportive psychotherapy? *Focus*. (2014) 12:285–9. doi: 10.1176/appi.focus.12.3.285
29. Markowitz JC, Kocsis JH, Bleiberg KL, Christos PJ, Sacks M. A comparative trial of psychotherapy and pharmacotherapy for "pure" dysthymic patients. *J Affect Disord*. (2005) 89:167–75. doi: 10.1016/j.jad.2005.10.001
30. Rush A, Gullion C, Basco M, Jarrett R, Trivedi M. The inventory of depressive symptomatology (IDS): psychometric properties. *Psychol Med*. (1996) 26:477–86. doi: 10.1017/S0033291700035558
31. Beck A, Kovasac M, Weissman A. Assessment of suicidal intention: the scale for suicide ideation. *J Consult Clin Psychol*. (1979) 47:343–52. doi: 10.1037/0022-006X.47.2.343
32. Derogatis LR, Melisaratos N. The brief symptom inventory: an introductory report. *Psychol Med*. (1983) 13:595–605. doi: 10.1017/S0033291700048017
33. Spitzer R, Kroenke K, Williams J, Löwe B. A brief measure for assessing generalized anxiety disorder: the GAD-7. *Arch Intern Med*. (2006) 166:1092–7. doi: 10.1001/archinte.166.10.1092
34. First M, Spitzer R, Gibbon M, Williams J. *Structured Clinical Interview for DSM-IV-TR Axis I Disorders, Research Version, Clinical Trials Version (SCID-CT)*. New York, NY: Biometrics Research, New York State Psychiatric Institute (2002).
35. First M, Gibbon M, Spitzer R, Williams J. *Structured Clinical Interview for DSM-IV Axis II Personality Disorders (SCID-II)*. Washington, DC: American Psychiatric Press (1997).
36. Endicott J, Spitzer R, Fleiss J, Cohen J. The Global Assessment Scale: a procedure for measuring overall severity of psychiatric disturbance. *Arch Gen Psychiatry*. (1976) 33:766–71. doi: 10.1001/archpsyc.1976.01770060086012
37. Duschek S, Schandry R, Hege B. *Soziale Aktivität Selbstbeurteilungs- Skala (SASS). Diagnostik Sozialer Funktionsstörungen bei Depressiven Störungen*. Göttingen: Beltz Test GmbH (2003).
38. Hunt SM, McKenna SP. *The QLDS: A Scale for The Measurement of Quality of Life in Depression*. New York, NY: Health Policy (1992). doi: 10.1037/t66810-000
39. Horowitz L, Strauß B, Kordy H. *Inventar zur Erfassung Interpersonaler Probleme IIP-D-Manual*. Göttingen: Göttingen Beltz – Test (2000).
40. Bernstein D, Stein J, Newcomb M. Development and validation of a brief screening version of the Childhood Trauma Questionnaire. *Child Abuse Negl*. (2003) 27:169–90. doi: 10.1016/S0145-2134(02)00541-0
41. Bernstein DP, Fink L. *Childhood Trauma Questionnaire: A Retrospective Self-Report and Manual*. San Antonio, TX: The Psychological Corporation (1998).
42. Kraemer HC. Discovering, comparing, and combining moderators of treatment on outcome after randomized clinical trials: a parametric approach. *Stat Med*. (2013) 32:1964–73. doi: 10.1002/sim.5734
43. Ninan PT, Rush AJ, Crits-Christoph P, Kornstein SG, Manber R, Thase ME, et al. Symptomatic and syndromal anxiety in chronic forms of major depression: effect of nefazodone, cognitive behavioral analysis system of psychotherapy, and their combination. *J Clin Psychiatry*. (2002) 63:434–41. doi: 10.4088/JCP.v63n0510
44. Manber R, Kraemer HC, Arnow BA, Trivedi MH, Rush AJ, Thase ME, et al. Faster remission of chronic depression with combined psychotherapy and medication than with each therapy alone. *J Consult Clin Psychol*. (2008) 76:459–67. doi: 10.1037/0022-006X.76.3.459
45. Schramm E, Kriston L, Elsaesser M, Fangmeier T, Meister R, Bausch P, et al. Two-year follow-up after treatment with the cognitive behavioral analysis system of psychotherapy versus supportive psychotherapy for early-onset chronic depression. *Psychother Psychosom*. (2019) 88:154–64. doi: 10.1159/000500189

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Characteristics of the Optimal Cognitive Behavioral Analysis System of Psychotherapy (CBASP) Therapist Role

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The characteristics of the optimal CBASP therapist role for the treatment of the Persistent Depressive Disorder patient (chronic depression) is delineated in this paper. This paper contains the opinions and experiences of the creator of CBASP who has developed and revised the model over more than 4 decades. The paper is not a rigorous study nor a review of rigorous studies. The difficulties of the patient are briefly discussed and then the characteristics of the optimal clinical role are presented. The clinical role of CBASP, the only model to have been developed specifically to treat the chronically depressive patient, is unique in the field of psychotherapy. Four role categories describing the behavior of the best therapists are presented and discussed: (1) the therapist is able to enact a Disciplined Personal Involvement clinical role with the patient; (2) the therapist is able to implement an acquisition-learning approach to therapeutic administration; (3) the practitioner is able to adhere to the standards of CBASP technique administration; and finally, (4) the clinician is able to implement several facilitative interpersonal skills.

Keywords: interpersonal psychotherapy, persistent depressive disorder, therapist role, disciplined personal involvement, cognitive behavioral analysis system of psychotherapy (CBASP)

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INTRODUCTION

Becoming a successful CBASP psychotherapist is not a simple undertaking. The reasons are two-fold: first, the early-onset Persistent Depressive Disorder patient (PDD) (1) presents unique and difficult challenges to practitioners, and secondly the CBASP clinical role is qualitatively unique given its combination of techniques and therapist role requirements. Chronic patients are difficult because of the entrenched cognitive-emotional-behavioral patterns many patients bring to treatment. They orbit in a trajectory of overlearned interpersonal-avoidance due to toxic developmental histories. Secondly, the patient's unique pathological and long-standing disorder requires practitioners to actualize a personal relationship that seeks to modify a primitive lifestyle. CBASP practitioners are trained to enact a clinical role which adds a "humanizing experience" to the patient. They become personal comrades to individuals who, more than likely, never had one—a friend-relationship where trust, support, and caring characterize the encounter. This clinical role, labeled *Disciplined Personal Involvement*, sets the CBASP therapist role apart from many other therapist role models in the field today. Other therapeutic models traditionally require clinical role behavior that precludes personal involvement. Personal attachments with patients have been labeled taboo or verboten (2, 3).

For almost half-a-century, I have studied the taxonomy of chronic depression and treated the chronically depressed patient—even before we had a diagnostic category to describe this disorder (4). As a university faculty member, I studied and focused on the treatment of chronic depression for almost fifty years. Participating in four national clinical trials conducted at 12 university sites, I served as Principal Investigator for my site as we randomized 2,200 chronically depressed outpatients in medication and psychotherapy investigations. In one trial, we reported the highest response rates ever recorded for the PDD-D patient (77%) in the combination CBASP and medication cell (5). In addition, I've treated ∼450 PDD outpatients in my career (6), and I was secondarily involved in the mood disorder revisions in *DSM-5* (1) where the first chronic depression category appeared as an independent taxonomy. PDD was no longer classified in *DSM-5* as a "specifier" for major depression. Lastly, I created the only psychotherapy model, Cognitive Behavioral Analysis System of Psychotherapy (CBASP) (6–10), that was developed specifically to treat the PDD disorder. Over the years, I have trained hundreds of professionals to administer CBASP. Retiring in 2017 from Virginia Commonwealth University, I feel qualified to comment below on the optimal characteristics of successful CBASP psychotherapists. I turn now to the early-onset PDD patient who, as stated above, is one of the most difficult outpatients we see in clinical practice.

THE PERSISTENT DEPRESSIVE DISORDER-DYSTHYMIA PATIENT

Social Dysfunction

During the training workshops I have conducted over the years, I asked the participants to list the characteristics that describe the early-onset PDD-D patients they have treated. The list frequently includes most of the following features (6):

- Traumatic developmental history involving either sexual, physical, and/or emotional abuse, or physical or emotional deprivation
- Little to no motivation to change one's behavior
- Pervasive social avoidance
- Generalized interpersonal withdrawal and detachment
- Thinks and talks in a primitive-illogical manner about interpersonal relationships
- Unable to generate interpersonal empathy
- Anger toward one or more significant others
- Overwhelming feelings of helplessness and hopelessness
- Generalized pessimistic view that nothing can ever be different
- Pervasive feelings of inadequacy
- Feeling guilt about the state of one's life
- Behavioral passivity
- Pervasive negativity
- Feeling unlovable and that no one could ever care for one
- Generalized feelings of being a failure
- Strong expectancy of interpersonal rejection
- Suicidal ideation that may also include actual suicide attempts

Sitting with a patient who embodies these characteristics pulls predictable interpersonal and counter-transference reactions from many psychotherapists (6). Workshop participants who have treated these patients have no difficulty listing the effects patients have on them:

- A noticeable feeling of interpersonal loneliness
- Feelings of incompetence and hopelessness when patients continue to complain that nothing they do matters
- Feelings of being "put in a rejection box" and interpersonally pushed away by the detached style of the patient
- Feelings of being frustrated and angry by the person's apparent lack of any motivation and by their pervasive interpersonal avoidance patterns
- Becoming tired, drained, and worn out—feeling that I am trying to pull a "dead weight" during the session
- "I want to quit seeing this individual and must force myself to continue treatment"
- "When patients tell me that no one likes them, I think they are correctly reading others—no one could like them!"

Etiology of Early-onset PDD

Etiological events in the histories of PDD patients derail normal social-emotional maturational development and entrap the child and adolescent in a preoperational state of development (11). All of the following clinical researchers [e.g., Spitz (12), "failure to thrive" researchers (e.g., (11, 13–17)), "paroxysms" which disrupt normal cognitive development] suggest that excessive emotionality, adverse familial circumstances of long duration, and severe neglect or trauma may interfere with normal cognitive-emotional maturation and physical development. Such events may also derail or retard normal developmental processes. A child's living environment, when it becomes an obstacle course with no resolution, inhibits normal growth and maturation. One characteristic of maturational derailment is suggested when adult PDD patients report an early-onset Dysthymia condition co-morbid with the chronic depression diagnosis (6, 10, 18). Under such circumstances, surviving the "hell of the family," not normal growth-directed behavior, becomes the child's only developmental goal (19). The hallmark emotions of chronic depression—helplessness and hopelessness—are appropriate and valid symptoms associated with a familial world that offers "no exit" (20). The categories of maltreatment often reported are *emotional mistreatment*, *parental loss*, *physical abuse*, *sexual abuse,* and *physical neglect* (21, 22). Frequently, early-onset patients bring the "results" of a catastrophic developmental history into treatment and present a difficult challenge to psychotherapists (e.g., extreme interpersonal detachment and withdrawal; pervasive withdrawal in interpersonal challenges, etc.).

Preoperational Functioning Among Early-onset PDD Adults

A unique picture of psychopathology unfolds as one listens carefully and observes the way chronic patients talk and behave. The individual is isolated interpersonally, talks in a monologue manner using a well-rehearsed script of rejection, and lives in

quiet despair within a self-contained world that is not informed by external influences. Nothing new enters and nothing leaves this phenomenological orbit. The patient presents with a terrible sense of "sameness." Existentially, the patient describes a lifestyle where time appears to have stopped—*the present reflects the past and the future bodes only more of the same.* (9) labeled this temporal outlook as a "snapshot view of reality." These internal snapshots of rejection and hurt are *freeze-framed* in the patient's brain as evidenced by the chronicity of the PDD disorder (6, 19).

Piaget's (11, 23, 24) second structural stage of maturational development, *preoperational functioning,* appropriately describes the cognitive-emotional functioning level of many early-onset PDD patients. The patient is dominated by the immediacy of experience. (a) Patients think in a *precausal* and *prelogical* manner, drawing conclusions about the external world, jumping from a premise to a conclusion without any hypothesis testing—the external world of others is the way it is simply because patients believe it to be so. Reasoned viewpoints of others have no informing effect on this entrenched perceptual outlook. The logical and causal strivings of therapists, at least at the outset of treatment, usually fail to modify this primitive cognitive outlook. An example of such illogic is illustrated in one adult patient's report concerning her experience at a company picnic:

> *Patient: Company photographer didn't take my picture at the company picnic. He took Susan, Jane, and Phyllis' pictures but not mine. He didn't take my picture because he doesn't like me.*
> *Therapist: Did you ask him to take your picture?*
> *Patient: It wouldn't have mattered. He would not have done it because he doesn't like me.*
> *Therapist: What evidence do you have for this assumption? How do you know he doesn't like you?*
> *Patient: I've never asked him. I don't have to. I just know he doesn't like me.*

(b) A pervasive *egocentric lifestyle* also characterizes the patient. All roads lead to the self. When listening to new patients' verbalizations, one rarely hears comments that shift the attentional focus away from *I, me,* and *my.* (c) Another preoperational characteristic is the inability *to generate interpersonal empathy.* Emotional sensitivity to interpersonal rejection must not be confused with empathy. Empathy generation requires abstractive ability and the beginning patient does not possess this in the interpersonal-social realm. Abstractive thought or the ability to disengage from the present situation and take a step back to consider alternatives is not an option.[1] Adept CBASP therapists will produce an observable maturational shift in cognitive-emotive functioning over the course of treatment that will enable the person to gain control of the PDD condition and move toward remission and maturity.

(d) The ability *to regulate one's emotional life* is non-existent at therapy outset. Emotional regulation requires the presence of an abstractive capability which the preoperational patient does not possess. As suggested above, to overthrow the "snapshot view of reality" requires the individual to be able to perceptually disengage from the immediacy of the moment and consider alternative strategies in a planful, problem-focused manner (25).

CBASP therapists move their patients from preoperational levels of functioning to formal operational (abstractive) levels by systematically exposing them to in-session behavioral consequences. Maturational shifts in treatment are well-documented in the Piagetian therapeutic literature [e.g., (26, 27)]. The CBASP construct of *perceived functionality* denotes this acquired maturational shift when the patient can identify the environmental consequences of their behavior—the attainment of *perceived functionality* suggests that the individual has reached a formal operations level of thinking.

Summarily, the etiology and preoperational levels of functioning make the PDD patient a significant and unique challenge. The refractory nature of the disorder, the etiology of a prolonged and toxic developmental upbringing which has produced a maturational derailment, the interpersonal fear-avoidance of the patient due to a history of maltreatment, the perceptual disconnection from one's social-interpersonal environment which inhibits the possibility of behavioral change, taken together, require a *clinical role* qualitatively different from the traditional roles. To say that the PDD patient is different vis-a-vis other patient types is an understatement! The patient *IS* different and, put in more frank terms, the early-onset, adult PDD patient enters psychotherapy functioning at the cognitive-emotional maturity level of a 4–6-year-old child. The most outstanding CBASP therapists appreciate the immaturity of this patient and do not overestimate the learning potential of the patient; instead, they adjust their teaching behavior accordingly.

OPTIMAL THERAPIST ROLE CHARACTERISTICS

The best and most effective CBASP psychotherapists I've worked with over the years evince characteristics that fall into four general categories: (1) Able to enact a Disciplined Personal Involvement clinical role with the patient; (2) Able to implement an acquisition-learning approach to therapeutic administration; (3) Able to adhere to the standards of CBASP technique administration; (4) Able to implement several facilitative interpersonal skills.

Able to Enact a Disciplined Personal Involvement Clinical Role

Disciplined Personal Involvement [DPI: (10)] is based upon the Kieslerian concept of interpersonal interaction (28–30). Therapists who master DPI create salubrious *person* [therapist] x *person* [patient] interactions with patients in all that they do. Perceiving relationships through an interpersonal lens requires these practitioners to implement an extreme *empathetic perspective.* From the clinician's perspective, there is always a reciprocal relationship between speaker and hearer from the first moment a patient steps into the office. But, at the outset of treatment with the chronically depressed preoperational patient, it is the therapist who works from this empathic

[1]Many patients are able to function abstractly in their professional capacity—sometimes brilliantly; however, this skill is not operative in their social-emotional interactions.

perspective—not the patient. However, by the end of treatment, the generation of empathy will become a reciprocal activity for both, because the patient will have learned from the therapist how to function empathically.

DPI also requires that one becomes adept at using the Impact Message Inventory (IMI) (28–30), an empirical instrument that measures the intensity of the impact messages of the patient. The best CBASP therapists are able to interpret the interpersonal "impacts" patients have on them, they are able to diagnose the interpersonal functioning of the patient from these impact messages and ultimately, they use this impact message information to teach patients to behave with them and others in more adaptive ways. Information describing how CBASP therapists utilize the IMI during therapy may be found in McCullough [(10), pp. 23–30]. These practitioners always directionally begin their in-session work *from themselves outward to the patient*—meaning they introspectively know the patient's impacts on them before they take the next step in the session.

The DPI role in CBASP is also the most misunderstood component of the model and the best CBASP therapists avoid misunderstanding DPI. What is meant here is that many CBASP-trained clinicians continue to speak of DPI as a "technique" to be administered. For example, some will say, "I am now doing DPI." DPI is *NOT* a technique! Rather, it describes *the way* CBASP therapists always relate interpersonally to patients. *DPI is a clinical style to be lived out in the session with the chronic patient.* Relating to the individual in a DPI style is directly related to achieving the first goal of CBASP—that is, the creation of *felt dyadic safety* within the relationship. Patients entering treatment and who report an abusive history as children are fearful and avoidant of interpersonal engagement, opting to remain inhibited and withdrawn. The DPI style denotes one's willingness to be a comrade with a person who, more than likely, never had one. It does not mean that therapists and patients become drinking buddies, business partners, date, sleep together, share gossip, meet for coffee after work hours, or become chat room pals. Rather, personal involvement describes the optimal practitioner's style that is grounded upon the well-established learning principles of Skinner (31, 32). This style is used to choreograph personal reaction contingencies (personal responsivity) in the session so patients learn new associations. In choreographing in-session learning contingencies (of which more will be said in a moment), the personal involvement style also utilizes Albert Bandura's concepts of imitation learning and modeling (33). Bandura notes that in many languages, the word for "teach" is the same as the word for "show," and the synonymity is literal in DPI.

Becoming an *authentic practitioner* of DPI is only learned through intense training and supervision. Most optimal CBASP practitioners had to un-learn many professionally trained behaviors that taught them to maintain interpersonal distance. These habits were replaced with more reciprocally interpersonal DPI patterns which they mastered.

Several personal requisites which the best CBASP therapists exhibit are discussed below. (1) One must know oneself emotionally. *Emotional maturity*, sometimes achieved by CBASP psychotherapists through a personal therapy or clinical supervision, is a *sine qua non* requirement for DPI administration. This includes being aware of one's interpersonal and cognitive reactions to patients, being able "to track" (self-monitor) one's feelings and thoughts moment-to-moment during the session, and possessing the skills to impart these reactions in ways that facilitate the patient's well-being. Having the skills to identify the interpersonal impacts patients have on practitioners (28–30, 34) enables the individual to utilize these impacts via verbal and non-verbal feedback in a disciplined and salubrious way. (2) The second requisite is *giving oneself permission to be oneself with the patient.* Psychiatric and psychological clinical training rarely teach trainees to utilize their emotions with patients. Often, the only trainee-emotions acceptable to supervisors and attendings are *acceptance* and *empathy*. The novelty of CBASP training is that participants are told frankly that they may be themselves with patients, and they are rigorously taught how to use their emotional and cognitive reactions in contingent ways. The difficult hurdle comes next—*they must then give themselves permission to be themselves with patients.* Master CBASP therapists have actualized the self-permission step with aplomb.

(3) *One must overcome the fear of hurting patients by being oneself.* Since all of us have been trained under the aegis of the personal involvement taboo, most don't know what will happen if they disclose something personal to patients. Many professionals I've trained are frankly afraid that expressing personal reactions in contingent ways will hurt patients and jeopardize their effectiveness. There are also some practitioners who for various reasons don't want to disclose or express their emotions—DPI is clearly not for them. Optimal CBASP practitioners who have taken the risk and are able to utilize their patient reactions in contingent ways have discovered that DPI is a robust vehicle for modifying maladaptive behavior. (4) Lastly, *the core word in DPI is "disciplined."* The *cardinal rule* of DPI is that one must never do anything to hurt the patient. The well-being of the patient is primary! CBASP therapists pay close attention to any negative side effects that may accrue from their interventions. I have never known of a case where a successful CBASP practitioner willfully damaged the patient. Conversely, utilizing DPI that offers patients a counter-conditioning relationship with a thoughtful and non-maltreating human being is facilitative and salubrious. Most preoperational patients must be taught to relate interpersonally. The learning is best imparted in the trenches of interaction with a personally involved and disciplined CBASP teacher.

Able to Implement an Acquisition-Learning Approach to Therapeutic Administration

CBASP is an operationalized model of psychotherapy and the two major operationalized goals of treatment, *felt dyadic safety* and *perceived functionality*, must be acquired over the process of therapy. CBASP measures in-session learning as a primary means for determining treatment effectiveness. The major acquisition learning assumption is stated in the following manner: *If one learns what the CBASP model teaches, disorder management will be achieved* (6, 10). This assumption is illustrated in the

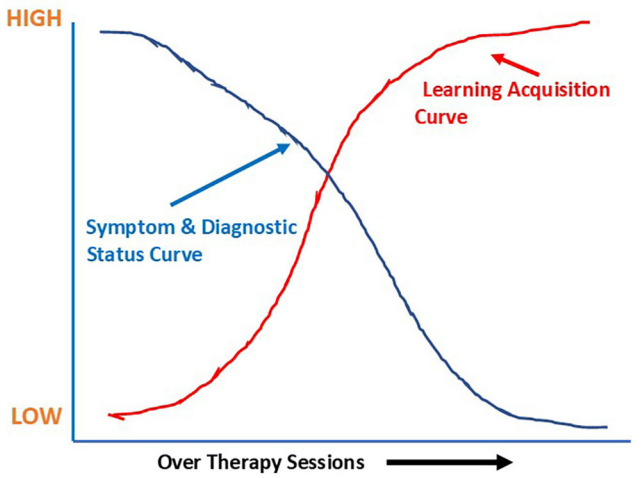

FIGURE 1 | CBASP acquisition learning and symptom assumption curves shown in a hypothetical design space.

hypothetical design space shown in **Figure 1**. **Figure 1** illustrates what happens to the symptom measures when patients learn the tasks of treatment.

Figure 2 illustrates data taken from the case of Sandra where she performs to criterion the two major learning goals of treatment (i.e., achieving felt *dyadic safety* with the IDE and achieving *perceived functionality* with the SA), and we observe a progressive decrease in one symptom measure [i.e., Beck Depression Inventory-II (35)].

One word of caution must be stated here. It is the author's firm belief that early-onset PDD is *never* fully cured. CBASP therapy is an endeavor striving to educate patients how to manage a lifetime disorder. Various forms of maintenance treatment will also be required after the weekly sessions end [e.g., (18, 36–38)]. Patients should be informed from the outset that their disorder is not curable but highly manageable (6); the lessons learned in psychotherapy, if one is to avoid further periods of depression, must be practiced daily for the remainder of one's life. PDD falls into a category similar to two other lifetime disorders: namely, *diabetes mellitus*, a metabolic disease produced by a systematic failure to adequately regulate blood sugar levels, and *hypertension*, a cardiovascular chronic medical condition in which the systemic arterial blood pressure is elevated. Both these physical disorders can be controlled and maintained by proper prophylactic behaviors—so can chronic depression. Failure to practice good preventive maintenance after treatment ends may lead to death in the case of the two physical disorders and to relapse and recurrence in the case of chronic depression. Achieving criterion performance with the two goals of treatment and generalizing the in-session gains to the daily living arena launch the patient into the post-therapy phase.

The Two Goals of CBASP Therapy. Premier CBASP practitioners approach their cases as learning endeavors and define their clinical role as "teachers." The prediction stated above that mastery of the goals of CBASP resolves the chronic disorder needs to be elaborated. The prediction suggests that the psychopathology of early-onset PDD is maintained because of two problem-variables addressed by the two major counter-conditioning treatment goals of CBASP.

The first treatment goal involves (1) *teaching the patient to experience "felt safety" with the clinician, meaning that patients acquire the ability to successfully discriminate the clinician from maltreating significant others.* Bouton (39) argues that when behavioral avoidance is present, fear is motivating it. The patient's interpersonal avoidance has long been conditioned by a fear of interpersonal encounter. The fear is well-learned and derives from a toxic family arena where significant others have hurt the patient. This fear and the subsequent social avoidance that accrues, taken together, prevented the individual from participating in normal adolescent social encounter which is a requisite for normal teen-age development. The inability to have learned the social lessons of adolescence due to interpersonal avoidance have come at a high price; it has left the patient unable to function adaptively with others. The interpersonal fear-avoidance is addressed in the first goal. The therapist, actualizing the DPI relationship and specifically teaching the person to correctly self-administer the Interpersonal Discrimination Exercise (IDE) (6, 10), teaches the individual to discriminate between maltreating significant others and the practitioner. Criterion performance in the self-administration of the IDE suggests that the creation of a *felt safety zone* has been achieved within the session—the first goal in successful CBASP therapy. More will be said about the IDE in the techniques section to follow.

The second problem-variable is addressed by the second treatment goal. The goal is stated as follows: (2) *Patients must learn to recognize the interpersonal consequences of their behavior as evidenced by the correct self-administration of the Situational Analysis (SA) exercise.* The achievement of the criterion performance in the self-administration of SA is labeled *perceived functionality*. As noted previously, an early maltreatment history exerts pernicious social effects on the patient. Patients, to survive the hell of the family and for self-protection, perceptually disconnect themselves from others to avoid hurtful social encounters. They erect interpersonal walls of isolation behind which they live in solitary confinement. *The most disastrous result of this self-protectionist strategy is that the chronic patient's perceptual disconnection from the social environment effectively removes the person from the social arena and precludes one from being informed by interpersonal feedback.* In short, the person now lives without a social environment. The environment has lost its shaping power to influence and left the individual in a trajectory of "isolated sameness." One consequence is that the perception of TIME stops for the patient as the *present* denotes only a replay of the *past* and the *future* bodes only more of the same. SA is designed to perceptually connect CBASP patients with their social environment so that interpersonal feedback can begin to shape behavior. This *person x environment* connection must occur first with the clinician. *Perceived functionality* means that the person x environment connection has been achieved. More will be said about SA in the techniques section to follow.

Summarily, good CBASP therapists are able to establish an arena of dyadic felt safety and perceptually connect their patients

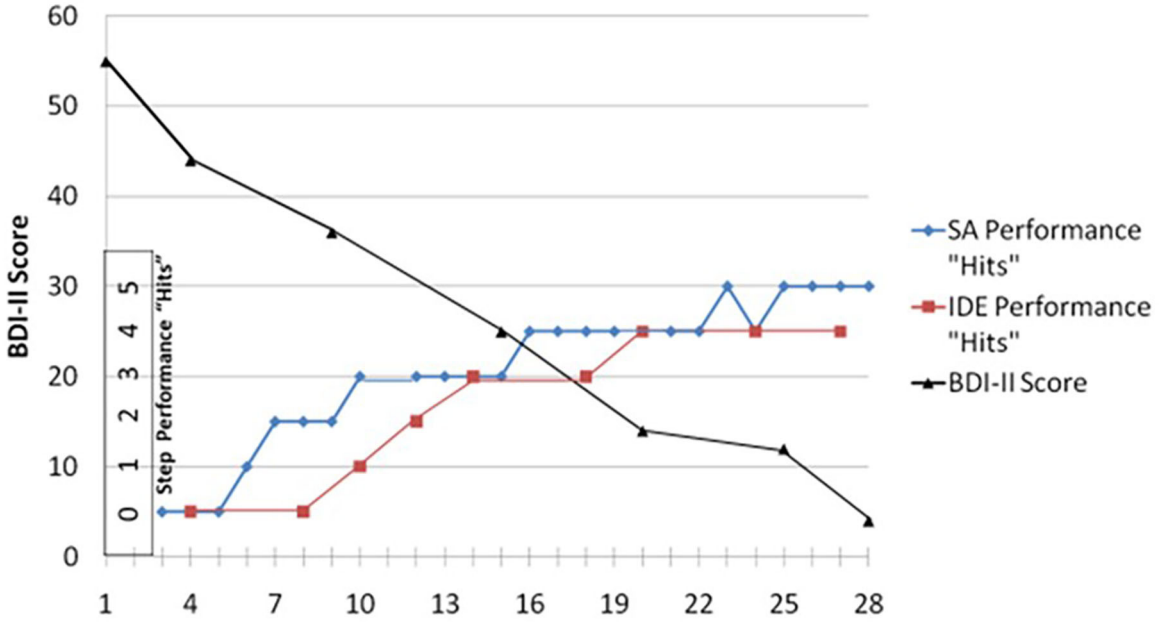

FIGURE 2 | Sandra's BDI-II scores "averaged" every fifth session: her SA step performance "hits" using the Patient Performance Rating Forum; and her IDE step performance "hits" using the IDE-Rating Forum. Both were rated by a clinical rater.

to themselves and others. With interpersonal fear now pushed aside, avoidance is diminished, and the patient is better equipped to learn the lessons of CBASP.

Able to Adhere to the Standards of CBASP Technique Administration

In this section, the techniques described will be the Significant Other History (SOH), Transference Hypothesis (TH) construction, the Interpersonal Discrimination Exercise (IDE), and Situational Analysis (SA). The best CBASP practitioners I've known become artists when it comes to administering these techniques. Relying on the clinical role of Disciplined Personal Involvement (DPI) and with a sound knowledge of the methods, they administer the techniques the way they were designed to be administered. These clinicians always remain cognizant of the two goals of the model which are the creation of in-session dyadic safety and secondly, helping patients learn to recognize the consequences they produce on the therapist as well as on others. The best practitioners I've worked with have also learned "to rely" on the model procedures to do the essential work of treatment.

This point cannot be made strongly enough: Administering a case and relying on the techniques of CBASP and its approach to PDD psychopathology is very different compared to working with the chronic patient and relying on other personal strategies of change such as being a caring personality, being empathic and nurturant, and providing unconditional positive regard. Not only is the DPI clinical role lost in the administration of these alternative approaches, acquisition learning and the focus of treatment are also compromised as they subtly shift the focus of the consequation of patient behavior, the main focus of treatment, to other personal role activities.

a) Significant Other History (SOH). Capable CBASP therapists use the SOH to elicit information identifying the patient's early abuse history and the maltreating significant others who administered the abuse. *Significant Others* denote the major players in the patient's life, persons who have influenced the individual to be who they are or informed the direction their life has taken. The SOH is administered in the second session. Developmental events with toxic significant others shape expectancies about what is likely to happen in psychotherapy. Knowledge of these negative injurious patient expectancies enables clinicians to identify potential relational *hot spots*. CBASP practitioners, who use the SOH wisely, become cognizant of the historical factors that contribute to the PDD disorder and, using this information, they avoid interpersonal rupture events that may fatally undermine the dyadic relationship.

An example will illustrate this point. A CBASP trainee, Tom, was overly helpful to everyone and always extended himself in nice gestures to patients and colleagues alike. Tom began his first session with a 21-year-old female patient. He was making coffee and when the patient entered his office, he offered her a cup of his newly brewed café-au-lait. The offer was extended with his usual kind demeanor. The sexual abuse history of his patient was not known to Tom. Her biological father had engaged in sexual relations with her for several years. The father, always when his wife was absent from home, would become very nice and solicitous of her needs, and then would begin his sexual advances which always ended in intercourse. The kind actions of Tom awakened her learned expectancy of what was coming next—she bolted from the room. Luckily, she returned to treatment and

Tom then understood what precipitated the departure. Behaving in his usual kind way, without benefit of the SOH, had had disastrous effects. With the SOH, good CBASP therapists do not "fly blind" with patients.

The interpersonal core fears of patients are identified with the SOH. Patients often enter treatment fearful of specific negative reactions from therapists when they behave in certain ways. The SOH pinpoints many fearful expectancies which may occur in four domains. The domains are the following: (1) *relational intimacy*; (2) *behavioral disclosures* of needs or highly personal content; (3) *mistakes* the patient makes during treatment; and (4) *negative emotions* patients feel toward therapists. To identify the most salient core fear, skilled CBASP clinicians identify the dominant domain that emerges as they proceed through the significant other history list. The interpersonal expectancy is that their clinician will react like hurtful significant others did (note the above example with Tom).

b) Transference Hypothesis Construction (TH). Excellent CBASP therapists productively use the recommended number of TH interventions in about 30% of the sessions (40) to help patients make an interpersonal discrimination between maltreating significant others and themselves. After reviewing all the information derived from the SOH in session two, practitioners construct a one-sentence TH. The sentence makes explicit the patient's core fear event and what consequences are likely to follow if this event occurs in the session. For example, if the "relational intimacy" domain is implicated as the salient core fear, the TH might be the following: *If* I (Joe, the patient) become interpersonally close with Bill (my therapist), *then* Bill will begin to point out my mistakes and weaknesses and tell me what a loser I am (the way my significant other *father* did). Notice that the TH sentence first identifies the fear event (relational closeness), and then spells out the expected consequence (derision and rejection). Whenever interactions enter the "relational intimacy" domain specified by the TH, the most effective CBASP clinicians will know that they are in *hot spot* territory. The patient will then be asked to discriminate between the consequences that accrued with *father closeness* and then the consequences of the closeness with the therapist. This task brings us to the next technique, the Interpersonal Discrimination Exercise (IDE), which is related to the first goal of CBASP (i.e., creating a dyadic safety zone).

c) Interpersonal Discrimination Exercise (IDE). The IDE is designed to interrupt the patient's orbit of "sameness" and focus the person's attention on the novel behavior of the practitioner. In the beginning of treatment, the behavior of clinicians is mistakenly perceived as being no different from that of maltreating significant others. This misperception must be revised, and optimal CBASP therapists use the IDE as the corrective tool.

The IDE, administered as the clinician and patient enter a *hot spot* zone, is a four-step exercise that asks four questions in this order:

- *What would your significant other (SO) have done when you said or did this? (core fear event)*
- *What did I just do when you said or did this?*
- *Now, compare and contrast my behavior with that of your SO.*
- *If I turn out to be different than your SO(s), what are the implications for you in this relationship?*

Patients learn to self-administer this four-step discrimination exercise without assistance from the clinician. Mastery of this goal is designed to drive a perceived wedge between the behavior of toxic significant others and the therapist. If the discrimination is not made explicit using the IDE, PDD patients will not make these distinctions. Acquiring these discriminations is not easy and requires repeated IDE trials. It cannot be achieved in one administration of the IDE. These erroneous perceptions are so entrenched in the brain's "granite memory system" that in 2000 (p. xxiv), McCullough wrote a description of what modifying them is like:

> *Treating the chronically depressed adult, dislodging the refractory cognitive-emotional and behavioral armor that is the disorder, is analogous to breaking through a granite wall using a ten-pound sledgehammer. One hits the wall repeatedly in the same area with little or no effect until, almost imperceptibly, a slight hairline crack appears. Under continuous pounding, the crack gradually enlarges until, finally, the wall breaks and crumbles.*

As noted earlier, the goal of IDE mastery and the first goal of CBASP is the creation of felt safety on the part of the patient. Able CBASP clinicians utilize the IDE to help patients extinguish these confining perceptions of the way life has had to be and frees them, in a safe interpersonal arena, to learn how to behave within new horizons of interpersonal relationship.

*d) Situational Analysis (SA).*Situational Analysis, a five-step exercise that patients will learn to self-administer, is designed to achieve the second goal of CBASP. That goal is to perceptually connect patients with their social environments so that the way they behave is informed by the therapist first, and then by others. In contrast to the operant functional analysis of behavior methodology (41, 42), SA teaches patients to cognitively identify/recognize the consequences of their behavior in contrast to the identification of behavioral consequences achieved through experimental reinforcement manipulation. The SA exercise also keeps patients in a *participant role* instead of talking about themselves in an observer role. The SA exercise is also the most difficult CBASP technique to learn. I have not seen many CBASP practitioners perform the exercise to perfection. When able clinicians administer SA correctly, it becomes high drama in the session as patients begin to learn that their behavior has consequences.

At the outset of treatment, most PDD patients do not understand that they produce the misery of which they complain because they are not social-interpersonal abstract thinkers. SA is designed to demonstrate tangibly in the session the consequences of behavior. Therapists do not talk about what patients do nor do they cajole the person into behaving otherwise; clinicians do not use logic to suggest alternative strategies, and they do not verbally punish the individual for behaving foolishly. SA is a learning exercise *that shows, illustrates, and demonstrates* visibly and auditorily the interpersonal consequences of one's behavior. Chronic patients can "talk about" themselves from an observer perspective forever and never change anything.

Therapists who ask observer questions keep the patient in a non-participant "neutral holding pattern," and the best clinicians know that observer questions are a waste of time for this patient. Examples of some observer questions which preclude one from having to participate in behavioral consequences are the following:

- *"How are you feeling right now?"*
- *"Why do you think you did this?"*
- *"Why do others react to you this way?"*
- *"What do you think your stimulus value is right now?"*
- *"What does the other person make you want to do?"*
- *"Why do you want to do these things?"*
- *"What effects do you have on others?"*
- *"What were you feeling when you did this?"*
- *"How might you behave differently?"*
- *"How did Patricia make you feel?"*
- *"Why do you think you stay depressed?"*
- *"Do you ever want to change and do things differently?"*
- *"Where did you learn to behave this way?"*

Optimal CBASP clinicians who administer treatment from a DPI perspective maintain a high-level of personal encounter, do not ask patients to "talk about" themselves, and potentiate participant encounters with SA. They are also mindful that the preoperational patient is easily confused with too much information at one time. That is why the best CBASP therapists keep SA simple and the patient highly focused during the exercise. Good therapists want their patients to learn to self-administer SA, that is why their administrational simplicity is so prominent. Watching these practitioners work is observing an art form taking shape. From personal experience over the years, the more the author has administered SA, the simpler his exercises have become and the more he highlights behavioral consequences.

The SA methodology teaches global-thinking patients to focus on one problem at a time. Many begin treatment complaining that they have so many problems, they don't see how focusing on one will do them any good. Despite this protest, patients learn to describe one situational event *(a slice of time)* occurring between the patient and another person (Situational Description: Step 1). The event must have a discrete beginning point in time, an endpoint that can be behaviorally observed, and some brief story in between. Next, one to three *interpretations* are requested which expose what the event meant to the individual. The interpretations or reads must be stated in one brief sentence (i.e., The event meant "blank") (Interpretation: Step 2). Third, patients describe how they behaved in the interpersonal situation (i.e., tone of their voice, their non-verbal expressions, the actual words they said, etc.) (Behavioral Description: Step 3). Fourthly, the individual, in one sentence, describes the endpoint or how the slice of time turned out. This step is called the Actual Outcome or the situational consequence (Actual Outcome, AO: Step 4). The final step asks patients to state in one sentence, how they would have liked the situation to have turned out. This step is called the Desired Outcome (DO) and in SA, the DO becomes the *situational goal* and *motivational component* of the exercise (Desired Outcome: Step 5). Many patients, having never thought about what they wanted nor set their desires as a behavioral goal, need considerable assistance in the beginning to construct a DO sentence. Patients are encouraged to frame the DO as something they could have done or said and avoid positing a DO in the social environment (e.g. *"I wanted her to like what I had done"* vs. *"To ask her if she approved of my behavior."*).

Desired Outcomes are rarely achieved in early SA administrations; rather, mismanaging interpersonal situations and not achieving one's DO are usually the norm, and this pattern becomes evident during the exercise. *Remember the goal of SA: to illustrate to the patient the consequences of their behavior.* Patients, in being bound within the slice of time and not allowed to move into global thinking (e.g., "No one likes me;" "Nothing will ever work out for me;" etc.), have to confront their cognitive and behavioral errors (in the presence of the therapist) that resulted in a poor Actual Outcome—and one that was not equivalent to their DO. Said another way, they didn't get what they wanted when the AO $\neq$ DO. Rarely has the patient ever confronted the consequences of their behavior, particularly when the consequences were not desirable. It is an anxiety-evoking experience but sets the motivational wheels in motion for change. SA leaves the burden of change in the patient's court. If they want to achieve their DOs, they will have to change their behavior. If nothing changes, then their DOs remain unattained—not a pleasant state-of-affairs. Exceptional clinicians can tolerate high levels of patient anxiety and by not decreasing patient discomfort with reduction strategies (e.g., "You'll do better next time," etc.), the stage is set for the patient to reduce their own anxiety by enacting more adaptive behavior.

Over time, patients learn to work within the small "slice of time" by using abstractive thought. For example, they begin to think *about* alternative things they could have done. They must think *about* what they want. They must think *about* others in realistic ways. They must *evaluate* their problem-solving efficacy in the slice of time and *self-correct* their mistakes. All these strategies require abstractive thinking—an ability the patient did not possess when therapy began. As they move toward mastery of SA, they look at themselves, others, and their social environment in alternative ways—all this entails abstractive thought. The upshot is that new interpersonal possibilities are now open and can be seriously considered. This new thinking counters the old negative preoperational thinking (i.e., *The way it is, is the way it must be*).

Able to Implement Several Facilitative Interpersonal Skills

a) *Introduction.* Over the years, the best CBASP psychotherapists I've observed move from session-to-session almost seamlessly and always appear to react to patients in appropriate ways. They are also keenly aware of what's happened between themselves and the patient in previous sessions which enhances the continuity of treatment—they "bridge" the past with the present with little effort. These

individuals choreograph contingencies to reinforce adaptive behavior when it arises—they just seem to know when the patient has made an adaptive move even when the behavior might appear to others small and insignificant. They catch it, make the behavior explicit and consequate it with reinforcing acknowledgment! In addition, they have a solid grasp of where patients are in terms of the CBASP learning goals and what steps in the IDE and SA need extra attention. Knowing the personal idiosyncrasies of the patient and where the end-goals of the case are, where the process of therapy stands in the present, and how much remains to be done to reach the goals of treatment characterize the work of optimal practitioners. These individuals actualize skills that I, frankly, do not know how to teach. Where does this quality performance come from? I cannot say it comes from clinical experience because I've seen seasoned veterans who do not achieve this quality in their work—they may be quite good and successful with chronically depressed patients, but there is a difference in their work-quality and it is observable.

b) *Authentic Disciplined Personal Involvement.* Some CBASP therapists I have known are *authentic* human beings. That is, they are real and genuine persons who don't practice psychotherapy *playing out* an interpersonal role that is not who they are. I've heard patients describe such individuals this way: *"What you see is what you get."* They don't have to be nice; they don't have to be accepting, caring or nurturing; but they can be nice, accepting, caring and nurturing if it's in the best interest of patients. They are themselves with patients, and, over the course of therapy, patients learn to relate to an honest and genuine human being who doesn't play professionally-learned therapy games. I once knew a practitioner who threw up in his office trash can in full view of the patient. I asked him why he didn't excuse himself and go to the bathroom. He told me that the patient had just disclosed a horrific sexual abuse story that nauseated him. He wanted the patient to see, first-hand, his reaction to what had happened to her.

c) *Exceptional CBASP clinicians feel comfortable with the chronic condition.* Not everyone works well with chronic conditions. Some like quick change and feel most comfortable moving on to the next thing. This is not possible for those who treat the early-onset PDD patient. Nothing changes quickly. Therapy moves slowly, new learning is acquired sluggishly, old perceptual and behavioral habits die hard, and clinicians must be willing to remain in the trench for the long haul. The best therapists are patient and understand the slowness that new learning requires and how much time it takes to achieve the extended processes of extinction. "Start and stop, start and stop and then, begin again"—it is an apt description of the challenge clinicians face who treat the chronic patient. Feeling comfortable with everything that working with chronicity entails, being able to tolerate the frustration and disappointment with patient failures all the while continuing to remain hopeful is only for a few courageous souls. I can spot those who feel comfortable with the chronic individual by the way they talk about patients. They evince patience and an explicit understanding of what is required to modify refractory behavior. Quite frankly, they are as tough as their patients are.

d) *The best therapists "trust" in the CBASP methodology.* This characteristic does not mean the person is "slavish" when it comes to the rules of technique administration. It means that the CBASP technique protocols will be administered by the "spirit of the Law" and not by the "letter of the Law" and the rules will be tailored to the patient's idiosyncrasies. The CBASP guidelines for technique administration provide a reliable roadmap delineating what needs to be done first, second, and so on, and optimal therapists count on the technique roadmaps for strategic direction. I've listened to many non-CBASP clinicians talk about treating chronic patients. They frequently talk like they have to start over with each new case—they have no proven process precedents to rely on, to fall back on, and to guide them. The exceptional CBASP therapist knows where to start, what must be done, and what the end-point goals are. There is no starting over with a new case. The CBASP roadmap protocol spells out the therapy trajectory and practitioners trust the map for guidance over the twists and turns of the case.

e) *The best CBASP therapists are talented acquisition learning teachers of the model.* The lesson plans are the protocols for CBASP administration; that is, teaching SA and the IDE to criterion as well as teaching assertive behavior so that patients may achieve their situational Desired Outcomes. The best teachers can effectively shape behavior and teach by small steps (31). Shaping mean being able to conceptualize behavioral goals in increments of learning—a skill that requires thinking small, breaking down the entire learning program (like SA) in small sequential steps, and being able to pinpoint what must be learned first, second, etc. Only later will the entire learning program be mastered. The learning acquisition approach to doing psychotherapy makes the CBASP model unique in the psychological and psychiatric field. Exceptional CBASP clinicians approach treatment as "teachers" whose primary mission is to teach a salubrious strategy which will enable patients to manage their chronic disorder for the remainder of their lives.

f) *Optimal CBASP clinicians verbally "control" the session.* Not being able to gain verbal control of patients precludes one from doing CBASP psychotherapy. I once worked with an analytically trained individual who let patients talk for 45" at a stretch without saying anything. No learning took place, and he and I finally agreed that CBASP was not for him. Good CBASP clinicians gain verbal control and guide the dyadic flow without being overly dominant or rude. They can effectively teach patients to talk in a dialogic manner. One of the interpersonal goals is learning to talk with the therapist reciprocally; this means, talking when appropriate, answering questions when asked, asking questions when the need arises, and remaining silent and listening attentively when spoken to. Individuals cannot learn if verbal control is absent. Many individuals enter treatment having never been listened to or taken seriously—they expect therapists to behave just like maltreating significant others.

Learning is not possible if the clinician has not obtained verbal control of the patient. This is not always easy to achieve, but until verbal control is established, the practitioner does not have a workable case. Some patients cry for most of the hour, others talk non-stop, some never say a word, some change the subject frequently, others refuse to make eye contact and instead look out the window, and a few complain endlessly that they fail at everything. Obtaining verbal control of the patient is the first thing that must be achieved before CBASP treatment commences. The best therapists work effectively with this obstacle and achieve the control they need. Then and only then, can CBASP treatment begin with one who is now in an optimal learning mode.

g) *Exceptional therapists have Interpersonal flexibility treating two modal types of chronically depressed patients—that is, (1) physically and sexually abused persons and (2) emotional and physically deprived patients.* These two patient types require different DPI styles. The physically, emotionally, and sexually abused individual needs a practitioner who can "hold back" in their reactions as they have already been over-powered by significant others who have hurt them. A gentle approach is called for which means the practitioner must tread lightly rather than rush in with queries or emotional reactions—such patients have already been the recipients of persons running over them in interpersonal encounter. Conversely, the physically/emotionally deprived patient will require therapist behavior that "moves in" and does not hold back. Such persons usually come to treatment expecting nothing to happen or little or no response from the practitioner. It is up to the therapist to see that these expectations are not fulfilled. Their developmental environments were devoid of caring and attention-giving and they were mostly left alone to fend for themselves. No one knew of their scholastic accomplishments, or athletic heroics, or what they needed emotionally or physically. They grew up in a world by themselves expecting nothing from others. The most gifted CBASP therapists have the interpersonal flexibility to respond differentially to these two individuals providing support to the notion that patient diversity means that "one size does not fit all."

h) *Talented CBASP clinicians can tolerate "silent periods."* Silence in the session may be anxiety-provoking for some therapists. As happens in those instances, therapists reduce their own felt discomfort by initiating more verbal discourse. Mature practitioners tolerate the discomfort of silence when it arises and use it to the patient's advantage. Silence is a "time for reflection—*where have we been and where are we now?*" It may be a time to identify what's prompted the stopping point but not to terminate it too quickly to make oneself feel better. If something blatantly obvious has happened between the interactants, time may be needed for the patient to recover. If clinicians are unsure about what interrupted the conversational flow, after an appropriate time has passed, they can ask patients to clarify the silence. Or they can just wait and see what happens. For the most mature clinicians, silences frequently yield productive dividends.

i) *Optimal therapists can manage anger in the session.* Anger is one of the most difficult emotions for mental health practitioners to deal with. Therapists usually react in one of three ways: (1) they work harder, (2) they interpersonally withdraw, or (3) they counter-aggress. None of these strategies are effective. The most effective tactic is to identify *why* the patient has pushed the therapist away—what is precipitating the hostile reaction? Kiesler (28, 29) opines that anger or hostility is an interpersonal impact that communicates: "Get away from me;" "Get out of my face!" One clinical psychology trainee was working with a very hostile patient who continued to denigrate his performance making the trainee feel incompetent. The trainee wanted to transfer the case because his Rogerian "unconditional acceptance" tactics were not working. I asked if he wanted to learn how to deal with anger. He said, "Yes!" The strategy he subsequently employed was directed toward identifying the source of the patient's anger. He began to ask his patient questions like the following: "Why are you beating up on me?" "Why do you keep punching me in the face?" The literal nature of these queries more often than not evoke surprise reactions as well as some verbal responses such as "I'm not doing that!" or other types of protest (e.g., "You ought to be able to handle my anger;" "You should have been trained to deal with such reactions."). Then, a more honest reply often follows. He confided his fears of relating to men and to maintain a safe distance, he always fought. The trainee's therapy then began to move in more profitable directions. If the therapist had not personally raised these questions, the causes of the anger might not have been addressed and more adaptive interpersonal strategies might never be learned. Optimal practitioners manage the hostile emotions of their patients by teaching them other ways to interpersonally relate.

j) *The best CBASP clinicians can tolerate their anxiety without reducing it.* All of us become anxious or uneasy when certain behaviors are emitted or when patients bring up particular topics. Exceptional therapists stand fast and do not change the subject to reduce their discomfort. The reward is that they can help individuals address the problematical areas that have been put on the table. It is not an easy challenge to master, for anxiety is painful, uncomfortable, and potentially fear-provoking. Examples might be not knowing what to do or say, being confused by the patient's behavior or comments and not knowing how to respond, reacting with anxiety when one mentions certain subjects or topics such as relational intimacy, hearing patients disclose that the therapist has disappointed or angered one by some comment or reaction, faced with a request for a hug or embrace, or listening to a story that awakens old anxieties about past experiences. What to do? The best CBASP therapists tell us to stop and ask oneself what the patient needs right now. Stop and identify where the source of the alarm is and then consider the practitioner's Desired Outcome in the moment which, hopefully, is in the best interest of the patient. What does the patient need right now and what must I do to deliver what's needed? The word that comes from the experts is the following rule: Stop, Look, and Listen, to myself first and then, to the patient.

k) *The best therapists know how to "walk with" the patient at their pace.* This skill is called "pacing" and the most effective among us walk with the patients we see. How does one learn to pace? There is a rule of thumb that helps. It is as follows: *the patient is always right and right where they ought to be.* It's not the therapist who is right, it's the patient. It's not where the therapist is, it's where the patient is and he or she cannot be anywhere else right then. The ablest clinicians remind us that our job is to identify *where* the patient is moment-to-moment and to recognize *what* is going on. If we can answer both these questions, then we can walk with the individual. If we cannot, we are either walking by ourselves or walking ahead or behind the person. Pacing means finding the learning rate of the person, stopping when necessary, backing up if the situation calls for it, and then, moving once more when the pace is picked up. We walk with the patient—we do not ask the patient to walk with us. How does one teach this skill? If progress halts and change is not forthcoming, we must be thrown on the alert. Are we asking too much too quick or have we neglected to motivate the person? Learning to listen *to the progress* of the individual will help us walk with and avoid pulling and pushing.

l) *The best therapists avoid preaching, exhorting or telling.* The modal statement of the best CBASP therapists is an interrogative one. Asking questions always allows the patient to play their cards first, and then the practitioner knows what and how to respond. Preaching, exhorting, and telling the interpersonal avoidant patient is a waste of breath and an ineffective therapy strategy. Since fear drives avoidance, telling someone what to do or exhorting one to act never extinguishes the fear. The excellent clinicians pinpoint/target the fear and extinguish it first. Then, the avoidance is modified. The fear may stem from skill deficits or from earlier learning where, in certain types of encounter, the patient has always run away. Teaching the individual to take an alternative action instead of running away is what is needed.

m) *The exemplary skill of introspectively tracking the "interpersonal impacts" patients have on practitioners, moment-to-moment, and when appropriate, acting on them, is rare.* This skill involves three things: (1) one must have a sound knowledge of Kieslerian (28) interpersonal theory and more specifically, possess a good working knowledge of the complementarity pulls on Kiesler's *Impact Message Inventory*; (2) clinicians must know that the beginning of sound CBASP practice requires that one be able to track the continuous movement of their emotions and be able to utilize this information to identify what is presently transpiring between the patient and practitioner; and finally, therapists must (3) trust their emotional impact interpretations that move from the verbal/non-verbal behavior of the patient to the clinician, and then make mature decisions about what they will respond to and what they will ignore. I have not known many clinicians who were able to master this skill. Emotional maturity and a sensitive awareness of one's emotional life is essential. I have seen a few practitioners who were able to perform this challenge to perfection. It adds a marvelous continuity and smoothness to the process of treatment.

CONCLUSION

We must listen to the best CBASP therapists and learn from them. They can teach all of us how to administer CBASP therapy more effectively. In this paper, I have attempted to delineate the optimal CBASP therapist characteristics to showcase how the most accomplished among us utilize the model to achieve notable outcomes. The unique difficulties of the PDD patient and the difficulties of administering this unique model of psychotherapy make successful outcomes wonderful achievements for those fortunate patients who work with practitioners who have taken the time to be the best they can be.

DATA AVAILABILITY STATEMENT

The contributions presented in the study are original. Further inquiries can be directed at the corresponding author.

AUTHOR'S NOTE

This article delineates the essential and optimal features of the therapists' role in the Cognitive Behavioral Analysis System of Psychotherapy (CBASP).

AUTHOR CONTRIBUTIONS

The author confirms being the sole contributor of this work and has approved it for publication.

REFERENCES

1. American Psychiatric Association (APA). *Diagnostic and Statistical Manual of Mental Disorders. 5th ed.* Washington, DC: Author (2013).
2. Freud S. *Character and Culture.* New York, NY: Collier Books (1963).
3. Rogers CR. *Counseling and Psychotherapy: Newer Concepts in Practice.* Boston, MA: Houghton Mifflin (1942).
4. Weissman MM, Klerman GL. The chronic depressive in the community: unrecognized and poorly recognized. *Comprehen Psychiatry.* (1977) 18:523–32. doi: 10.1016/S0010-440X(97)90002-X
5. Keller MB, McCullough JP Jr, Klein DN, Arnow BA, Dunner DL, Gelenberg AJ, et al. A comparison of nefazadone, the cognitive behavioral analysis system of psychotherapy and their combination for the treatment of chronic depression. *N Engl J Med.* (2000) 322:1462–70. doi: 10.1056/NEJM200005183422001
6. McCullough JP Jr, Schramm E, Penberthy JK. *CBASP as a Distinctive Treatment for Persistent Depressive Disorder: Distinctive Features.* London: Routledge (2015).
7. McCullough JP Jr. Helping depressed patients regain control over their lives. *Behav Med.* (1980) 7:33–4.

8. McCullough JP Jr. CBASP: am interactional treatment approach for dysthymia disorder. *Psychiatry*. (1984) 47:234–50. doi: 10.1080/00332747.1984.11024245
9. McCullough JP Jr. *Treatment for Chronic Depression: Cognitive Behavioral Analysis System of Psychotherapy (CBASP)*. New York, NY: Guilford Press (2000).
10. McCullough JP Jr. *Treating Chronic Depression with Disciplined Personal Involvement: CBASP*. New York, NY: Springer Press (2006).
11. Piaget J. *Intelligence and Affectivity: Their Relationship during Child Development*. Palo Alto, CA: Annual Reviews (1981/1954).
12. Spitz R. Hospitalism: A follow-up report on investigation described in volume I, 1945. *Psychoanal Study Child.* (1946) 2:113–7. doi: 10.1080/00797308.1946.11823540
13. Drotar D, Sturm L. Psychosocial influences in the etiology, diagnosis, and prognosis of nonorganic failure to thrive. In: Fitzgerald HE, Lester BM, Yogman MW, editors. *Theory and Research in Behavioral Pediatrics*. New York, NY: Plenum Press (1991). p. 19–59.
14. Money J. *The Kaspar Hauser Syndrome of "Psychosocial Dwarfism": Deficient Structural, Intellectual, and Social Growth Induced by Child Abuse*. Buffalo, NY: Prometheus Books (1992).
15. Money J, Annecillo C, Hutchinson JW. Forensic and family psychiatry in abuse dwarfism: Munchausen's syndrome by proxy, atonement, and addiction to abuse. *J Marital Sex Ther.* (1985) 11:30–40. doi: 10.1080/00926238508405956
16. Cicchetti D, Ackerman BP, Izard CE. Emotions and emotion regulation in developmental psychopathology. *Dev Psychopathol.* (1995) 7:1–10. doi: 10.1017/S0954579400006301
17. Cicchetti D, Toth SL. The development of depression in children and adolescents. *Am Psychol.* (1998) 53:221–41. doi: 10.1037/0003-066X.53.2.221
18. Klein DN, Shankman SA, Rose S. Ten-year prospective follow-up study of the naturalistic course of dysthymic disorder and double depression. *Am J Psychiatry.* (2006) 163:872–80. doi: 10.1176/ajp.2006.163.5.872
19. McCullough JP Jr. *Swimming Upstream: A Story about Becoming Human*. Pittsburgh, PN: Dorrance Publishing Company (2019).
20. Sartre JP. *No Exit and Three Other Plays*. New York, NY: Vintage Books (1961).
21. Nemeroff CB, Heim CM, Thase ME, Klein DN, Rush AJ, Schatzberg AF, et al. Differential responses to psychotherapy versus pharmacotherapy in the treatment of patients with chronic forms of major depression and childhood trauma. *Proc Natl Acad Sci USA*. (2003) 100:14293–6. doi: 10.1073/pnas.2336126100
22. Cicchetti D, Barnett D. Attachment organization in maltreated preschoolers. *Dev Psychopathol.* (1991) 3:397–411. doi: 10.1017/S0954579400007598
23. Piaget J. Six psychological studies. In: Elkind D, editor. New York, NY: Random House (1967/1964).
24. Piaget J. *The Language and Thought of the Child*. New York, NY: Harcourt Brace (1926/1923).
25. Folkman S, Lazarus RS. An analysis of coping in a middle-aged community sample. *J Health Soc Behav*. (1980) 21:219–39. doi: 10.2307/2136617
26. Cowan PA. *Piaget with Feeling: Cognitive, Social, and Emotional Dimensions*. New York, NY: Hold Rinehart & Winston (1978).
27. Gordon DE. Formal operations and interpersonal and affective disturbances in adolescents. In: Nannis ED, Cowan PA, editors. *Developmental Psychopathology and Its Treatment*. San Francisco, CA: Jossey-Bass (1988). p. 51–73.
28. Kiesler DJ. *Contemporary Interpersonal Theory & Research, Personality, Psychopathology, and Psychotherapy*. New York, NY: Wiley (1996).
29. Kiesler DJ. *Therapeutic Metacommunication.* Palo Alto, CA: Consulting Psychologists Press (1988).
30. Kiesler DJ, Schmidt JA. *The Impact Message Inventory: Form IIA Octant Scale*. Palo Alto, CA: Mind Garden (1993).
31. Skinner BF. *Science and Human Behavior*. New York, NY: Free Press (1953).
32. Skinner BF. *The Technology of Teaching*. New York, NY: Appleton- Century-Crofts (1968).
33. Bandura A. *Social Learning Theory*. Englewood Cliffs, NJ: Prentice-Hall (1977).
34. Winnicott DW. Hate in the countertransference. *Int J Psycho Anal.* (1949) 30:69–75.
35. Beck AT. *Beck Depression Inventory-II*. San Antonia, TX: Psychological Corporation (1996).
36. Greden JF. *Treatment of Recurrent Depression.* Washington, DC: American Psychiatric Association (2001).
37. Keller MB, Kocsis JH, Thase ME, Gelenberg AJ, Rush AJ, Koran L, et al. Maintenance phase efficacy of sertraline for chronic depression. *J Am Med Assoc.* (1998) 280:1665–72. doi: 10.1001/jama.280.19.1665
38. Klein DN, Santiago NJ, Vivian D, Arnow B, Blalock JA, Dunner DL, et al. Cognitive-behavioral analysis system of psychotherapy as a maintenance treatment for chronic depression. *J Consult Clin Psychol.* (2004) 72:681–8. doi: 10.1037/0022-006X.72.4.681
39. Bouton ME. *Learning and Behavior: A Contemporary Synthesis*. Sunderland, MA: Sinauer Associates Inc (2007).
40. McCullough JP Jr. *Skills Training Manual for Diagnosing and Treating Chronic Depression: CBASP*. New York, NY: Guilford Press (2001).
41. Hersen M, Barlow DH. *Single Case Experimental Designs*. New York, NY: Pergamon General Psychology Series (1974).
42. Sidman M. *Tactics of Scientific Research: Evaluating Experimental Data in Psychology*. New York, NY: Basic Books (1960).

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Social Cognition and Interpersonal Problems in Persistent Depressive Disorder vs. Episodic Depression: The Role of Childhood Maltreatment

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Objective: Little is known about the specific psychological features that differentiate persistent depressive disorder (PDD) and episodic depression (ED). Thus, the present study aimed to investigate differences in social cognition and interpersonal problems between these two forms of depression and healthy controls. In addition, we aimed to examine childhood maltreatment (CM) as a possible origin of these alterations.

Methods: In a cross-sectional study, adult patients with a current PDD ($n = 34$) or in a current episode of ED ($n = 38$), and healthy controls ($n = 39$) completed questionnaires about depression severity, empathy, interpersonal problems, and CM, as well as tests of affective theory of mind and facial emotion recognition.

Results: Patients with PDD reported higher empathic distress than patients with ED and healthy controls. Both depressive groups recognized angry faces with higher accuracy and reported more interpersonal problems, with no differences between PDD and ED. Empathic distress and interpersonal problems mediated the link between CM and depression in the combined sample.

Limitations: Patient groups were not drug-naïve and antidepressant intake might have influenced social-cognitive functions. Self-report measures of empathy and interpersonal problems are vulnerable to bias. The cross-sectional design does not allow causal conclusions.

Conclusion: Depressed patients may not show deficits in decoding the affective states of others and in feeling with others. However, depressed individuals—in particular patients with PDD—may feel easily overwhelmed by emotionally tense situations, resulting in empathic distress and avoidant/submissive interpersonal behavior. Exposure to CM might be an origin of alterations in social cognition and interpersonal problems.

Keywords: social cognition, childhood maltreatment, persistent depressive disorder, interpersonal problems, empathy

INTRODUCTION

According to the DSM-5 diagnostic criteria, a persistent depressive disorder (PDD) is characterized by symptoms of depressed mood for at least 2 years (1). Approximately 30% of depressed individuals develop a chronic course of the disorder, as defined by the PDD criteria (2). PDD is associated with an earlier age of onset, higher rates of comorbid mental and somatic disorders, more frequent suicide attempts, and higher treatment resistance when compared with episodic depression (ED) (3). Since approximately 75–80% of chronically depressed patients were exposed to at least moderate to severe childhood maltreatment (CM) (4), exposure to abuse and neglect in childhood is assumed to be a major risk factor for the development of PDD. Previous research shows a dose-response relationship between CM and depression severity as well as an association between CM and chronicity of depression (5). However, studies comparing the prevalence of CM in PDD and ED are rare and resulted in inconsistent findings (3, 6, 7).

In his interpersonal model of chronic depression, James McCullough — founder of the Cognitive Analysis System of Psychotherapy (CBASP) — describes pervasive interpersonal fear-avoidance and a perceptual disconnection from the interpersonal environment as the core psychopathology of PDD patients (8). He argues that specific theory of mind and empathy deficits in chronically depressed patients are rooted in early adverse relational experiences (9). His model also proposes that the interpersonal fear-avoidance in patients with PDD is characterized by a hostile-submissive interpersonal style, developed as an adaptation to a hostile, abusive, and neglectful environment in childhood. This behavior, in turn, deprives them of positive interpersonal experiences which contributes to the development and maintenance of depressive symptoms. There is good evidence for the efficacy of CBASP in the treatment of PDD (10, 11) and it is widely used to treat chronic depression, however, there is a lack of studies that comprehensively examine the underlying theoretical model.

Social Cognition in Episodic and Persistent Depression

The term *theory of mind* (ToM) is defined as the cognitive ability to attribute mental states to oneself and others (12). While cognitive ToM refers to the attribution of thoughts and intention, affective ToM refers to the attribution of emotions (13). The ToM concept is overlapping with the term *perspective-taking* which has been described as the capacity to understand others' viewpoints and to consider these viewpoints when solving interpersonal problems (14). *Empathy* is defined as a multidimensional construct (14): the cognitive dimension of empathy is mostly overlapping and interchangeably used with the affective ToM concept while the affective dimension can be defined as the degree to which someone responds emotionally to the feelings of another person (15). Affective empathy may elicit (a) *empathic distress* which refers to aversive and self-oriented responses of personal anxiety and stress (14, 16) or (b) *empathic concern* which refers to other-oriented feelings of concern and warmth, facilitating pro-social behavior (14).

The most consistent finding in a review of empathy in adults with depressive symptoms was a link between depression and high levels of empathic distress (15). Results of another recent meta-analysis indicated that patients with depression show deficits in ToM and that the magnitude of these deficits is linked to depression severity (17). However, to our knowledge, only three studies to date have compared patients with PDD and ED in measures of empathy or ToM. Van Randenborgh et al. (7) and Ladegaard et al. (18) found no differences between patients with PDD and ED in self-report and objective measures of ToM. In the third study, patients with PDD reported more empathic distress than patients with ED and healthy controls (19). Depressed patients reported more difficulties in perspective-taking, with no differences between PDD and ED. No differences were found regarding empathic concern (19). Further studies are needed to clarify whether there are differences between ED and PDD in terms of empathy and ToM and, if so, in which specific domains they occur.

The ability to recognize emotions correctly is essential for positive interactions with others. Dalili et al. (20) report in their meta-analysis impaired emotion recognition in patients with depression for all emotions except for sadness. Other studies indicate that depressed patients have a negative response bias or lack a positive response bias compared with healthy controls, in particular when ambiguous or neutral faces are presented [e.g., (21–24)]. This bias to misinterpret faces as negative could contribute to the development and maintenance of depressive symptoms. To our knowledge, no study so far has investigated differences between ED and PDD with regard to emotion recognition biases.

Interpersonal Problems in Episodic and Persistent Depression

According to the Interpersonal Circumplex Model (25), all interpersonal behavior can be classified in two-dimensional space on the axes *affiliation* and *dominance*. A recent meta-analysis supports McCullough's (8) assumption of elevated submissiveness, hostility, and hostile-submissiveness in patients with PDD and, to a smaller degree, in patients with ED (26). However, to date, only very few studies directly compared the two patient groups. Constantino et al. found that patients with PDD and ED did not differ in submissiveness, friendly-submissiveness, or hostile-submissiveness, but they differed in levels of hostility (27). A recent study also indicates higher levels of specific interpersonal skill deficits (peroperational thinking) in patients with PDD when compared with ED and an association between these deficits and depression severity over the course of 2 years (28).

Childhood Maltreatment, Social Cognition, and Interpersonal Problems

CM has been consistently identified as a major risk factor for the development of a lifetime diagnosis of a major depression (5) and, as described above, possible mediators of this relationship are alterations in social cognition and interpersonal behavior (9, 29).

A negative impact of CM on affective ToM performance has been shown in several samples, e.g., in a large online convenience sample (30), and in patients with borderline personality disorder (31). Two recent studies investigated the link between CM and affective ToM in adult patients with depression (32, 33). Both studies found a link between emotional abuse and deficits in affective ToM. Regarding emotion recognition, previous studies suggest a general impairment in maltreated children (34). However, there is also evidence for a threat bias in abused children and young adults who recognized anger at a lower emotion intensity when compared with controls (35–37). There is a lack of studies investigating the relationship between CM and emotion recognition accuracy and biases in patients with depression (38).

Previous research also suggests an association between CM and interpersonal problems (39–41) and a recent study indicates that interpersonal fears mediate the effect of CM on specific interpersonal skill deficits (42). However, most studies to date have used healthy college samples, so that more findings on the relationship between CM and interpersonal problems in patients with depression are needed.

Aims of the Study

In the current study, we aim to test some of McCullough's theoretical views empirically. First, we aim to examine differences in social cognition between patients with PDD and ED and healthy controls. Based on the literature mentioned above, we expect impaired affective ToM abilities and higher levels of empathic distress (a) in patients with PDD when compared with patients with ED and (b) in both depressed groups when compared with healthy controls. We also hypothesize a negative emotion recognition bias in patients with depression. We expect that both patient groups recognize more sadness and anger and less happiness in morphed faces. Second, we aim to compare interpersonal problems between groups. Based on the previous research findings, we hypothesize (a) higher levels of submissiveness in all patients with depression when compared with healthy controls and (b) higher levels of hostile-submissiveness in patients with PDD when compared with patients with ED and healthy controls. Finally, we aim to investigate CM as a possible origin of these alterations. We expect higher levels of CM in individuals with PDD when compared with patients with ED and healthy controls. We hypothesize a link between CM and deficits in ToM, increased empathic distress, increased negative emotion recognition bias, and increased interpersonal hostility and submissiveness in the combined sample. Finally, we will explore if social cognitive variables and interpersonal problems mediate the link between CM and depression severity in the combined sample.

MATERIALS AND METHODS

Participants

The sample of the present cross-sectional study consisted of 111 individuals: 38 patients with an ED, 34 patients with a PDD, and 39 healthy control participants. The ethics committees of the Department of Medicine and the Department of Psychology at the University of Marburg approved the protocol. Patients were recruited from one outpatient and two inpatient facilities through invitations to participate (e.g., after psychoeducational lectures or via flyers). Healthy controls were recruited via advertisements in regional newspapers, notices in public places, and online advertisements. Participants received financial compensation. Written informed consent was obtained from all participants. General inclusion criteria were an age between 18 and 65 and adequate German language skills. The healthy control group additionally met the following criteria: no current mental disorder assessed by the Structured Clinical Interview for DSM-IV Interview (SCID) (43) and no diagnosed mental disorder in the last 10 years according to self-report. Patients were included if they met either criteria for a current major depressive disorder (duration $<$ 24 months, ED group) or criteria for a current persistent depressive disorder (duration $\geq$ 24 months, PDD group) according to DSM-5 criteria (1). This was assessed by SCID interviews and an additional interview using a life chart covering the last 24 months [based on (44)]. Participants were excluded if they met any of the following criteria: acute suicidality, a diagnosis of schizophrenia or bipolar disorder, dementia, or severe cognitive impairments. A total of 119 participants were assessed for eligibility of which eight were excluded: five patients because they no longer met criteria for a current episode of ED or PDD and three patients because of missing data/incomplete study participation, resulting in the final sample of $N = 111$. Due to difficulties in data collection, emotion recognition data was missing from seven of the subjects. After screening for outliers of the emotion recognition data, two healthy subjects were excluded for the emotion recognition analyses because of strong evidence of careless responding. Further individual outliers were considered valid answers and therefore not excluded. This resulted in a reduced sample of 102 individuals for the emotion recognition analyses (35 ED, 30 PDD, 37 HC).

The demographic and clinical characteristics of the three groups are presented in **Table 1**. Briefly, groups did not differ with respect to age, gender, and years of education. When comparing patients with ED and PDD, there were no significant differences with respect to the age of onset, number of inpatient and outpatient treatments, and the use of antidepressants. The three groups differed with regard to depression severity, with the highest scores in the PDD group, followed by the ED group, and the lowest scores in the healthy control group. Repeating the comparison of demographic and clinical characteristics between groups in the reduced sample for the emotion recognition analyses yielded in the same results, with the exception that the ED and PDD group differed in the use of antidepressants, with significantly higher use in the PDD group (ED = 51.4%, PDD = 76.7%).

The 34 patients with PDD had the following subtypes of PDD: $n = 1$ (2.9%) with pure dysthymic syndrome; $n = 15$ (44.1%) with persistent major depressive episode; $n = 16$ (47.1%) with intermittent major depressive episode, with current episode; $n = 2$ (5.9%) with intermittent depressive episode, without current episode.

TABLE 1 | Demographic and clinical characteristics of the sample.

	HC ($n = 39$)		ED ($n = 38$)		PDD ($n = 34$)		Test statistic $F/t/\chi^2$	p
Characteristic	***M***	***SD***	***M***	***SD***	***M***	***SD***		
Age	39.92	14.93	41.63	12.76	44.85	12.98	[a]1.21	0.3
% Female	53.80%		50.00%		55.90%		[b]0.26	0.88
Years of education	14.26	2.23	13.53	2.09	13.5	2.36	[a]1.41	0.25
% Married/ in partnership	30.80%		52.60%		44.10%		[b]3.83	0.15
Age of onset	–	–	30.45	14.55	25.21	14.35	[c]1.52	0.13
Number outpatient treatments	–	–	1.87	3.84	4.26	9.46	[c]−1.44	0.16
Number inpatient treatments	–	–	1.61	1.64	1.65	1.48	[c]−0.11	0.91
% Antidepressants	–		55.30%		76.50%		[b]3.56	0.06
Depression (BDI–II)	3.95	4.23	25.95	12.68	33.79	13.54	[d]116.25	**<0.001**

CTQ, Childhood Trauma Questionnaire; HC, healthy control group; ED, episodic depression; PDD, persistent depressive disorder; BDI-II, Beck Depression Inventory.
[a]ANOVA.
[b]Chi-Square Test.
[c]t-Test.
[d]Welch-ANOVA.
Bold values are statistically significant with $p < 0.05$.

Measures

Beck Depression Inventory-II (BDI-II)

The severity of depressive symptoms was measured by self-report using the Beck Depression Inventory, assessing depressive symptoms in the last 2 weeks with 21 Items [BDI-II, (45); German version: (46)]. The internal consistency of the BDI-II was between $\alpha = 0.84$ and $\alpha = 0.90$ in a previous study (47).

Childhood Trauma Questionnaire (CTQ)

CM was assessed by retrospective self-report with the 28-item version of the Childhood Trauma Questionnaire [CTQ-SF; (48), German version: (49)]. The CTQ measures five types of CM: emotional abuse ($\alpha = 0.87$), physical abuse ($\alpha = 0.83$), sexual abuse ($\alpha = 0.96$), emotional neglect ($\alpha = 0.89$), and physical neglect ($\alpha = 0.61$, all α in this sample). The response options range from 1 (= *never true*) to 5 (= *very often true*).

Interpersonal Reactivity Index (IRI)

A shortened and validated German version of the interpersonal reactivity index (IRI) self-report survey was used to measure dispositional empathic traits in four subscales [(50); German version: (51)]. The *perspective-taking* subscale assesses spontaneous attempts to adopt the perspectives of other people and see things from their point of view ($\alpha = 0.78$); the *empathic concern* subscale assesses feelings of warmth, compassion, and concern for others when confronted with negative experiences of others ($\alpha = 0.76$); the *personal distress* subscale (synonym for *empathic distress*) measures personal feelings of anxiety and discomfort resulting from observing another's negative experiences ($\alpha = 0.78$); and the *fantasy* subscale assesses the tendency to identify with characters in movies, novels, plays and other fictional situations ($\alpha = 0.73$, all α in this sample) (50). The shortened German version consists of four items per scale (51).

Reading the Mind in the Eyes Test (RMET)

The revised version of the Reading the Mind in the Eyes Test (RMET) was used to measure affective ToM (52). In this test, subjects are presented with 36 black-and-white photographs only showing the eye region of faces. Four attributes (e.g., serious, ashamed, alarmed, and bewildered) are displayed around the eyes and subjects are asked to choose the word that matches the person's mental state best. The total number of errors was counted, as well as separate error sums for pictures with positive valence (9 items), negative valence (12 items), and neutral valence (15 items) based on a valence analysis by Kometer et al. (53).

Facial Expression Recognition Task (FERT)

Emotion recognition was assessed with the facial expression recognition task previously described (54). For this task, pictures of facial expressions presenting the six basic emotions happiness, sadness, fear, anger, surprise, and disgust were taken from the Ekman and Friesen Pictures of Affect Series (55) and were morphed between each prototype (100%) and neutral (0%) in 10% steps. A total of 250 stimuli were presented: four examples of each emotion at each intensity and 10 neutral faces. Each stimulus was presented for 500 ms and then replaced by a blank screen. Subjects were asked to give their response as quickly and accurately as possible by pressing one of the seven labeled keys on a response box.

Inventory of Interpersonal Problems (IIP)

The German short version of the Inventory of Interpersonal Problems (IIP) was used to assess self-reported interpersonal problems in 32-items (56). The scale is based on the Interpersonal Circumplex Model which describes all interpersonal behavior in a two-dimensional space along the two main axes *affiliation* and *dominance* (25). The IIP measures eight domains of interpersonal problems: behavior that is overly, 1. domineering/controlling (PA), 2. vindictive/self-centered (BC), 3. cold/distant (DE),

4. socially inhibited/avoidant (FG), 5. nonassertive (HI), 6. accommodating/exploitable (JK), 7. self-sacrificing/nurturant (LM), 8. intrusive/needy (NO). The dimension cold/distant (DE) corresponds to hostile interpersonal behavior, socially inhibited/avoidant (FG) to hostile-submissive, and nonassertive (HI) to submissive behavior in McCullough's model (9). The German version of the IIP-32 has shown good psychometric properties (57). In the current sample, Cronbach's alpha of the total IIP score was 0.90, alphas of the relevant scales ranged from 0.69 (JK) to 0.82 (FG).

Statistical Analyses

Statistical Analyses were conducted using IBM SPSS Statistics 22.0. Scale means were calculated if at least 75% of the items were answered. Group differences regarding demographic and clinical characteristics, social cognitive variables, interpersonal problems, and CM were assessed using one-way independent analyses of variance (ANOVA). Welch-Tests were applied in case of unequal variances. *Post-hoc* tests were Bonferroni-corrected for multiple comparisons. To test the hypothesized socio-developmental origin of differences in social cognition and interpersonal behaviors, associations between CM and ToM, empathy, interpersonal problems, and depression were explored with partial correlations controlled for age and gender. Next, to examine the hypothesized mediation with CM as the independent variable, social-cognitive variables as mediators and depression severity as dependent variable, a mediation analysis using the PROCESS Macro [(58); Model 4] for SPSS was performed. Only socio-cognitive variables related to CM and depression in the correlational analyses were included as mediators (explorative selection of relevant mediators). To test the statistical significance of the indirect effects, we used bias-corrected 95% bootstrap confidence intervals based on 5,000 bootstrap samples.

RESULTS

Between-Group Differences in Social Cognition

The statistics and effect sizes of the comparison of empathy, ToM, emotion recognition accuracy, and interpersonal problems between groups are presented in **Table 2**.

Regarding empathic distress, groups differed significantly. Bonferroni-corrected *post-hoc* tests revealed that patients with PDD reported significantly more empathic distress compared to healthy controls and patients with ED. The difference between healthy controls and patients with ED was also statistically significant. Regarding empathic concern, groups also differed significantly. Patients with PDD and ED reported significantly more empathic concern compared with healthy controls, with no significant difference between patients with PDD and ED. Regarding perspective-taking, groups also differed significantly. Patients with ED reported significantly less perspective-taking when compared with healthy controls. There were no differences in reported perspective-taking between patients with PDD when compared with healthy controls or patients with ED. The three groups did not differ with respect to RMET errors (see **Table 2**). Even when the valences (positive, negative, neutral) were considered separately, there were no significant differences between patients with ED, PDD, and healthy controls in any valence of the RMET (see **Supplementary Material 1**).

Patients with ED and PDD recognized angry emotional expressions with higher accuracy than healthy controls. The diagnostic groups did not differ in the recognition of happiness, sadness, and global emotion recognition. These results did not change when we included the use of antidepressants as a covariate. Further analyses of differences in accuracy and reaction times for recognition of all facial expressions are presented in **Supplementary Material 2**.

Between-Group Differences in Interpersonal Problems

Regarding interpersonal problems, there were significant differences between groups (see **Table 2**). With respect to the IIP total score and all examined subscales, patients with ED and PDD reported significantly more interpersonal problems when compared with healthy controls. Patients with ED and PDD did not differ significantly in any of the examined subscales or the total IIP. See **Supplementary Material 1** for the IIP subscales not considered in our hypothesis.

Between-Group Differences in Childhood Maltreatment

The statistics and effect sizes of the prevalence of different types of CM in the three groups are presented in **Table 3**. The groups differed in the CTQ total score and all subscales of the CTQ. Patients with PDD reported more CM of all types when compared with healthy controls. They also reported more emotional abuse, physical abuse, and higher total CM than patients with ED. Patients with ED reported increased levels of emotional abuse, emotional neglect, and total CM when compared with healthy controls.

Associations Between CM, Social Cognition, and Interpersonal Problems and Test of Mediation

Partial correlations between CM, empathy variables, emotion recognition accuracy, interpersonal problems, and depression severity, controlled for age and gender in the full sample are presented in **Table 4**. CM was positively correlated with depression severity with large effect size and with empathic distress and interpersonal problems with medium to large effect size. There was a small to medium negative correlation between CM and the recognition of happiness, which can be interpreted as a trend ($p = 0.055$). Depression severity correlated with large effect size positively with empathic distress and interpersonal problems, with medium to large effect size positively with empathic concern, and with small to medium effect size positively with the recognition accuracy of anger. Bivariate correlations are presented in **Supplementary Material 3** and partial correlation between CM and different facets of interpersonal problems in **Supplementary Material 4**. CM correlated with all subscales of the IIP, apart from too domineering/controlling

TABLE 2 | Comparison of social cognition and interpersonal problems between groups.

	Group							Effect size		
	HC ($n = 39$)		ED ($n = 38$)		PDD ($n = 34$)		Test statistic	HC vs. ED	HC vs. PDD	ED vs. PDD
Characteristic	***M***	***SD***	***M***	***SD***	***M***	***SD***	$F_{2,108}$	***d***	***d***	***d***
Empathy (IRI)										
Empathic concern	3.39	0.79	3.84	0.64	3.93	0.56	6.851**	0.63*	0.79**	0.15
Perspective taking	3.79	0.73	3.32	0.74	3.51	0.74	3.881*	−0.64*	−0.38	0.26
Empathic distress	2.3	0.61	3.15	0.66	3.56	0.85	30.347***	1.34***	1.70***	0.54*
Affective ToM (RMET)										
Total error	12.69	4.61	12.68	5.06	11.74	3.54	0.534	< 0.01	−0.23	−0.22
Emotion Recognition Accuracy (FERT)[a]										
Anger[a]	50.95	19.16	61.64	11.61	60.17	9.26	[c]4.31*	0.67**	0.61*	−0.14
Sadness[a]	56.35	17.03	58.64	16.6	61.92	12.61	1.04	0.14	0.37	0.22
Happiness[a]	78.78	7.85	76.64	8.11	77.5	8.2	0.65	−0.27	−0.16	0.11
Global[a]	56.58	10.53	58.7	8.29	59	5.29	[c]0.75	0.22	0.29	0.04
Interpersonal Problems (IIP)										
IIP–total[b]	1.2	0.5	1.9	0.44	2.07	0.41	37.231***	1.49***	1.90***	0.4
Hostile/DE	0.76	0.75	1.61	0.85	1.75	0.83	16.491***	1.06***	1.25***	0.17
Hostile–submis./FG	1.12	0.8	2.12	0.72	2.45	1.04	[c]24.318***	1.31***	1.43***	0.37
Submissive/HI	1.71	0.86	2.24	0.8	2.72	0.97	12.099***	0.64*	1.10***	0.54
Friendly–submis./JK	1.75	0.82	2.49	0.79	2.71	0.77	14.937***	0.92***	1.21***	0.28

CTQ, Childhood Trauma Questionnaire; HC, healthy control group; ED, episodic depression; PDD, persistent depressive disorder; IRI, Interpersonal Reactivity Index; RMET, Reading the Mind in the Eyes Test; FERT, Facial Expression Recognition Task; IIP, Inventory of Interpersonal Problems; DE, cold/distant; FG, socially inhibited; HI, nonassertive; JK, accommodating.
[a]N = 102 (HC n = 37, ED n = 35, PDD n = 30).
[b]n = 107.
[c]Welch–ANOVA; Bonferroni Pos–hoc Tests for all comparisons.
**p <.05, **p <.01, ***p <.001.*

TABLE 3 | Comparison of self-reported childhood maltreatment between groups.

	Group							Effect size		
	HC ($n = 39$)		ED ($n = 38$)		PDD ($n = 34$)		Test statistic	HC vs. ED	HC vs. PDD	ED vs. PDD
Characteristic	***M***	***SD***	***M***	***SD***	***M***	***SD***	$F_{2,108}$	***d***	***d***	***d***
CTQ total score	34.97	9.77	43.63	11.95	53.26	19.76	[a]14.43***	0.79*	1.17***	0.59*
Emotional abuse	7.56	2.82	10.76	4.86	13.71	5.45	[a]19.96***	0.81**	1.42***	0.57*
Physical abuse	5.9	2.1	6.47	2.24	9.21	4.92	[a]6.61**	0.26	0.88***	0.72**
Sexual abuse	5.26	0.79	5.63	1.58	7.35	5.34	[a]3.23*	0.3	0.55*	0.44
Emotional neglect	9.77	4.63	12.82	4.75	14.03	5.21	[b]7.60**	0.65*	0.86**	0.24
Physical neglect	6.49	1.89	7.95	3.24	8.97	3.76	[a]7.45**	0.55	0.83**	0.29

CTQ, Childhood Trauma Questionnaire; M, mean; SD, standard deviation; HC, healthy control group; ED, episodic depression; PDD, persistent depressive disorder.
[a]Welch-ANOVA.
[b]ANOVA; Bonferroni Post-hoc Tests.
**p < 0.05, **p < 0.01, ***p < 0.001.*

and too vindictive/self-centered interpersonal behavior. CM was most strongly associated with socially inhibited/avoidant behavior ($r = 0.41$, $p < 0.001$).

Based on these correlational findings, we examined a mediational model with empathic distress and interpersonal problems as mediators of the link between CM and depression severity in the combined sample. Results provided support for the hypothesized mediation model (**Figure 1**). There were significant indirect effects of CM on depression via interpersonal problems, β = 0.17, 95% CI [0.09, 0.26] and via personal distress, β = 0.16, 95% CI [0.06, 0.27]. The direct effect of CM on depression remained significant after including the mediators, β = 0.17, $p = 0.01$, supporting a partial mediation model.

TABLE 4 | Partial correlations between childhood maltreatment, social cognitive variables, interpersonal problems, and depression, controlled for age and gender.

Variable	1	2	3	4	5	6	7	8	9	10
1. Childhood Maltreatment	1									
2. Empathic Concern	0.18	1								
3. Perspective Taking	−0.17	0.28**	1							
4. Empathic Distress	0.45***	0.24*	−0.20*	1						
5. RMET errors	−0.08	−0.13	−0.06	−0.02	1					
6. Anger accuracy[a]	0.11	0.12	−0.11	0.17	−0.16	1				
7. Happiness accuracy[a]	−0.20[†]	−0.07	0.03	−0.26**	−0.21*	0.13	1			
8. Sadness accuracy[a]	0.14	0.03	0.06	0.07	−0.25*	0.29**	0.19	1		
9. FERT global accuracy[a]	0.02	0.18	0.11	0.05	−0.34**	0.65***	0.37***	0.60***		
10. Interpersonal Problems[b]	0.43***	0.21*	−0.33**	0.75***	0.03	0.11	−0.14	0.12	−0.01	1
11. Depression	0.52***	0.35***	−0.18	0.73***	−0.02	0.22*	−0.12	0.19	0.11	0.75***

RMET, Reading the Mind in the Eyes Test; FERT, Facial Expression Recognition Task.
*[†]p < 0.06, *p < 0.05, **p < 0.01, ***p < 0.001.*
[a]n = 102; [b]n = 107.

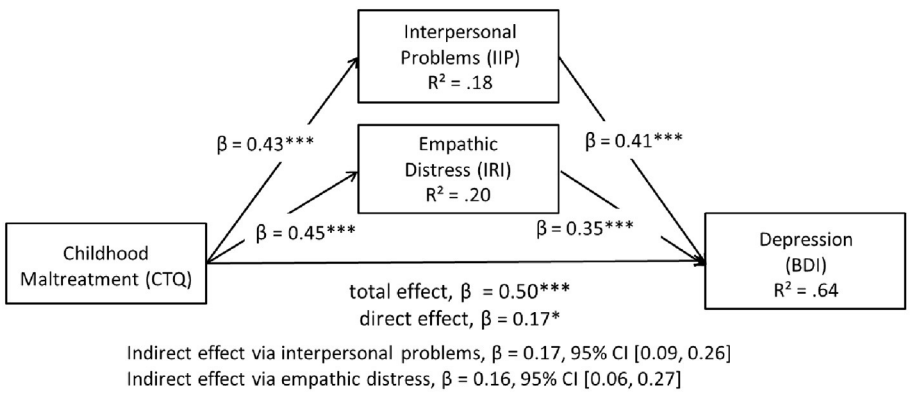

FIGURE 1 | Model of childhood maltreatment as a predictor of depression severity mediated by interpersonal problems and empathic distress in the combined sample. Standardized coefficients are reported for each path. *$p < 0.05$, ***$p < 0.001$.

DISCUSSION

Social Cognition in Episodic and Persistent Depression

The first aim of the current study was to compare social cognition in patients with PDD, ED, and in healthy controls. As hypothesized, we found increased empathic distress in patients with PDD, followed by patients with ED and healthy controls. Interestingly, we also found increased empathic concern in both depressive groups. However, in contrast to our hypothesis, there were no differences in affective ToM between groups. In parts we could confirm the assumption of a negative emotion recognition bias in depression: both patient groups were more sensitive in the recognition of anger in faces; however, this was not the case for sadness and the two patient groups did not differ in the recognition of anger, sadness, or happiness.

Interestingly, our results indicate that depressed patients do not show deficits in decoding the affective states of others but that they have difficulties in handling another person's negative emotional state or suffering and might be overwhelmed by emotionally tense situations resulting in empathic distress. This feeling of empathic distress might be even more pronounced in patients with PDD compared with ED, which is in accordance with a previous study by Domes et al. (19). In fact, the higher empathic concern in the depressive groups and the correlation of empathic concern with depression severity also suggest that depressed patients might be even hypersensitive to the feelings of others which is in line with some previous findings and theories [(59, 60); however see also (15)]. Recent findings suggest that deficits in emotion regulation (61), high levels of alexithymia (62), and generalized guilt and shame (59) in depressed patients might result in high levels of affective empathy no longer having a protective effect. Under these conditions, high levels of affective empathy might even lead to a feeling of being overwhelmed and trigger empathic distress and depressive symptoms. More research on mechanisms and moderators regarding the relationship between affective empathy, emotional contagion, empathic distress, and depression is therefore needed.

Contrary to our hypothesis, we did not find any differences in affective ToM (as measured by the RMET) between groups, in

neither of the depressive groups and for no valence. It is unlikely that this was due to low statistical power, as the effect sizes were small and contrary to our hypothesis (lowest error score in the PDD group) and we found no correlation between RMET errors and depression severity. Previous research comparing depressed patients with healthy controls in the RMET has been very inconsistent [e.g., (63–66)]. One possible explanation is that the depressive groups in the various studies differed in clinical or demographic variables. More moderator analyses are needed to explain the inconsistencies. It is also possible that the RMET is not sensitive enough to reliably detect a potential negative recognition bias. It should be noted, that the RMET is not a typical ToM test and has also been labeled as emotion recognition task instead (67). In contrast to the RMET results, we were able to show a negative recognition bias in the analyses of the emotion recognition data measured with the FERT which uses morphed images and thus has a variation in the emotional intensity of displayed facial expressions. In line with some previous findings [(21); however, see also (20)], patients with depression recognized anger with higher accuracy compared with healthy controls. Surprisingly, we found no bias in the recognition of sadness and no deficits in the recognition of facial expression with positive valence as in previous studies (21, 24). However, particularly with regard to the emotion recognition data, we need to discuss the statistical power to detect small effects (see below).

Interpersonal Problems in Episodic and Persistent Depression

Our second aim was to compare interpersonal problems in patients with ED, PDD, and in healthy controls. We hypothesized (a) higher levels of submissiveness in all patients with depression when compared with healthy controls and (b) higher levels of hostile-submissiveness in patients with PDD when compared with patients with ED and healthy controls. Our results confirmed the first part of the hypothesis as both patient groups reported more interpersonal problems resulting from submissive behavior compared with the healthy control group. The effect size was medium for the ED group and large for the PDD group. This is in line with previous findings (26). However, the second part of the hypothesis could not be confirmed: patients with PDD did not report significantly more interpersonal problems resulting from hostile-submissive behavior than patients with ED. At a descriptive level, there was a trend for the PDD group to report more interpersonal problems, and the subscale on which the two depressive groups differed the most was the subscale of problems resulting from submissive behavior (non-significant, but medium effect size). This trend indicates that this difference between ED and PDD might be significant when replicated in a larger sample (see Limitations).

Interestingly, interpersonal problems corresponding to hostile and submissive behavior were strongly correlated with empathic distress, while there was no association with affective ToM and emotion recognition abilities. Based on these findings we argue that the experience of empathic distress could strengthen fears of interaction with others and might lead to a more avoidant interpersonal style, while deficits and biases in decoding emotions might play a less prominent role in the development of interpersonal problems than previously assumed. The causal relationship between empathic distress and interpersonal problems could also be bidirectional, in the form that a lack of interpersonal skills leads to a faster overload in difficult situations resulting in empathic distress.

Childhood Maltreatment as an Origin of Alteration in Social Cognition and Interpersonal Problems

Our third aim was to examine CM as a possible origin of these alterations and to test a mediation model with CM as independent variable, social cognition and interpersonal problems as mediators, and depressive symptoms as outcome. Patients with PDD reported more CM of all types when compared with healthy controls, and more physical abuse, emotional abuse, and higher general CM levels when compared with patients with ED. As hypothesized, CM was associated with increased depression severity, empathic distress, and interpersonal problems. However, there was no association with affective ToM abilities. At a trend level, CM was negatively associated with the recognition of happiness in faces. Results of the hypothesized mediation model suggest that interpersonal problems and empathic distress mediate the link between CM and depression.

Our findings suggest that the alterations in empathy and interpersonal problems in depressed patients might be partially rooted in a history of exposure to CM. It has been argued that CM can lead to changes in social cognition in two ways: (a) via a lack of learning and developmental opportunities due to a lack of positive stimulation (neglect) and (b) via a sensitization to threat-relevant stimuli as an adaptation to the repeated exposure to threat (abuse) (68).

Consistent with earlier findings in non-clinical samples (39, 41), CM was linked with interpersonal problems and empathic distress, and the association between CM and depression severity was mediated by interpersonal problems and empathic distress. This finding also supports McCullough's theoretical model (9), proposing that depressed patients who were exposed to histories of CM show pervasive interpersonal fear-avoidance resulting in dysfunctional interpersonal behavior. Possibly, those interpersonal problems lead to higher depression severity via lower perceived social support and weaker social ties (69, 70). However, contrary to our hypothesis, CM and depression severity were not associated with general deficits in affective ToM. Taken together, CM was not associated with difficulties in decoding affective states of others, but with a feeling of being overwhelmed by negative affective states of others.

Limitations

Some limitations of the current study should be noted. First, we used self-report measures of empathic abilities and interpersonal problems which might be state-dependent and biased by social desirability. It has also been argued, that socio-cognitive deficits in depressed patients might not be detectable with laboratory tests because they are not comparable with

daily interpersonal interactions in which the participant is directly and actively involved (71). Therefore, further studies should develop and use more objective and behavioral measures with participants ideally being actively involved themselves. Another limitation is that our depressed sample was diverse regarding the intake of antidepressants with differences between the ED and PDD groups. Previous studies showed that antidepressant administration might ameliorate the negative emotion recognition bias (54) and reduce emotional contagion when confronted with the pain of others (72). Thus, the effects of antidepressants could have led to an underestimation of the differences between groups regarding biases in emotion recognition and empathic distress. However, controlling for the use of antidepressants in our emotion recognition analyses did not change the results. More studies investigating social cognition in drug naïve samples are needed. A further limitation is the cross-sectional design of the study which does not allow to draw causal conclusions. Although the hypothesized temporal sequence of exposure to CM, social cognitive functioning/interpersonal problems, and clinical outcome in the mediation model is theoretically plausible, a reverse order cannot be excluded: e.g., symptoms of depression could influence interpersonal submissiveness or empathic distress. Therefore, the mediation analysis should be interpreted with caution and more longitudinal studies are needed. As the RMET only measures a small facet of ToM, overlapping with the concept of emotion recognition, further studies should include more tests covering other aspects of ToM, e.g., also the cognitive dimension. Limitations regarding the statistical power to detect small effect sizes—especially regarding expected small biases in facial emotion recognition and regarding the differences between ED and PDD in interpersonal problems—should also be mentioned. We must, therefore, be careful with statements regarding effects that we have not been able to show in this study.

Practical Implications

Applying these results to the treatment of depression in general and of PDD in particular, emphasizes the importance of practical interpersonal skill training, as implemented e.g. in CBASP situational analyses using role plays. As depressed patients appear to have no deficits in "feeling with" others (rather may even do so more strongly) but to deal with their own feelings resulting from this, our findings also suggest a therapeutic focus on emotion regulation abilities. A focus on emotion regulation abilities corresponds to psychotherapeutic strategies in the Dialectic Behavior Therapy [DBT; (73)] for the treatment of Borderline Personality Disorders, another disorder characterized by a very high prevalence of histories of CM exposure (6). Once more, the results of this study highlight the outstanding importance of efforts to prevent CM and programs to support maltreated children and adolescence to reduce further consequences as the risk of chronic mental illness.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Department of Psychology University of Marburg and the Department of Medicine University of Marburg. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

NS and E-LB planned the study. NS conducted the statistical analyses and drafted the manuscript. NS, TG, TK, and E-LB all contributed to organizing data collection, providing feedback, and revising the manuscript. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2020.608795/full#supplementary-material

REFERENCES

1. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders (DSM-5®)*. Washington, DC: American Psychiatric Pub (2013).
2. Murphy JA, Byrne GJ. Prevalence and correlates of the proposed DSM-5 diagnosis of chronic depressive disorder. *J Affect Disord*. (2012) 139:172–80. doi: 10.1016/j.jad.2012.01.033
3. Köhler S, Chrysanthou S, Guhn A, Sterzer P. Differences between chronic and nonchronic depression: systematic review and implications for treatment. *Depress Anxiety*. (2019) 36:18–30. doi: 10.1002/da.22835
4. Brakemeier E-L, Radtke M, Engel V, Zimmermann J, Tuschen-Caffier B, Hautzinger M, et al. Overcoming treatment resistance in chronic depression: a pilot study on outcome and feasibility of the cognitive behavioral analysis system of psychotherapy as an inpatient treatment program. *Psychother Psychosom*. (2015) 84:51–6. doi: 10.1159/000369586

5. Nelson J, Klumparendt A, Doebler P, Ehring T. Childhood maltreatment and characteristics of adult depression: meta-analysis. *Br J Psychiatry*. (2017) 210:96–104. doi: 10.1192/bjp.bp.115.180752
6. Brakemeier EL, Dobias J, Hertel J, Bohus M, Limberger MF, Schramm E, et al. Childhood maltreatment in women with borderline personality disorder, chronic depression, and episodic depression, and in healthy controls. *Psychother Psychosom*. (2018) 87:49–51. doi: 10.1159/000484481
7. Van Randenborgh A, Hüffmeier J, Victor D, Klocke K, Borlinghaus J, Pawelzik M. Contrasting chronic with episodic depression: an analysis of distorted socio-emotional information processing in chronic depression. *J Affect Disord*. (2012) 141:177–84. doi: 10.1016/j.jad.2012.02.039
8. McCullough JP Jr, Schramm E, Penberthy JK. *CBASP as a Distinctive Treatment for Persistent Depressive Disorder: Distinctive Features*. New York, NY: Routledge (2015).
9. McCullough JP Jr. Treatment for chronic depression using cognitive behavioral analysis system of psychotherapy (CBASP). *J Clin Psychol*. (2003) 59:833–46. doi: 10.1002/jclp.10176
10. Jobst A, Brakemeier EL, Buchheim A, Caspar F, Cuijpers P, Ebmeier KP, et al. European Psychiatric Association Guidance on psychotherapy in chronic depression across Europe. *Eur Psychiatry*. (2016) 33:18–36. doi: 10.1016/j.eurpsy.2015.12.003
11. Negt P, Brakemeier E-L, Michalak J, Winter L, Bleich S, Kahl KG. The treatment of chronic depression with cognitive behavioral analysis system of psychotherapy: a systematic review and meta-analysis of randomized-controlled clinical trials. *Brain Behav*. (2016) 486:e00486. doi: 10.1002/brb3.486
12. Premack D, Woodruff G. Does the chimpanzee have a theory of mind? *Behav Brain Sci*. (1978) 1:515–26. doi: 10.1017/S0140525X00076512
13. Shamay-Tsoory SG, Shur S, Barcai-Goodman L, Medlovich S, Harari H, Levkovitz Y. Dissociation of cognitive from affective components of theory of mind in schizophrenia. *Psychiatry Res*. (2007) 149:11–23. doi: 10.1016/j.psychres.2005.10.018
14. Davis MH. A mulitdimensional approach to individual differences in empathy. *Pers Soc Psychol*. (1983) 44:113–26. doi: 10.1037/0022-3514.44.1.113
15. Schreiter S, Pijnenborg GHM, aan het Rot M. Empathy in adults with clinical or subclinical depressive symptoms. *J Affect Disord*. (2013) 150:1–16. doi: 10.1016/j.jad.2013.03.009
16. Singer T, Klimecki OM. Empathy and compassion. *Curr Biol*. (2014) 24:R875–78. doi: 10.1016/j.cub.2014.06.054
17. Bora E, Berk M. Theory of mind in major depressive disorder: a meta-analysis. *J Affect Disord*. (2016) 191:49–55. doi: 10.1016/j.jad.2015.11.023
18. Ladegaard N, Lysaker PH, Larsen ER, Videbech P. A comparison of capacities for social cognition and metacognition in first episode and prolonged depression. *Psychiatry Res*. (2014) 220:883–9. doi: 10.1016/j.psychres.2014.10.005
19. Domes G, Spenthof I, Radtke M, Isaksson A, Normann C, Heinrichs M. Autistic traits and empathy in chronic vs. episodic depression. *J Affect Disord*. (2016) 195:144–7. doi: 10.1016/j.jad.2016.02.006
20. Dalili MN, Penton-Voak IS, Harmer CJ, Munafo MR. Meta-analysis of emotion recognition deficits in major depressive disorder. *Psychol Med*. (2015) 45:1135–44. doi: 10.1017/S0033291714002591
21. Bomfim AJL, Ribeiro RA, Chagas MHN. Recognition of dynamic and static facial expressions of emotion among older adults with major depression. *Trends Psychiatry Psychother*. (2019) 41:159–66. doi: 10.1590/2237-6089-2018-0054
22. Bourke C, Douglas K, Porter R. Processing of facial emotion expression in major depression: a review. *Aust N Z J Psychiatry*. (2010) 44:681–96. doi: 10.3109/00048674.2010.496359
23. Gollan JK, Pane HT, McCloskey MS, Coccaro EF. Identifying differences in biased affective information processing in major depression. *Psychiatry Res*. (2008) 159:18–24. doi: 10.1016/j.psychres.2007.06.011
24. Münkler P, Rothkirch M, Dalati Y, Schmack K, Sterzer P. Biased recognition of facial affect in patients with major depressive disorder reflects clinical state. *PLoS ONE*. (2015) 10:e0129863. doi: 10.1371/journal.pone.0129863
25. Kiesler DJ. The 1982 interpersonal circle: a taxonomy for complementarity in human transactions. *Psychol Rev*. (1983) 90:185–214. doi: 10.1037/0033-295X.90.3.185
26. Bird T, Tarsia M, Schwannauer M. Interpersonal styles in major and chronic depression: a systematic review and meta-analysis. *J Affect Disord*. (2018) 239:93–101. doi: 10.1016/j.jad.2018.05.057
27. Constantino MJ, Manber R, DeGeorge J, McBride C, Ravitz P, Zuroff DC, et al. Interpersonal styles of chronically depressed outpatients: profiles and therapeutic change. *Psychother Theory Res Pract Train*. (2008) 45:491–506. doi: 10.1037/a0014335
28. Sondermann S, Stahl J, Grave U, Outzen J, Moritz S, Klein JP. Preoperational thinking as a measure of social cognition is associated with long-term course of depressive symptoms. A longitudinal study involving patients with depression and healthy controls. *Front Psychiatry*. (2020) 11:652. doi: 10.3389/fpsyt.2020.00652
29. Liu RT. Childhood adversities and depression in adulthood: current findings and future directions. *Clin Psychol Sci Pract*. (2017) 24:140–53. doi: 10.1111/cpsp.12190
30. Germine L, Dunn EC, McLaughlin KA, Smoller JW. Childhood Adversity Is Associated with Adult Theory of Mind and Social Affiliation, but Not Face Processing. *PLoS ONE*. (2015) 10:e0129612. doi: 10.1371/journal.pone.0129612
31. Petersen R, Brakoulias V, Langdon R. An experimental investigation of mentalization ability in borderline personality disorder. *Compr Psychiatry*. (2016) 64:12–21. doi: 10.1016/j.comppsych.2015.10.004
32. Rnic K, Sabbagh MA, Washburn D, Bagby RM, Ravindran A, Kennedy JL, et al. Childhood emotional abuse, physical abuse, and neglect are associated with theory of mind decoding accuracy in young adults with depression. *Psychiatry Res*. (2018) 268:501–7. doi: 10.1016/j.psychres.2018.07.045
33. Simon M, Németh N, Gálber M, Lakner E, Csernela E, Tényi T, et al. Childhood adversity impairs theory of mind abilities in adult patients with major depressive disorder. *Front Psychiatry*. (2019) 10:867. doi: 10.3389/fpsyt.2019.00867
34. da Silva Ferreira GC, Crippa JAS, de Lima Osório F. Facial emotion processing and recognition among maltreated children: a systematic literature review. *Front Psychol*. (2014) 5:1–10. doi: 10.3389/fpsyg.2014.01460
35. Gibb BE, Schofield CA, Coles ME. Reported history of childhood abuse and young adults' information processing biases for facial displays of emotion. *Child Maltreat*. (2009) 14:148–56. doi: 10.1177/1077559508326358
36. Pollak SD, Messner M, Kistler DJ, Cohn JF. Development of perceptual expertise in emotion recognition. *Cognition*. (2009) 110:242–7. doi: 10.1016/j.cognition.2008.10.010
37. Pollak SD, Tolley-Schell SA. Selective attention to facial emotion in physically abused children. *J Abnorm Psychol*. (2003) 112:323–38. doi: 10.1037/0021-843X.112.3.323
38. Rokita KI, Dauvermann MR, Donohoe G. Early life experiences and social cognition in major psychiatric disorders: a systematic review. *Eur Psychiatry*. (2018) 53:123–33. doi: 10.1016/j.eurpsy.2018.06.006
39. Christ C, De Waal MM, Dekker JJM, van Kuijk I, Van Schaik DJF, Kikkert MJ, et al. Linking childhood emotional abuse and depressive symptoms: the role of emotion dysregulation and interpersonal problems. *PLoS ONE*. (2019) 14:1–18. doi: 10.1371/journal.pone.0211882
40. Huh HJ, Kim SY, Yu JJ, Chae JH. Childhood trauma and adult interpersonal relationship problems in patients with depression and anxiety disorders. *Ann Gen Psychiatry*. (2014) 13:26. doi: 10.1186/s12991-014-0026-y
41. Paradis A, Boucher S. Child maltreatment history and interpersonal problems in adult couple relationships. *J Aggress Maltreat Trauma*. (2010) 19:138–58. doi: 10.1080/10926770903539433
42. Klein JP, Stahl J, Hüppe M, McCullough JP, Schramm E, Ortel D, et al. Do interpersonal fears mediate the association between childhood maltreatment and interpersonal skills deficits? A matched cross-sectional analysis. *Psychother Res*. (2020) 30:267–78. doi: 10.1080/10503307.2018.1532125
43. Wittchen HU, Wunderlich U, Gruschwitz S, Zaudig M. *SKID I. Strukturiertes Klinisches Interview für DSM-IV. Achse I: Psychische Störungen. Interviewheft und Beurteilungsheft. Eine deutschsprachige, erweiterte Bearb. d. amerikanischen Originalversion des SKID I*. Göttingen: Hogrefe (1997).
44. Klein JP, Backenstrass M, Schramm E. *Therapie-Tools CBASP*. Basel: Beltz Verlag (2018).
45. Beck AT, Steer RA, Brown GK. *Manual for the Beck Depression Inventory-II*, Vol. 1. San Antonio: TX Psychol Corp. (1996). p. 82. doi: 10.1037/t00742-000

46. Hautzinger M, Keller F, Kühner C. *Beck Depressions-Inventar (BDI-II)*. Frankfurt: Harcourt Test Services (2006).
47. Kühner C, Bürger C, Keller F, Hautzinger M. Reliabilität und validität des revidierten Beck- Depressionsinventars (BDI-II). *Befunde aus deutschsprachigen stichproben Nervenarzt.* (2007) 78:651–6. doi: 10.1007/s00115-006-2098-7
48. Bernstein DP, Stein JA, Newcomb MD, Walker E, Pogge D, Ahluvalia T, et al. Development and validation of a brief screening version of the childhood trauma questionnaire. *Child Abus Negl.* (2003) 27:169–90. doi: 10.1016/S0145-2134(02)00541-0
49. Wingenfeld K, Spitzer C, Mensebach C, Grabe HJ, Hill A, Gast U, et al. The German version of the childhood trauma questionnaire (CTQ): preliminary psychometric properties. *PPmP Psychother Psychosom Medizinische Psychol.* (2010) 60:442–50. doi: 10.1055/s-0030-1247564
50. Davis MH. A mulitdimensional approach to individual differences in empathy. *J Pers Soc Psychol.* (1980) 44:113–26.
51. Paulus, C. (2009). *Der Saarbrücker Persönlichkeitsfragebogen (SPF). Psychometrische Evaluation der deutschen Version des Interpersonal Reactivity Index*. P. 1–11. Retrieved from: http://hdl.handle.net/20.500.11780/3343
52. Baron-Cohen S, Wheelwright S, Hill J, Raste Y, Plumb I. The "reading the mind in the eyes" test revised version: a study with normal adults, and adults with Asperger syndrome or high-functioning autism. *J Child Psychol Psychiatry*. (2001) 42:241–51. doi: 10.1111/1469-7610.00715
53. Kometer M, Schmidt A, Bachmann R, Studerus E, Seifritz E, Vollenweider FX. Psilocybin biases facial recognition, goal-directed behavior, and mood state toward positive relative to negative emotions through different serotonergic subreceptors. *Biol Psychiatry*. (2012) 72:898–906. doi: 10.1016/j.biopsych.2012.04.005
54. Harmer CJ, O'Sullivan U, Favaron E, Massey-Chase R, Ayres R, Reinecke A, et al. Effect of acute antidepressant administration on negative affective bias in depressed patients. *Am J Psychiatry*. (2009) 166:1178–84. doi: 10.1176/appi.ajp.2009.09020149
55. Ekman P, Friesen WV. *Pictures of Facial Affect*. Palo Alto, CA: Consulting Psychologist Press (1976).
56. Horowitz LM, Strauß B, Thomas A, Kordy H. *IIP-D Inventar zur Erfassung Interpersonaler Probleme-Deutsche Version [Inventory for the assessment of interpersonel problems-German version](Vol. 3, überarbeitete 3rd Auflage)*. Hogrefe: Boston, MA (2016).
57. Thomas A, Brähler E, Strauß B. IIP-32: Entwicklung, Validierung und Normierung einer Kurzform des Inventars zur Erfassung interpersonaler Probleme. *Diagnostica.* (2011) 57:68–83. doi: 10.1026/0012-1924/a000034
58. Hayes AF. *Introduction to Mediation, Moderation, and Conditional Process Analysis: A Regression-Based Approach*. New York, NY: Guilford Publications (2017).
59. Gambin M, Sharp C. The relations between empathy, guilt, shame and depression in inpatient adolescents. *J Affect Disord*. (2018) 241:381–7. doi: 10.1016/j.jad.2018.08.068
60. Tone EB, Tully EC. Empathy as a risky strength: a multilevel examination of empathy and risk for internalizing disorders. *Dev Psychopathol.* (2014) 26:1547–65. doi: 10.1017/S0954579414001199
61. Powell PA. Individual differences in emotion regulation moderate the associations between empathy and affective distress. *Motiv Emot*. (2018) 42:602–13. doi: 10.1007/s11031-018-9684-4
62. Banzhaf C, Hoffmann F, Kanske P, Fan Y, Walter H, Spengler S, et al. Interacting and dissociable effects of alexithymia and depression on empathy. *Psychiatry Res*. (2018) 270:631–8. doi: 10.1016/j.psychres.2018.10.045
63. Kettle JWL, O'Brien-Simpson L, Allen NB. Impaired theory of mind in first-episode schizophrenia: comparison with community, university and depressed controls. *Schizophr Res*. (2008) 99:96–102. doi: 10.1016/j.schres.2007.11.011
64. Nejati V, Zabihzadeh A, Maleki G, Tehranchi A. Mind reading and mindfulness deficits in patients with major depression disorder. *Procedia Soc Behav Sci*. (2012) 32:431–7. doi: 10.1016/j.sbspro.2012.01.065
65. Szily E, Kéri S. Anomalous subjective experience and psychosis risk in young depressed patients. *Psychopathology*. (2009) 42:229–35. doi: 10.1159/000218520
66. Wolkenstein L, Schönenberg M, Schirm E, Hautzinger M. I can see what you feel, but i can't deal with it: impaired theory of mind in depression. *J Affect Disord*. (2011) 132:104–11. doi: 10.1016/j.jad.2011.02.010
67. Oakley BFM, Brewer R, Bird G, Catmur C. Theory of mind is not theory of emotion: a cautionary note on the reading the mind in the eyes test. *J Abnorm Psychol*. (2016) 125:818–23. doi: 10.1037/abn0000182
68. McLaughlin KA, Sheridan MA, Lambert HK. Childhood adversity and neural development: deprivation and threat as distinct dimensions of early experience. *Neurosci Biobehav Rev*. (2014) 47:578–91. doi: 10.1016/j.neubiorev.2014.10.012
69. Santini ZI, Koyanagi A, Tyrovolas S, Mason C, Haro JM. The association between social relationships and depression: a systematic review. *J Affect Disord*. (2015) 175:53–65. doi: 10.1016/j.jad.2014.12.049
70. Struck N, Krug A, Feldmann M, Yuksel D, Stein F, Schmitt S, et al. Attachment and social support mediate the association between childhood maltreatment and depressive symptoms. *J Affect Disord*. (2020) 273:310–7. doi: 10.1016/j.jad.2020.04.041
71. Wilbertz G, Brakemeier EL, Zobel I, Härter M, Schramm E. Exploring preoperational features in chronic depression. *J Affect Disord*. (2010) 124:262–9. doi: 10.1016/j.jad.2009.11.021
72. Rütgen M, Pletti C, Tik M, Kraus C, Pfabigan DM, Sladky R, et al. Antidepressant treatment, not depression, leads to reductions in behavioral and neural responses to pain empathy. *Transl Psychiatry*. (2019) 9:164. doi: 10.1038/s41398-019-0496-4
73. Linehan MM. *Cognitive-Behavioral Treatment of Borderline Personality Disorder*. New York, NY: Guilford Publications (2018).

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Interpersonal Change During Inpatient CBASP Treatment: Focus on Group Therapy

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Background: The Cognitive Behavioral Analysis System of Psychotherapy (CBASP) has been tailored specifically to the demands of patients with persistent depressive disorder (PDD). According to the CBASP model, PDD patients are supposed to live perceptually disconnected from their social environment, which consequently maintains depression. While initially developed as an individual treatment modality, the adaptation for group therapy yields an important interpersonal space. However, little is known about the specific factors that contribute to patients' benefit from the CBASP group modality.

Methods: The analyzed sample comprised $N = 87$ PDD patients who completed a 12 week multimodal inpatient treatment including 2 weekly CBASP-specific individual and group sessions, respectively, as well as CBASP-unspecific medical contacts, pharmacotherapy and complementary therapies. Group sessions included trainings in situational analysis and interpersonal skills. Interpersonal change over therapy was examined based on the patients' self-perceived interpersonal problems (IIP) and the impact messages as perceived by their individual therapists (IMI). Pre and post-treatment data were compared using within-sample *t*-tests. Additionally, patients evaluated CBASP group therapy on a feedback form. They were invited to reflect on individual benefits and its helpful and unhelpful aspects. Qualitative content analysis with inductive category development was used to analyze feedback. Inter-rater reliability was computed to confirm categories before summarizing the frequencies of reported factors.

Results: Self-perceived interpersonal distress significantly decreased over therapy. Patients reported reduced interpersonal problems and therapists reported more friendly and dominant impact messages. Interestingly, patients who showed a significant depressive symptom reduction described higher change scores. Regarding qualitative data, patients reported five main benefits from group therapy: Gain in social competence, self-confidence, self-reflection, interpersonal dynamics, and optimism/universality. Patients responding to CBASP identified significantly more factors than non-responders.

Conclusions: Compared to studies with individual CBASP only, the present findings suggest that CBASP group therapy may contribute to the improvement of interpersonal behavior. Group therapy is discussed as a potential boosting effect for individual CBASP.

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However, as the present data were collected in a multimodal inpatient setting without competitor, randomized controlled trials are warranted that investigate the specific benefits of the group modality or the combined individual and group therapy over individual CBASP only.

Keywords: CBASP, group therapy, interpersonal problems, interpersonal style, change factors in group therapy, situational analysis, Kiesler's circle training

INTRODUCTION

Chronicity of depression is associated with high individual and economic disease burden (1). Compared to non-chronic forms of depression, pharmacotherapy and psychotherapy are less effective in patients with persistent depressive disorder [PDD, e.g., (2, 3)]. This may be due to specific features of PDD that impede treatment success, such as higher comorbidity rates and more avoidant, submissive and hostile interpersonal behavior (4). These risk factors are assumed to have their roots in childhood and require specific interventions. The Cognitive Behavioral Analysis System of Psychotherapy [CBASP; (5)] is an interpersonally oriented treatment approach specifically developed for the demands of patients with PDD (6). The CBASP model emphasizes childhood maltreatment as a cause of interpersonal dysfunctions that sustain chronicity of depression. Particularly emotional abuse and neglect by significant others during childhood elevate the risk of early-onset, severe, chronic and treatment-resistant depression (7–9). An unsafe or threatening home life is expected to redirect the normal cognitive-emotional development of a child toward survival rather than growth (5). Consequently, acquisition of behavioral, cognitive and emotional skills to build satisfying relationships later in life is impeded [e.g., (10)] and "primitive verbal thought and behavioral patterns serve to keep them perceptually disconnected from the environment" [(11) p. 834].

The interpersonal circumplex (IPC) model, which was developed in the middle of the last century (12), constitutes a useful tool for research and clinical practice to explain psychopathology within an interpersonal context. The model has two orthogonal axes which define a circular space that places normality and abnormality on a continuum (13). The vertical axis of *agency* represents the behavioral dimension of control that can range from dominance to submissiveness. The horizontal axis of *communion* represents the behavioral dimension of affiliation that can range from friendliness to hostility. Divided into eight segments that are arranged in equal increments (every 45°) around the circle, each octant represents a blend of these two axial dimensions and characterize a person's interpersonal profile. In contrast to non-clinical individuals, patients with depression show elevated levels of submissiveness and hostility (14–16) and PDD patients demonstrate even more hostile and less friendly interpersonal behavior than patients in acute depression (16, 17). Besides the characterization of the individual in the IPC space, the model incorporates dynamic transactional processes that continuously emerge between interaction partners. In terms of agency, dynamic transactions are reciprocal, whereas in terms of communion they are corresponding (18). Thus, submissive behavior of the chronically depressed patient invites dominant reactions by others, whereas hostile behavior evokes hostility in return. These principles of social interaction might account for the fact that PDD patients suffer from interpersonal problems and behavioral avoidance (19).

CBASP techniques intend to build (1) a feeling of interpersonal safety against the background of childhood adversity and (2) increase the patients' perceived social functionality. Therefore, CBASP therapists fulfill two central functions: They are to heal the interpersonal traumas patients have received in their significant other history by enacting a 'Disciplined Personal Involvement Role' (DPI); and they are to teach interpersonal skills in accordance with the dynamic transactional processes posited by the IPC model (20). Both these components of CBASP are supposed to (re)connect patients with their social environment. Realizing their interpersonal impact, patients are thought to become empowered to overcome submissiveness and hostility for the sake of acquiring satisfactory relationships with others. Thus, patients who respond to CBASP should change their interpersonal behavior from submissive to dominant and from hostile to friendly, corresponding to an increase in the dimensions of both agency (y-axis) and communion (x-axis).

In the outpatient and individual setting, CBASP has demonstrated efficacy in a growing number of randomized controlled trials (RCT) in PDD patients: CBASP proved to be as effective as medication (2, 21), particularly when CBASP was combined with medication (2); CBASP was more effective than psychotherapy as usual (22), Interpersonal therapy (23) and Supportive Psychotherapy (24), and yielded benefits particularly in patients with childhood maltreatment (25–27). CBASP has also been adopted and modified for the inpatient setting (28–30), which offers the possibility to combine individual and group treatment. CBASP group therapy is expected to boost the effects of individual therapy, since the relationships with other group members may promote interpersonal safety through an increased number of corrective interpersonal experiences. Group-CBASP may further provide a social network for exercising personal agency and communion, thereby fostering the patients' perceived functionality in the social domain. Previous studies have pointed to the feasibility (29) and effectiveness of CBASP group therapy regarding the reduction of depressive symptoms and the improvement of interpersonal functioning (17, 31–35), also as continuation therapy after acute treatment (36). However, little is known about the specific factors

that contribute to patients' benefit from the group modality or a potential deterioration of symptoms that may be caused by the group setting itself. The present study aimed to elucidate interpersonal change within a naturalistic design by considering quantitative data on interpersonal functioning that derived from the entire multimodal CBASP inpatient setting and qualitative data that derived from the CBASP group modality in particular. Interpersonal change from pre- to post-treatment was evaluated from two perspectives. We expected that both, patients and their therapists would report a development from less agentic and less communal behavior at the beginning to increased agency and communion scores at the end of CBASP, particularly in responders. We also expected decreased levels of general distress in social interactions. Although limited to the naturalistic setting, which impedes strong conclusions with regard to the causal impact of CBASP group therapy, we further assumed the group to boost the effects of individual therapy. In our qualitative data, we therefore expected patients to identify CBASP-specific features when evaluating the specific benefits of group modality at the end of treatment.

MATERIALS AND METHODS

Study Sample and Group Concepts

The present study was conducted at the general acute unit for affective disorders of the Department of Psychiatry and Psychotherapy of Charité Berlin (Campus Mitte), which offers a 12-week CBASP treatment for PDD patients. Ethical approval was obtained from the Ethics Committee of the Charité—Universitätsmedizin Berlin. Between April 2013 and August 2020, $N = 105$ patients were included in the CBASP program. Thereof, $n = 18$ were designated dropouts since they did not start therapy ($n = 2$) or discontinued therapy after fewer than 12 weeks. There was no difference between dropouts and completers regarding self-reported interpersonal problems at baseline ($t_{(17.4)} = 0.47, p = 0.641$).

The present retrospective study reports data from $N = 87$ inpatients who completed a structured and manualized, multimodal inpatient CBASP concept (37), that is, dropouts are not considered. The majority of patients attended the first 6 weeks in an inpatient setting and the second half in a day-clinical setting on the same ward. Detailed descriptions of treatment components including pharmacotherapy, criteria of inclusion and exclusion as well as the effects of CBASP regarding the primary outcome, that is, depression change, were published elsewhere (30). In brief, the acute treatment consisted of 24 individual sessions and 24 group sessions. Besides 2 weekly individual sessions, patients attended 2 weekly manualized group therapies, one for the training of situational analyses [SA; (37)] and one for the training of interpersonal skills based on the IPC model, the so-called Kiesler's Circle Training [KCT; (38)]. Both groups originated from CBASP (5), but were adopted and modified for the inpatient setting and the group modality. They were half-open for three to eight patients at a time. SA group sessions lasted 100 min and were guided by a psychologist or psychiatrist trained in Cognitive Behavioral Therapy with further certification for CBASP therapy and training by the German national CBASP network (www.cbasp-network.de); KCT group sessions lasted 60 min and were guided by two masters-level psychologists in training for CBASP. Therapists got weekly supervision to guarantee adherence to the manuals.

The *SA training* constitutes the main skill acquisition exercise in CBASP. SAs were practiced during both CBASP individual and group sessions. During every group session, one patient mentions a conflictual interpersonal issue that he or she wants to analyze with the help of the other group members. The SA follows specific steps. The elicitation phase involves the description of the situation from an objective viewpoint followed by the interpretations that were involved during the situation. The protagonist of the SA is then encouraged to reflect on verbal and non-verbal behavior according to the interpersonal circle and the actual observable outcome this behavior entailed. This step is intended to make the patients appreciate their interpersonal impact and simultaneously serves to elucidate why they are left dissatisfied in social situations. The most important step comprises the specification of an interpersonal goal for the outlined situation, the so-called "Desired Outcome," which needs to be realistic, attainable and under the protagonist's control. The end of the elicitation phase encompasses a comparison between the actual and the desired outcome. The subsequent remediation phase is intended to practice the achievement of the desired outcome. Dysfunctional interpretations are examined and transformed, complemented by an active interpretation. Subsequently, the patient's behavior is modified in theory and in practice. At the end of the group session, the therapist encourages every group member to derive a take home message from the protagonist's SA and to reflect on similar situations, in which the desired outcome of the present SA could be helpful for him- or herself. This is considered to facilitate learning transfer to similar conflictual interpersonal situations.

Within the KCT group, patients get familiar with the circumplex model and practice different techniques, which are taught in five modules: (1) Getting to know the circle, (2) non-verbal communication, (3) verbal communication, (4) conflict training, (5) empathy and corrective interpersonal experiences. Each session comprises a mixture of psychoeducational and experience-activating techniques to practice different interpersonal behaviors based on the octant IPC model. The KCT sessions do not follow a specific sequence due to the half-open group format; therapists rather select the topics according to the relevance for the group members at a specific time, so that KCT modules often complement SA training. For instance, patients learn to identify different adjectives that describe agency and communion (module 1), they learn to assign mimicry to the octant positions, (2) they try out how to actively express personal needs and demands (module 3), also in conflict scenarios (module 4), they reflect on individual experiences with other group members and learn to discriminate their reactions from former reactions with significant others (module 5). Handouts and worksheets support the consolidation of interpersonal learning.

Quantitative Data

Change in interpersonal functioning over therapy was examined based on the patients' self-perceived interpersonal problems [IIP-64; (39)] and the impact messages as perceived by their individual therapists [IMI; (40)].

On the IIP-64, patients rate the extent to which a number of behaviors, thoughts and feelings in social interactions poses difficulties for them on 64 Likert-scaled items that range from 0 (not at all) to 4 (absolutely). The eight subscale scores (PA=domineering, BC=vindictive, DE=cold, FG=avoidant, HI=non-assertive, JK=exploitable, LM=overly-nurturant, NO=intrusive) cover the IPC space and reflect a particular combination of the interpersonal dimensions of agency and communion. The mean score of all 64 items further indicates the general level of interpersonal distress. Higher values represent more severe interpersonal problems. The psychometric properties of the German version of the IIP-64 are acceptable to good (41) and comparable to the English original version (42). Internal consistencies of the octant scales ranged from $\alpha = 0.71$ to 0.88 and were slightly higher than in the present study (pre-treatment: $\alpha = 0.059$ to 0.84, post-treatment: $\alpha = 0.68$ to 0.88). However for self-reports in general, external validity may be reduced due to the limited ability to accurately characterize oneself with regard to interpersonal behavior. Therefore, we additionally assessed therapist-rated impact messages with the IMI. According to Altenstein-Yamanaka et al. (43), the agency scores of IIP-64 and IMI correlated moderately, whereas the communion scores did not, suggesting that others provide important additional information on interpersonal change.

On the IMI, observers rate the feelings, thoughts, and action tendencies evoked by a target person. For the purpose of the present study, individual CBASP therapists assessed their respective patients' interpersonal impact messages at week 2 and at the end of treatment. The IMI consists of 64 items rated on a 4-point Likert scale ranging from 1 (not at all) to 4 (very much). Paralleling the IIP-64, means of 8 items per octant are based on the underlying dimensions of agency and communion. In contrast to the IIP, higher values on the IMI indicate higher intensity of a specific octant, which does not necessarily entail more severe interpersonal problems. The psychometric criteria of the IMI demonstrated adequate psychometric and structural validation (44). Also the German IMI revealed acceptable internal consistencies of $\alpha = 0.68$ to $\alpha = 0.97$, both in a normative sample and in patients (40). Cronbach's alpha for the present IMI octant data was similarly satisfying, ranging from 0.85 to 0.91 at pre-treatment and 0.72 to 0.90 at post-treatment.

In accordance with earlier studies that have evaluated interpersonal functioning in depressed patients over therapy based on the IIP and/or IMI, we hypothesized decreased scores for all IIP-64 octant scores, so that also *general distress* would decrease over therapy (42, 43). For IMI, we considered that impact messages for dominant, friendly-dominant and friendly behavior (quadrant I) would increase, whereas hostile, hostile-submissive and submissive behavior (quadrant III) would decrease over therapy (17, 31, 45). We also considered that the reduction of general distress would be greater in patients who benefited from CBASP (43). Therefore, we considered self-reported depression scores measured at pre and post treatment using the Beck Depression Inventory [BDI, revised version; (46)]. We additionally differentiated between responders and non-responders, using a reduction of depressive symptoms by 50% as demarcation line.

All statistical analyses were performed with SPSS version 25. $N = 85$ patients answered IIP-64 at week 1 and $n = 79$ at week 12. Three individuals at week 1 and two individuals at week 12 missed the second page of the IIP-64 questionnaire. To keep the sample size constant, in these cases missing subscales for PA, JK, LM, NO were replaced by the group means, respectively. The impact messages (IMI) of $n = 83$ patients were assessed by the individual therapists at both pre and post treatment.

Changes over therapy were analyzed using paired *t*-tests. To protect against type I error due to multiple comparisons, we set the cut-off value for significance at $p \leq 0.003$ and calculated effect sizes according to Cohen (1992), that is, $d \leq 0.2$ represents small, $d = 0.5$ medium and $d \geq 0.8$ large effects. In accordance with the CBASP model we further associated treatment response with interpersonal change (5). Therefore we calculated Spearman correlation coefficients between BDI change ($BDI_{change} = BD_{pre} - BDI_{post}/BDI_{pre}$) and change in IIP general distress ($IIP\text{-}64 = distress_{pre}\text{-}distress_{post}/IIP\text{-}64_{pre}$), corrected for the respective baseline values. Missing data for BDI (at pre: $n = 13$, at post: $n = 12$; that is, 14.4% missing values) were replaced by a multiple imputation with five iterations since data were confirmed to be completely random (little MCAR test: $Chi^2_{(2)} = 4.6$, $p = 0.103$; $n = 3$ patients neither had pre nor post BDI scores). Imputed and observed results showed comparable values, so that pooled imputed values are reported. This resulted in a subsample of $n = 76$ complete data sets for the above mentioned correlation analysis between interpersonal functioning and severity of depression.

Qualitative Data: Evaluation Form

At the end of treatment, patients evaluated their experiences with CBASP group therapy on a feedback form, which consisted of a shortened and modified version from Brakemeier, Strunk, Normann and Schramm used in the study by Sabaß et al. (29). Amongst others the feedback form comprised quantitative measures regarding patients' motivation and engagement in group therapy as well as an overall grade for the group using the German educational grading system (1 = "very good" to 6 = "insufficient"). Additionally, patients were invited to reflect on (1) what they have learned throughout group-CBASP in retrospect, and (2) what they experienced as helpful and (3) not helpful, respectively, through three qualitative measures, which constitute the main focus of the present study. These items were analyzed according to the procedures of the qualitative content analysis with inductive category development (47). In contrast to deductive category development where categories originate from existing theoretic models or data, inductive categories derive out of the text. First, the material is step-by-step divided into content analytic units. Out of these units, subsequently categories are generated by formulating a criterion

of definition. In the present study, one author (YZ) first deduced the formulation of categories, while in a second step, these categories were revised within a feedback loop with a second author (AG). Both raters then worked through the material independently and analyzed the content units a second time by following the final set of criteria for categorization (see **Supplementary Table**). The inter-coder reliability for question one (259 units) was Cohen's $\kappa = 0.63$, for question two (142 units) $\kappa = 0.78$ and for question three (68 units) $\kappa = 0.79$, that is, the overall inter-coder reliability was $\kappa = 0.73$, demonstrating sufficient intersubjective comprehensibility (47). Finally, both raters discussed their mismatches to agree on the respective category for each unit that matched the criterion best, so that quantitative aspects concerning the frequencies of coded categories could be analyzed. Paralleling the quantitative data analyses, responders and non-responders according to BDI change were compared with regard to the frequency of individual profits during group therapy (question one).

RESULTS

Sample Characteristics

A total of $N = 87$ patients (44 men, 43 women) with a mean age of 44.2 years (±10.8) participated in the study. Twenty-six patients were employed (30%), the majority was either unemployed (35%), in early retirement (24%), retired (5%) or in educational training (6%). Fifty-four patients (62%) lived without partner. Sixty patients (69%) reported an early onset of depression (<21 years) with a mean age of 16 years (±9.2), 11 patients (13%) did not remember the beginning of depressive symptoms. All patients fulfilled the criteria for PDD. Comorbid diagnoses are limited to information obtained from discharge letters, since we did not carry out structured clinical interviews. This may explain why only 25 patients (29%) were treated for a comorbid diagnosis, such as alcohol dependence with more than 6 months abstinence ($n = 7$), panic disorder with/without agoraphobia ($n = 6$), bulimia nervosa ($n = 3$), attention-deficit-(hyperactivity)-disorder ($n = 3$), psychosomatic disorders ($n = 2$), social phobia ($n = 1$), obsessive compulsive disorder ($n = 1$), enuresis nocturna ($n = 1$). One patient was diagnosed with Alzheimer's disease during CBASP treatment. According to the self-assessment of personality disorders according to DSM-IV [ADP-IV; (48)], the majority of patients (69%) fulfilled the criteria for at least one comorbid personality disorder, particularly in cluster C (avoidant, dependent, obsessive-compulsive). The frequency of childhood adversity was high (mean CTQ total score = 54.6±16.5), particularly concerning emotional neglect (mean subscale score = 16.6±5.7) and emotional abuse (14.1±5.4), whereas physical neglect (9.7±3.8) and abuse (8.4±4.5) were rather low to minimal; sexual abuse was mentioned very rarely (5.8±2). The majority of patients (86 %) had at least moderate to severe traumatization in one out of five subscales (49).

Regarding treatment outcome, patients reported severe depressive symptoms at pre-treatment ($BDI_{pre} = 32.8 \pm 10.3$), which decreased significantly to post-treatment ($t_{(83)} = 7.0$, $p < 0.001$, $d = 0.8$), although BDI scores remained on a moderate level ($BDI_{post} = 22.9 \pm 13.3$). Twenty-seven patients (32.1%) showed a significant response as demonstrated by a reduction of 50% from pre-treatment BDI score.

Quantitative Data: IIP-64 and IMI

As predicted, patients showed a significant reduction in general distress over therapy ($t_{(77)} = 4.9$, $p < 0.001$, $d = -0.6$; see **Table 1**). Regarding the IIP-64 octant scales, patients reported reduced interpersonal problems with most of the octant scales after therapy, except for domineering (PA) and vindictive behavior (BC) where patients posed almost no difficulties with at both time points. Therapists also perceived significant changes from pre to post treatment with values increasing particularly in IMI quadrant I (dominant, friendly-dominant, friendly) and decreasing particularly in quadrant III (hostile, hostile-submissive, submissive) of the IPC, as predicted. **Table 1** provides descriptive and change statistics with effect sizes for all octant subscale scores; **Figure 1** depicts the according graphical illustration on the IPC model.

Paralleling these results, change in general distress and change in depression severity showed a moderate association over all patients ($r_{s(76)} = 0.57$, $p < 0.001$), that is, the higher the symptom improvement was from pre to post-treatment the higher was the reduction of interpersonal distress or vice versa.

Group Evaluation

Out of the investigated sample, $n = 69$ patients (79%) answered the feedback form at the end of treatment. They reported satisfying motivation (M = 2.0±0.9) and engagement (M = 2.2±0.9) for group therapy and evaluated the group with an overall grade of 1.7 (±0.7) indicating very good acceptance.

"What Have You Learned Throughout Group Therapy?"

From $n = 58$ patients who answered question 1 of the feedback form, 259 content units were derived for qualitative content analysis. These units comprised the following specific aspects, which were defined to facilitate allocation to content categories: Patients differentiated between acquisition of skills (active) and gain in knowledge (passive), both of which concerned either themselves as individuals (intrapersonal) or their interactions with others (interpersonal). Following these aspects, five inductive content categories were derived (**Supplementary Table 1**): (a) *social competence,* (b) *self-confidence,* (c) *self-reflection,* (d) *interpersonal dynamics,* and (e) *optimism/universality*. Accordingly, we specified content units that matched the category *self-reflection* to represent a progress in insights to personal needs as passive and intrapersonal, while a progress in *social competence* represented a combination of active and interpersonal aspects. Concerning the number of categories (**Figure 2**), the most frequent answers delineated gain in *social competence* (reported from 69% of patients), followed by gain in *self-confidence* (62.1%) and *self-reflection* (60.3%). As expected, patients who responded to CBASP (ΔBDI≥50%, $n = 22$) reported significantly more individual benefit (M = 3.2±0.9 out of five categories) than those with response rates of <50% ($n = 36$, M = 2.5±1.1) from baseline ($U = 253.5$, $Z = -2.4$, $p = 0.02$). Importantly, data availability

TABLE 1 | IIP-64 and IMI subscale scores (M, SD).

IIP-64 subscales	pre ($n = 85$)	post ($n = 79$)	Statistics	Cohen's *d*
PA—domineering	1.1 (0.6)	1.0 (0.6)	$t_{(77)} = 1.8$, $p = 0.079$	−0.2
BC—vindictive	1.5 (0.6)	1.5 (0.7)	$t_{(77)} = 1.4$, $p = 0.156$	−0.2
DE—cold	2.1 (0.8)	1.8 (0.8)	$t_{(77)} = 3.9$, $p < 0.001$*	−0.4
FG—avoidant	2.6 (0.8)	2.1 (0.8)	$t_{(77)} = 4.8$, $p < 0.001$*	−0.5
HI—non-assertive	2.7 (0.8)	2.4 (0.7)	$t_{(77)} = 3.4$, $p = 0.001$*	−0.4
JK—exploitable	2.4 (0.6)	2.0 (0.7)	$t_{(77)} = 4.8$, $p < 0.001$*	−0.6
LM—overly nurturant	2.5 (0.6)	2.1 (0.7)	$t_{(77)} = 4.5$, $p < 0.001$*	−0.6
NO—intrusive	1.4 (0.7)	1.2 (0.6)	$t_{(77)} = 3.5$, $p = 0.001$*	−0.3
General distress	2.0 (0.4)	1.8 (0.5)	$t_{(77)} = 4.9$, $p < 0.001$*	−0.6
IMI subscales	**pre (n = 83)**	**post (n = 83)**	**Statistics**	**Cohen's *d***
Dominant	2.0 (0.6)	2.4 (0.5)	$t_{(80)} = -6.1$, $p < 0.001$*	0.6
Friendly-dominant	2.1 (0.6)	2.7 (0.5)	$t_{(80)} = -8.6$, $p < 0.001$*	0.9
Friendly	2.4 (0.5)	3.2 (0.5)	$t_{(80)} = -9.8$, $p < 0.001$*	1.2
Friendly-submissive	2.5 (0.6)	2.6 (0.4)	$t_{(80)} = -0.8$, $p = 0.446$	0.1
Submissive	2.7 (0.7)	2.3 (0.6)	$t_{(80)} = 5.5$, $p = 0.001$*	−0.6
Hostile-submissive	2.7 (0.6)	2.2 (0.6)	$t_{(80)} = 6.6$, $p < 0.001$*	−0.7
Hostile	2.2 (0.6)	1.6 (0.5)	$t_{(80)} = 7.7$, $p < 0.001$*	−0.9
Hostile-dominant	2.0 (0.7)	1.8 (0.5)	$t_{(80)} = 2.7$, $p = 0.009$	−0.3

**Significant result (p-value ≤ 0.003, Bonferroni-corrected).*

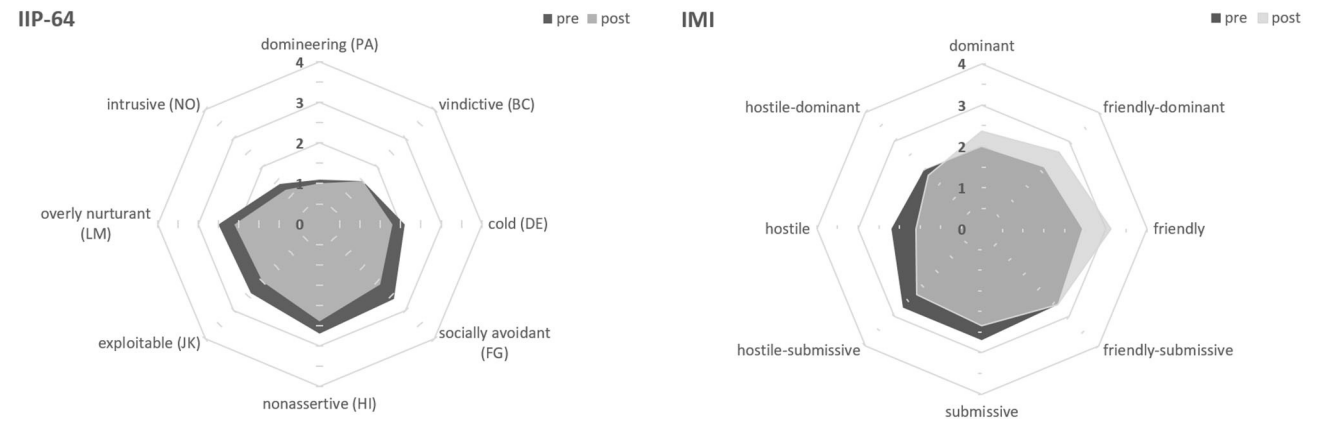

FIGURE 1 | Circumplex models of the IIP-64 and IMI octants. Pre-treatment values (dark gray) represent interpersonal problems as perceived by patients (IIP-64, left) and impact messages as perceived by their therapists (IMI, right). Post-treatment values (light gray) indicate change over therapy.

was not biased by response to treatment, i.e. responders and non-responders did not differ in providing feedback at all ($\chi^2_{(1)} = 1.6$, $p = 0.207$).

"What Was Particularly Helpful or Unhelpful During Group Therapies?"

Fourty-nine patients made comments with regard to particularly helpful aspects of CBASP group therapy, $n = 40$ patients commented on negative aspects (**Supplementary Table 2**).

Six categories regarding helpful factors were derived from content analysis, that is, *specific CBASP techniques* (role play, SA, IPC model) mentioned by $n = 30$ patients (61.2%), *working atmosphere and therapeutic competence* ($n = 25$, 51%), *group cohesion* ($n = 22$, 44.9%), *individual progress* in the behavioral domain ($n = 13$, 26.5%), *feedback* ($n = 12$, 24.5%), and *handouts and work sheets* ($n = 2$, 4.1%).

Regarding the factors that impeded progress during group therapy, patients mentioned *conceptual issues* mostly regarding time limits ($n = 36$, 90%), *outside disturbances* ($n = 15$, 37.5%), *deficits in group cohesion* ($n = 6$, 15%), *doubts upon the CBASP concept* ($n = 3$, 7.5%) and *group size* ($n = 2$, 5.6%). Concerning the main category *conceptual issues*, some patients criticized a

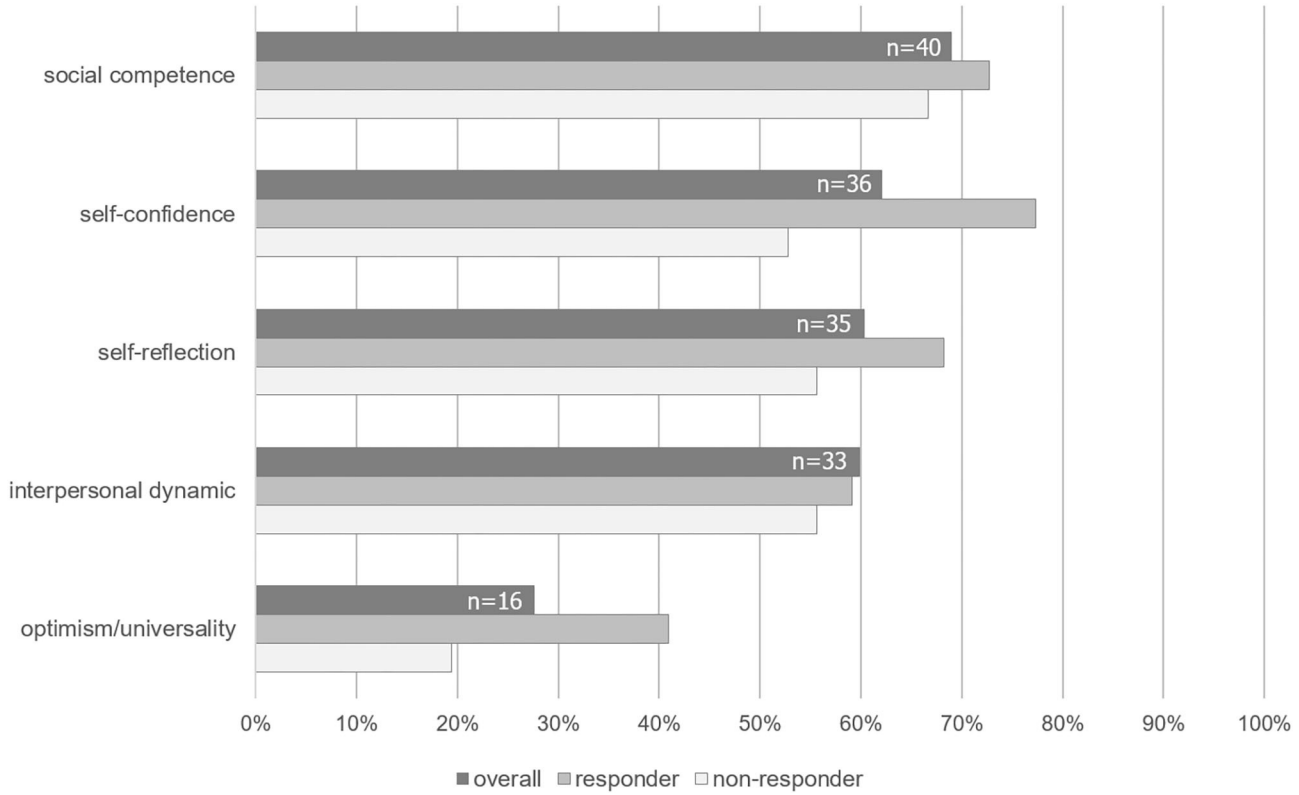

FIGURE 2 | Frequencies of categories mentioned as benefit from group therapy derived from qualitative data. Dark gray bars depict the overall sample of $n = 58$ PDD patients, who answered the feedback form (question 1). Lighter bars represent the frequencies of categories identified by responders and non-responders to CBASP according to BDI. Note that frequencies differ due to the open format of the questionnaire.

lack of introduction to the group that felt like throwing them into cold water [*direct quotation*]. These patients would have wished for individual sessions prior to entering group therapy. Another issue comprised the long duration of the SA training group; three patients reported having felt pressured to provide enough material for the SA group.

DISCUSSION

The present study investigated interpersonal change during a multimodal inpatient CBASP treatment with a special focus on CBASP group therapy. Since the goals of CBASP group therapy parallel those described for individual therapy, the group was expected to boost the treatment effects regarding (1) felt interpersonal safety and (2) perceived functionality. In a nutshell, the group should counter-condition the interpersonal fear of emotional neglect and abuse rooted in the PDD patients' learning history. Both treatment goals aim at (re)connecting patients with their social environment, since overcoming social isolation is considered indispensable for the successful treatment of chronic depression (5).

As derived from our quantitative and qualitative data in a naturalistic setting, CBASP group therapy may contribute to the improvement of interpersonal functioning in PDD patients. Patients reported reduced general distress after therapy, which may indicate reduced feelings of hopelessness as proposed by the CBASP model. They described themselves as having less problems in the domains of submissiveness and hostility, which paralleled the patients' impact messages on their therapists. As predicted, patients changed from submissive and hostile interpersonal style to more friendly and dominant behavior.

Since the effects of group therapy on these quantitative interpersonal changes could not be separated from those of individual therapy in our treatment setting, we additionally asked patients to reflect on competencies learned specifically during CBASP group therapy. From the patients' perspective, five factors contributed to the benefit of group therapy: Gain in social competence, self-confidence, self-reflection, interpersonal dynamics, and optimism/universality. These factors were derived from inductive qualitative content analysis, but can be related to common factors in group therapy identified in quantitative research (50), that is, social learning, secure emotional learning, awareness of relational impact, and installation of hope. The majority of our PDD patients reported gain in social competence throughout CBASP group sessions. We suggest that the highly structured skill training within SA and KCT group, made social competence the most frequently mentioned benefit of CBASP group therapy. This interpretation of social competence as

specific change factor to CBASP is limited by our naturalistic design, but in accordance with Klein et al. (51), who found patients receiving CBASP to exhibit significantly greater gains in social problem solving and positive problem orientation than patients receiving brief supportive therapy. The second and third frequent categories, self-confidence and self-reflection, refer to intrapersonal processes of the individual as a group member and may indicate that CBASP patients started to reflect on themselves as part of a social network, therewith overcoming the cycle of isolation. An insight into interpersonal dynamics the fourth change factor, can be regarded as necessary precondition to approach social interactions. Again, interpersonal dynamics might be a common factor, but it may also be specific to CBASP, since CBASP therapists provide explicit feedback to their patients (DPI) and encourage fellow patients to provide feedback as well. The fifth change factor identified in the present study was optimism/universality. It incorporates a sense of belonging and acceptance by others. Although the installation of hope is regarded a common factor in group therapy, it is remarkable that PDD patients draw strengths from a group, although they are supposed to live disconnected from others, which may explain the high rate of patients living without partner in the present sample. This may indicate progress in felt interpersonal safety, one of the two treatment goals in CBASP.

Considering the CBASP model, identification of change factors should contribute to positive treatment outcome. Accordingly, patients who responded to CBASP identified significantly more beneficial factors than non-responders, particularly with regard to self-confidence and self-reflection, and CBASP benefit was related to less interpersonal distress as provided by the CBASP model (5). Obviously, this finding may be biased given the fact that responders might have expressed their gratitude to therapists by filling in the evaluation form. However, responders were not more likely to provide feedback than non-responders.

The reported factors that boosted or impeded the effect of group therapy both surprisingly comprised group cohesion amongst others. On one hand, a sense of belonging seems to match the need for social contacts of PDD patients, on the other hand a lack of group cohesion may increase distrust and impede progress in CBASP goals. Leading group therapies thus places high demands on CBASP therapists. Accordingly, patients evaluated the therapists' expertise as second most helpful aspect. This category included clear instructions, for instance while doing SAs, and active inclusion of all group members. Most units of this category related to the DPI principles, that is, patients appreciated to be promoted and challenged at the same time, and described a feeling of safety within the group due to the actively communicated empathy including constructive feedback and the establishment of group rules by the therapists. CBASP therapists' expertise probably promoted another common factor of psychotherapy, that is therapeutic alliance (52), which in turn may have contributed to interpersonal functioning [see (53, 54).

Major limitations of the present study need to be discussed. Interpersonal change during CBASP inpatient treatment considering particularly the feasibility and efficacy of CBASP group therapy comprised the main focus of our study; however, group therapy was only one out of several treatment components. Although we consider CBASP group therapy very important for PDD patients, the present data must be regarded as reflecting a combined influence of the individual and group modality on interpersonal functioning. For comparison, Constantino et al. (17) found lower effect sizes for IMI changes particularly concerning friendly, dominant, hostile, and friendly-submissive behavior in outpatients receiving 16 individual CBASP sessions, suggesting superior effectiveness of the inpatient setting including group therapy on interpersonal functioning. However, it should be noted that, besides CBASP group therapy, inpatient treatment entails other ingredients that might have positively influenced outcome. Future studies are warranted that investigate the benefits of combined individual and group CBASP therapy over individual CBASP in a randomized controlled design. Furthermore, CBASP group therapy was evaluated in a naturalistic design without an active competitor. Thus, although it is tempting to trace the qualitative and quantitative results on interpersonal functioning back to CBASP (51), it is an open question whether a treatment irrespective of the CBASP model would have obtained similar results. In this regard, unspecific effects of the inpatient setting such as treatment duration [e.g. (55, 56)] might also account for the reduction of general distress. Results from previous studies conducting other interventions than CBASP were heterogeneous with regard to effects on interpersonal functioning: Cognitive interventions yielded effect sizes that were comparable to our results (57) or even larger (58) while effects of interpersonal psychotherapy were smaller (59). Notably, the present inpatient sample suffered from a higher degree of interpersonal problems than the outpatients included in these previous studies, which limits comparability. Future studies should compare interventions directly to differentiate intervention-specific from more general treatment effects on interpersonal functioning. A further limitation refers to the lack of a structured diagnostic interview to characterize the sample with regard to comorbid disorders. Importantly, but limited to self-report, there was a high comorbidity with personality disorders. It is tempting to speculate that the proposed group interventions for situational analysis and Kiesler's Circle Training may be similarly advantageous for patients with personality disorders irrespective of a PDD diagnosis. Future studies should investigate the benefit of both group therapies also for other diagnosis with interpersonal problems. Independent raters who evaluate interpersonal behavior from videotaped therapy sessions [e.g., (60)] or raters who are familiar to the patient, but not related to the therapeutic process, such as partners or friends [e.g., (43, 45)] may further increase the validity of the observed interpersonal changes.

To summarize the present results, we conclude with recommendations for CBASP group therapy while considering helpful and unhelpful factors identified by CBASP inpatients:

1. Patients should be prepared for entering into CBASP group therapy in individual sessions. CBASP therapists should encourage patients to reflect on concerns or fears of the group with regard to the individual significant other history (e.g., "When I disclose my feelings, other group members will laugh

at me."). These concerns are suitable for defining a specific treatment goal for the group (e.g., "I will learn to express my feelings."), which will increase the number of corrective interpersonal experiences.

2. CBASP therapists should support patients to actively practice CBASP techniques (SA, interpersonal circle), since patients benefitted from increased social competence the most. Therefore, role plays, work sheets and transcripts during group sessions seem important.

3. Therapists should be aware of group cohesion by considering specific stages of group development [cf. (61)]. They should actively integrate rather than force more submissive group members to contribute to the group and should be aware of interpersonal situations arising within the group to apply SA and IPC techniques, therewith demonstrating their effectiveness in coping with conflictual interpersonal situations within the group.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Charité's Ethics Committee, Charitéplatz 1, 10117 Berlin. The patients provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

AG: conceptualization and implementation of the study design, data collection, data analyses, and writing the original draft. DS: quantitative data analysis and editing the draft. YZ: qualitative data analysis and editing the draft PS: conceptualization and implementation of the study design, supervision of data analyses, editing the draft, revision. SK: conceptualization and implementation of the study design, funding acquisition, and editing the draft. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2021.620037/full#supplementary-material

REFERENCES

1. Nübel J, Guhn A, Mullender S, Le HD, Cohrdes C, Köhler S. Persistent depressive disorder across the adult lifespan: results from clinical and population-based surveys in Germany. *BMC Psychiatry*. (2020) 20:58. doi: 10.1186/s12888-020-2460-5
2. Keller MB, McCullough JP, Klein DN, Arnow B, Dunner DL, Gelenberg AJ, et al. A comparison of nefazodone, the cognitive behavioral-analysis system of psychotherapy, and their combination for the treatment of chronic depression. *N Engl J Med*. (2000) 342:1462–70. doi: 10.1056/NEJM200005183422001
3. Cuijpers P, Andersson G, Donker T, van Straten A. Psychological treatment of depression: results of a series of meta-analyses. *Nord J Psychiatry*. (2011) 65:354–64. doi: 10.3109/08039488.2011.596570
4. Schramm E, Klein DN, Elsaesser M, Furukawa TA, Domschke K. Review of dysthymia and persistent depressive disorder: history, correlates, and clinical implications. *Lancet Psychiatry*. (2020) 7:801–12. doi: 10.1016/s2215-0366(20)30099-7
5. McCullough JP. *Treatment for Chronic Depression: Cognitive Behavioral Analysis System of Psychotherapy*. New York, NY: Guilford Press (2000).
6. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. Arlington, VA: American Psychiatric Publishing (2013).
7. Nanni V, Uher R, Danese A. childhood maltreatment predicts unfavorable course of illness and treatment outcome in depression: a meta-analysis. *Am J Psychiatry*. (2012) 169:141–51. doi: 10.1176/appi.ajp.2011.11020335
8. Nelson J, Klumparendt A, Doebler P, Ehring T. Childhood maltreatment and characteristics of adult depression: meta-analysis. *Br J Psychiatry*. (2017) 210:96–104. doi: 10.1192/bjp.bp.115.180752
9. Struck N, Krug A, Yuksel D, Stein F, Schmitt S, Meller T, et al. Childhood maltreatment and adult mental disorders—the prevalence of different types of maltreatment and associations with age of onset and severity of symptoms. *Psychiatry Res*. (2020) 293:113398. doi: 10.1016/j.psychres.2020.113398
10. Huh HJ, Kim SY, Yu JJ, Chae JH. Childhood trauma and adult interpersonal relationship problems in patients with depression and anxiety disorders. *Ann Gen Psychiatry*. (2014) 13:26. doi: 10.1186/s12991-014-0026-y
11. McCullough JP. Treatment for chronic depression using Cognitive Behavioral Analysis System of Psychotherapy (CBASP). *J Clin. Psychol*. (2003) 59:833–46. doi: 10.1002/jclp.10176
12. Leary T. *Interpersonal Diagnoses of Personality*. New York, NY: Ronald Press (1957).
13. Pincus AL, Wright AGC. Interpersonal diagnosis of psychopathology. In: Horowitz LM, Strack S, editors. *Handbook of Interpersonal Psychology: Theory, Research, Assessment And Therapeutic Interventions*. New Jersey: John Wiley and Sons, Inc. (2011). p. 359–81.
14. Barrett MS, Barber JP. Interpersonal profiles in major depressive disorder. *J Clin Psychol*. (2007) 63:247–66. doi: 10.1002/jclp.20346
15. Grosse Holtforth M, Altenstein D, Krieger T, Flückiger C, Wright AG, Caspar F. Interpersonal differentiation within depression diagnosis: relating interpersonal subgroups to symptom load and the quality of the early therapeutic alliance. *Psychother Res*. (2014) 24:429–41. doi: 10.1080/10503307.2013.829253
16. Bird T, Tarsia M, Schwannauer M. Interpersonal styles in major and chronic depression: a systematic review and meta-analysis. *J Affect Disord*. (2018) 239:93–101. doi: 10.1016/j.jad.2018.05.057
17. Constantino MJ, Manber R, Degeorge J, McBride C, Ravitz P, Zuroff DC, et al. Interpersonal styles of chronically depressed outpatients: Profiles and therapeutic change. *Psychotherapy*. (2008) 45:491–506. doi: 10.1037/a0014335
18. Kiesler DJ. The 1982 Interpersonal circle: a taxonomy for complementarity in human transactions. *Psychol Rev*. (1983) 90:185–214.

19. Köhler S, Chrysanthou S, Guhn A, Sterzer P. Differences between chronic and nonchronic depression: systematic review and implications for treatment. *Depress Anxiety.* (2019) 36:18–30. doi: 10.1002/da.22835
20. McCullough JP. *Treating Chronic Depression With Disciplined Personal Involvement*. New York, NY: Springer Science, Business Media (2006).
21. Schramm E, Zobel I, Schoepf D, Fangmeier T, Schnell K, Walter H, et al. Cognitive Behavioral Analysis System of Psychotherapy versus Escitalopram in Chronic Major Depression. *Psychother Psychosom.* (2015) 84:227–40. doi: 10.1159/000381957
22. Wiersma JE, Van Schaik DJ, Hoogendorn AW, Dekker JJ, Van HL, Schoevers RA, et al. The effectiveness of the cognitive behavioral analysis system of psychotherapy for chronic depression: a randomized controlled trial. *Psychother Psychosom.* (2014) 83:263–9. doi: 10.1159/000360795
23. Schramm E, Zobel I, Dykierek P, Kech S, Brakemeier EL, Kulz A, et al. Cognitive behavioral analysis system of psychotherapy versus interpersonal psychotherapy for early-onset chronic depression: a randomized pilot study. *J Affect Disord.* (2011) 129:109–16. doi: 10.1016/j.jad.2010.08.003
24. Schramm E, Kriston L, Zobel I, Bailer J, Wambach K, Backenstrass M, et al. Effect of disorder-specific vs nonspecific psychotherapy for chronic depression: a randomized clinical trial. *JAMA Psychiatry.* (2017) 74:233–42. doi: 10.1001/jamapsychiatry.2016.3880
25. Nemeroff CB, Heim CM, Thase ME, Klein DN, Rush AJ, Schatzberg AF, et al. Differential responses to psychotherapy versus pharmacotherapy in patients with chronic forms of major depression and childhood trauma. *Proc Natl Acad Sci.* (2003) 100:14293–6. doi: 10.1073/pnas.2336126100
26. Klein JP, Erkens N, Schweiger U, Kriston L, Bausch P, Zobel I, et al. Does childhood maltreatment moderate the effect of the cognitive behavioral analysis system of psychotherapy versus supportive psychotherapy in persistent depressive disorder? *Psychother Psychosom.* (2018) 87:46–8. doi: 10.1159/000484412
27. Serbanescu I, Walter H, Schnell K, Kessler H, Weber B, Drost S, et al. Combining baseline characteristics to disentangle response differences to disorder-specific versus supportive psychotherapy in patients with persistent depressive disorder. *Behav Res Ther.* (2020) 124:103512. doi: 10.1016/j.brat.2019.103512
28. Brakemeier E-L, Radtke M, Engel V, Zimmermann J, Tuschen-Caffier B, Hautzinger M, et al. Overcoming treatment resistance in chronic depression: a pilot study on outcome and feasibility of the cognitive behavioral analysis system of psychotherapy as an inpatient treatment program. *Psychother Psychosom.* (2015) 84:51–6. doi: 10.1159/000369586
29. Sabaß L, Padberg F, Normann C, Engel V, Konrad C, Helmle K, et al. Cognitive Behavioral Analysis System of Psychotherapy as group psychotherapy for chronically depressed inpatients: a naturalistic multicenter feasibility trial. *Eur Arch Psychiatry Clin Neurosci.* (2017) 268:783–96. doi: 10.1007/s00406-017-0843-5
30. Guhn A, Köhler S, Brakemeier E-L, Sterzer P. Cognitive Behavioral Analysis System of Psychotherapy for inpatients with persistent depressive disorder: a naturalistic trial on a general acute psychiatric unit. *Eur Arch Psychiatry Clin Neurosci.* (2019). doi: 10.1007/s00406-019-01038-5
31. Constantino MJ, Laws HB, Arnow BA, Klein DN, Rothbaum BO, Manber R. The relation between changes in patients' interpersonal impact messages and outcome in treatment for chronic depression. *J Consult Clin Psychol.* (2012) 80:354–64. doi: 10.1037/a00283510
32. Sayegh L, Locke KD, Daniele Pistilli D, Penberthy JK, Chachamovich E, McCullough JP, et al. Cognitive behavioural analysis system of psychotherapy for treatment-resistant depression: adaptation to a group modality. *Behav Change.* (2012) 29:97–108.
33. Michalak J, Schultze M, Heidenreich T, Schramm E. A randomized controlled trial on the efficacy of mindfulness-based cognitive therapy and a group version of cognitive behavioral analysis system of psychotherapy for chronically depressed patients. *J Consult Clin Psychol.* (2015) 83:951–63. doi: 10.1037/ccp0000042
34. Locke KD, Sayegh L, Penberthy JK, Weber C, Haentjens K, Turecki G. Interpersonal circumplex profiles of persistent depression: goals, self-efficacy, problems, and effects of group therapy. *J Clin Psychol.* (2017) 73:595–611. doi: 10.1002/jclp.22343
35. Potijk MR, Aan Het Rot M, Parlevliet FM, Schoevers RA, Eldering MJ. Group cognitive behavioural analysis system of psychotherapy (CBASP) for persistently depressed outpatients: a retrospective chart review. *Br J Clin Psychol.* (2020) 59:552–64. doi: 10.1111/bjc.12266
36. Brakemeier E-L, Merkl A, Wilbertz G, Quante A, Regen F, Bührsch N, et al. Cognitive-behavioral therapy as continuation treatment to sustain response after electroconvulsive therapy in depression: a randomized controlled trial. *Biol Psychiatry.* (2014) 76:194–202. doi: 10.1016/j.biopsych.2013.11.030
37. Brakemeier EL, Guhn A, Normann C. *Praxisbuch CBASP*. Behandlung chronischer Depression und Modifikationen der traditionellen CBASP-Therapie. Weinheim: Beltz (2021).
38. Guhn A, Köhler S, Brakemeier EL. *Kiesler-Kreis-Training.* Manual zur Behandlung interpersoneller Probleme. Weinheim: Beltz (2019).
39. Horowitz LM, Strauß B, Kordy H. *Inventar zur Erfassung Interpersonaler Probleme.* Deutsche Version (IIP-D). Göttingen: Beltz (2000).
40. Caspar F, Berger T, Fingerle H, Werner M. Das deutsche IMI. *Psychotherapie im Dialog.* (2016) 17:1–10. doi: 10.1055/s-0042-105981
41. Brähler E, Horowitz LM, Kordy H, Schumacher J, Strauß B. Zur Validierung des Inventars zur Erfassung Interpersonaler Probleme (IIP)—Ergebnisse einer Repräsentativbefragung in Ost- und Westdeutschland. [Validation of the Inventory of Interpersonal Problems (IIP)—Results of a representative study in East and West Germany.]. *Psychotherapie Psychosomatik Medizinische Psychologie.* (1999) 49:422–31.
42. Vittengl JR, Clark LA, Jarrett RB. Interpersonal problems, personality pathology, and social adjustment after cognitive therapy for depression. *Psychol Assess.* (2003) 15:29–40. doi: 10.1037/1040-3590.15.1.29
43. Altenstein-Yamanaka D, Zimmermann J, Krieger T, Dorig N, Grosse Holtforth M. Self-reported interpersonal problems and impact messages as perceived by significant others are differentially associated with the process and outcome of depression therapy. *J Couns Psychol.* (2017) 64:410–23. doi: 10.1037/cou0000221
44. Schmidt JA, Wagner CC, Kiesler DJ. Psychometric and circumplex properties of the octant scale impact message inventory (IMI-C): a structural evaluation. *J Counseling Psychol.* (1999) 46:325–34. doi: 10.1037/0022-0167.46.3.325
45. Grosse Holtforth M, Altenstein D, Ansell E, Schneider C, Caspar F. Impact messages of depressed outpatients as perceived by their significant others: profiles, therapeutic change, and relationship to outcome. *J Clin Psychol.* (2012) 68:319–33. doi: 10.1002/jclp.20854
46. Beck AT, Steer RA, Brown GK. *Manual for the Beck Depression Inventory-II.* San Antonio, TX: Psychological Corporation (1996).
47. Mayring P. Qualitative Content Analysis [28 paragraphs]. *Forum Qualitative Sozialforschung/Forum: Qualitative Social Research.* (2000) 1(2), Art. 20.
48. Schotte CK, De Doncker DA, Dmitruk D, Van Mulders I, D'Haenen H, Cosyns P. The ADP-IV questionnaire: differential validity and concordance with the semi-structured interview. *J Pers Disord.* (2004) 18:405–19. doi: 10.1521/pedi.18.4.405.40348
49. Bernstein D, Fink L. *Childhood Trauma Questionnaire: A Retrospective Self-Report*. San Antonio, TX: The Psychological Corporation (1998).
50. Macnair-Semands RR, Ogrodniczuk JS, Joyce AS. Structure and initial validation of a short form of the therapeutic factors inventory. *Int J Group Psychother.* (2010) 60:245–81. doi: 10.1521/ijgp.2010.60.2.245
51. Klein DN, Leon AC, Li C, D'Zurilla TJ, Black SR, Vivian D, et al. Social problem solving and depressive symptoms over time: a randomized clinical trial of cognitive-behavioral analysis system of psychotherapy, brief supportive psychotherapy, and pharmacotherapy. *J Consult Clin Psychol.* (2011) 79:342–52. doi: 10.1037/a0023208
52. Köhler S, Guhn A, Betzler F, Stiglmayr C, Brakemeier E-L, Sterzer P. Therapeutic Self-Disclosure within DBT, Schema Therapy, and CBASP: opportunities and challenges. *Front Psychol.* (2017). 8:73. doi: 10.3389/fpsyg.2017.02073
53. Constantino MJ, Laws HB, Coyne AE, Greenberg RP, Klein DN, Manber R, et al. Change in patients' interpersonal impacts as a mediator of the alliance-outcome association in treatment for chronic depression. *J Consult Clin Psychol.* (2016) 84: 1135–44. doi: 10.1037/ccp0000149
54. Klein JP, Probst T, Kriston L, Assmann N, Bailer J, Eich H, et al. Changes in therapeutic alliance and in social inhibition as mediators of the effect of the cognitive behavioral analysis system of psychotherapy: a secondary analysis

from a randomized clinical trial. *Psychother Psychosom.* (2020) 89:261–2. doi: 10.1159/000506082
55. Härter M, Sitta P, Keller F, Metzger R, Wiegand W, Schell G, et al. Stationäre psychiatrisch-psychotherapeutische Depressionsbehandlung. *Der Nervenarzt.* (2004) 75:1083–91. doi: 10.1007/s00115-004-1705-8
56. Hölzel L, Wolff AV, Kriston L, Härter M. Unter welchen Bedingungen bleibt eine stationäre Depressionsbehandlung erfolglos? *Psychiatrie Praxis.* (2010) 37:27–33. doi: 10.1055/s-0029-1223348
57. Grosse-Holtforth M, Lutz W, Grawe K. Structure and change of the IIP-D pre- and postpsychotherapy: a replication using a Swiss clinical sample. *Eur J Psychol Assess.* (2006) 22:98–103. doi: 10.1027/1015-5759.22.2.98
58. Vittengl JR, Clark LA, Thase ME, Jarrett RB. Longitudinal social-interpersonal functioning among higher-risk responders to acute-phase cognitive therapy for recurrent major depressive disorder. *J Affect Disord.* (2016) 199:148–56. doi: 10.1016/j.jad.2016.04.017
59. Ravitz P, Maunder R, McBride C. Attachment, contemporary interpersonal theory and ipt: an integration of theoretical, clinical, and empirical perspectives. *J Contemporary Psychother.* (2007) 38:11–21. doi: 10.1007/s10879-007-9064-y
60. Richtberg S, Jakob M, Höfling V, Weck F. Assessment of patient interpersonal behavior: development and validation of a rating scale. *Psychother Res.* (2016) 26:106–19. doi: 10.1080/10503307.2014.94739
61. Tuckman BW, Jensen MAC. Stages of small group development revisited. *Group Organization Studies.* (1977) 2:419–27.

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Borderline Personality Features in Patients With Persistent Depressive Disorder and Their Effect on CBASP Outcome

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Introduction: The Cognitive Behavioral Analysis System of Psychotherapy (CBASP) was developed for the treatment of persistent depressive disorder (PDD), where comorbid personality disorders (PD) are common. In contrast to other PD, comorbid borderline personality disorder (BPD) is often regarded as an exclusion criterion for CBASP. In clinical settings, however, subthreshold BPD symptoms are prevalent in PDD and may not be obvious at an initial assessment prior to therapy. As data on their impact on CBASP outcome are very limited, this naturalistic study investigates BPD features in PDD and their relevance for the therapeutic outcome of a multimodal CBASP inpatient program.

Method: Sixty patients (37 female, mean age 38.3, SD 11.9 years) meeting DSM-5 criteria for PDD underwent a 10 weeks CBASP inpatient program. BPD features (i.e., number of fulfilled DSM-5 criteria) together with childhood maltreatment and rejection sensitivity were assessed on admission. Before and after treatment, severity of depressive symptoms was measured using the Montgomery-Asberg Depression Rating Scale (MADRS) and the Beck Depression Inventory (BDI-II). BPD symptoms were assessed using the Borderline Personality Disorder Severity Index (BPDSI-IV) and the Borderline Symptom List (BSL-23). Intercorrelations of baseline characteristics and symptom change during treatment were analyzed.

Results: Patients with PDD met a mean of 1.5 (SD 1.6) BPD criteria with 4 patients fulfilling ≥5 criteria. BPD symptoms and depressive symptoms showed a strong correlation, and BPD symptoms were additionally correlated with emotional abuse and rejection sensitivity. There was no association between BPD features at baseline and improvement on the MADRS, however, BPD features tended to be associated with a lower response according to the BDI-II score after 10 weeks of treatment. Furthermore, BPD symptoms (i.e., abandonment, impulsivity and affective instability) were reduced after 10 weeks of CBASP treatment.

Discussion: BPD symptoms are prevalent in patients with PDD and highly intertwined with the experience of depressive symptoms. In this naturalistic study in PDD, BPD

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features at baseline did not limit the clinical response to CBASP. Future studies may extend the spectrum of PDD to comorbid subsyndromal or even syndromal BPD in order to develop tailored psychotherapeutic treatment for these complex affective disorders.

Keywords: persistent depressive disorder, borderline personality disorder, comorbidity, CBASP, childhood maltreatment, rejection sensitivity

INTRODUCTION

Persistent depressive disorder (PDD) is a highly debilitating psychological condition characterized by interpersonal difficulties and a high rate of comorbidities (1–3). PDD is defined by a duration of depressive symptoms for a minimum of 2 years and ranging in severity from dysthymia to chronic major depression [according to DSM-5, (4)]. Findings suggest that about a third of all depressed patients develop a chronic form of depression (3, 5, 6). Compared to non-chronic forms of depression, PDD patients tend to have a significantly earlier onset and higher levels of treatment resistance (1, 2, 5).

PDD and personality disorders (PD) often co-occur and presence of both may result in higher severity and duration of depressive symptoms. Studies suggest that the prevalence of comorbid PD in PDD patients is ranging from 51.2% (7) up to 70% (8, 9). Comorbid PD has been shown to be related to higher severity of depressive symptoms (8). Vice versa, it has been indicated that an increasing duration of depressive episodes is associated with a higher frequency of PD diagnoses (10). For PDD, early onset of depression has been linked to higher rates of comorbid PD than late onset (8, 11). In addition, common factors between PDD and PD may exist and symptoms like interpersonal difficulties may overlap (12, 13).

Borderline personality disorder (BPD) is characterized by a pattern of affective instability, impulsivity and identity problems including dissociative symptoms, chronic feelings of emptiness, difficulty in controlling anger and suicidal behavior or threats (4). Evidence suggests that prevalence of BPD in depression is quite common: Comorbid BPD was found in 28% of dysthymic patients and was even more pronounced in early onset dysthymics with 42% (8). Other epidemiological studies suggest lower prevalence rates of lifetime BPD in lifetime major depressive disorder (MDD) and dysthymia, i.e., 11.5% and 16.7%, respectively (14). The other way around, mood disorders are highly prevalent in BPD patients with an 83% lifetime prevalence of comorbid MDD (15). Patients suffering from both, depression and BPD, seem to be more likely to experience a chronic course of depression (16) and BPD is a robust predictor of persistence of MDD (17). This finding persisted even after controlling for other prognostic indicators such as age at onset, treatment history or previous episodes (18).

PDD and BPD share similar risk factors and it has been suggested that high rates of comorbidity between PD and PDD might be due to shared etiological factors such as genetics, temperamental vulnerability, self-generated interpersonal stress or childhood maltreatment (CM) including invalidating educational patterns (13, 19). PDD patients experience a higher number of traumatic events during their lifetime than patients with non-chronic forms of depression (1, 3, 20). CM has been associated with severity and chronicity of depression in numerous studies (21, 22). BPD has also been associated with CM and an invalidating family environment according to Linehan's biopsychosocial model (23). Indeed, CM (including family adversity, exposure to physical and sexual abuse or neglect) has been found to be a robust BPD risk factor in a systematic review (24) and both PDD and BPD patients showed a high trauma load in the Childhood Trauma Questionnaire [CTQ, (25)]. One putative link from CM to later psychopathology may be an induced trait of rejection sensitivity, i.e., oversensitivity to and expectation of social rejection (26). Rejection sensitivity has been found to be associated with PDD (27, 28) and BPD (29). Thus, rejection sensitivity may theoretically mediate the path from CM to both PDD and BPD symptoms.

A psychotherapy approach that has been specifically developed for the treatment of PDD is the Cognitive Behavioral Analysis System of Psychotherapy [CBASP, (30)]. CBASP has been shown to be an effective treatment for PDD [e.g., (31, 32)], and the combination of CBASP with antidepressant medication is recommended by a guidance paper from the European Psychiatric Association for the treatment of PDD (33). In addition, Schramm et al. (34) found that CBASP outperformed nonspecific supportive psychotherapy in a sample of 268 PDD outpatients without antidepressant medication. CBASP may be particularly effective in patients with a history of CM (35, 36).

In terms of the effect of comorbid PD on CBASP treatment outcome, previous findings have been quite heterogeneous. Erkens et al. (12) found no significant main effect of PD (mostly cluster C PD) reducing the effectiveness of CBASP. Similarly, Maddux et al. (37) found no significant effect of comorbid PD on the outcome after receiving CBASP, pharmacotherapy or the combination. In those two and many other studies investigating the effectiveness of CBASP, the spectrum of comorbid PD has been limited by the in- and exclusion criteria applied and mainly focused on cluster C PD. That is, patients with comorbid BPD [e.g., (12, 34, 38)] or severe forms of BPD [e.g., (37, 39)] were not included. Such exclusion of BPD patients might have been due to the fact that it has been suggested that comorbid BPD symptoms could interfere with CBASP [e.g., (40, 41)]. This seems reasonable from a practitioner's point of view as there is evidence that comorbid BPD can hamper the response to treatment in episodically depressed patients [e.g., (18)]. Also, higher levels of subthreshold BPD symptoms were the only PD features that significantly affected time to remission after a 12 weeks treatment with interpersonal therapy (IPT) or pharmacotherapy in episodically depressed patients (42). Recent developments in the clinical diagnostics of PD have introduced dimensional approaches besides the categorical

conceptualization (4, 43). Dimensional measures allow to assess symptoms on a subthreshold level that are apparent and may already cause impairment but do not yet justify the PD diagnosis. The introduction of dimensional models is seen as an opportunity to increase clinical utility (44) and it has been shown that subclinical BPD features in patients with mood disorder lead to higher levels of impairment (45).

The assumption of BPD diagnosis or subthreshold BPD features hampering the CBASP treatment response has not been specifically investigated in studies with PDD patients. Therefore, we formulated two research questions in our naturalistic pilot study: (1) What is the prevalence of BPD features and symptoms in a naturalistic sample of PDD inpatients seeking CBASP treatment? (2) Does the presence of BPD features in PDD patients reduce the effectiveness of a multimodal 10 weeks CBASP inpatient program in terms of less reduction of depressive symptoms? In addition, we explored the effect of a CBASP inpatient program on BPD symptoms.

MATERIALS AND METHODS

Sample

Data for this study were collected at the Department of Psychiatry and Psychotherapy of the University Hospital, LMU Munich, Germany. Participants took part in a larger naturalistic and still on-going study assessing the effectiveness of 10 weeks disorder-specific psychotherapy (German Clinical Trial Register ID: DRKS00019821). The study was designed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its subsequent amendments or comparable ethical standards and approved by the local ethics committee (Faculty of Medicine, Ludwig Maximilian University Munich, Munich, Germany, EK-No. 713-15).

After admission to the psychotherapy ward specialized in treating PDD with CBASP, 124 inpatients were screened for eligibility between June 2018 and March 2020 (see **Figure 1**). Patients were included if they took part in the 10 weeks CBASP program, were fluent in German and were aged between 18 and 65 years. Exclusion criteria contained acute suicidality, bipolar disorder, psychosis, a primary psychiatric diagnosis of PTSD, social phobia, panic disorder or generalized anxiety disorder, current pregnancy and/or a somatic unstable condition that needed to be treated primarily. Furthermore, patients that were admitted for a 5 weeks booster session were excluded. A diagnosis of BPD was explicitly no exclusion criterion. According to our exclusion criteria, 34 patients were not eligible after screening (5 weeks booster session: $n = 23$; bipolar disorder: $n = 6$; age >65 years: $n = 3$; non-fluent German: $n = 2$). Participants were then informed about the study and n = 22 patients decided to not take part in the study. From the remaining $n = 68$ patients that provided written informed consent prior to inclusion, $n = 8$ were excluded after the SCID-interview because they did not fulfill criteria for PDD but episodic depression. Though baseline data were collected for all 60 PDD patients, post intervention data were available only for 50 patients due to missing information ($n = 5$, 8.3%) and dropouts ($n = 5$, 8.3%).

Treatment: CBASP Inpatient Program

All participants underwent 10 weeks of multimodal CBASP treatment following the CBASP manual (30), modified for an inpatient setting (9, 41). The CBASP program included two individual sessions per week (i.e., 20 sessions in total, 50 min each), two group sessions per week (100 + 50 min), mindfulness training (50 min), group physical therapy (50 min) and occupational therapy (100 min). In addition, patients had regular medical rounds by the attending physician as well as the senior physician and a weekly nurse-patient encounter (25 min). The whole team received regular CBASP trainings and supervision (by ELB and FP). One psychotherapist was a certified CBASP therapist (FK), the rest of the team (three medical doctors, seven psychologists) were at an advanced psychotherapy and CBASP training stage with weekly supervision.

Patients received algorithm-based psychopharmacological treatment following national guidelines for depression (46). **Table 1** presents medication rates on admission and discharge.

Furthermore, a specifically trained nurses' team offered an optional weekly group skills training (90 min) based on the Dialectical Behavioral Therapy (DBT) manual by Bohus and Wolf-Arehult (47). The DBT skills training included sessions on mindfulness, distress tolerance, emotion regulation and interpersonal effectiveness. For each patient, the number of participated group sessions was assessed. Skills group dosage ranged from 0 to 10 sessions.

PDD and Comorbidity Assessment - BPD Features

On admission, a trained and supervised psychological research assistant assessed PDD and comorbid diagnoses with the German version of the Structured Clinical Interview for DSM-IV [SCID-I and SCID-II, (48, 49)]. In addition to SCID-I, diagnostic criteria for PDD were assessed according to DSM-5, as the German version of the DSM-5 preceded the publication of SCID-5-CV and was already available at the beginning of the study. Since its publication in 2019, the respective German interviews for DSM-5 [SCID-5-CV and SCID-5-PD, (50, 51)] were used. BPD criteria (i.e., BPD features) were rated for each participant even in the absence of BPD symptoms in the screening questionnaire.

Alongside the categorial assessment of a BPD diagnosis, SCID-II already allowed to calculate a dimensional (D-)score by summing up the scores of the nine BPD criteria (1 = absent, 2 = subthreshold, 3 = present). SCID-5-PD also offers the possibility to take subthreshold criteria into account and to characterize BPD features in more detail. However, answers are rated differently (0 = absent, 1 = subthreshold, 2 = true/threshold). As the diagnostic criteria for BPD have not changed from DSM-IV to DSM-5, we transformed SCID-II ratings to match SCID-5-PD scores. Consequently, the reported dimensional BPD score ranges between 0 and 18.

Depressive Symptom Severity

Depressive symptoms were assessed on admission and after 10 weeks. The Montgomery–Asberg Depression Rating Scale [MADRS, (52)] was defined as primary outcome. MADRS is

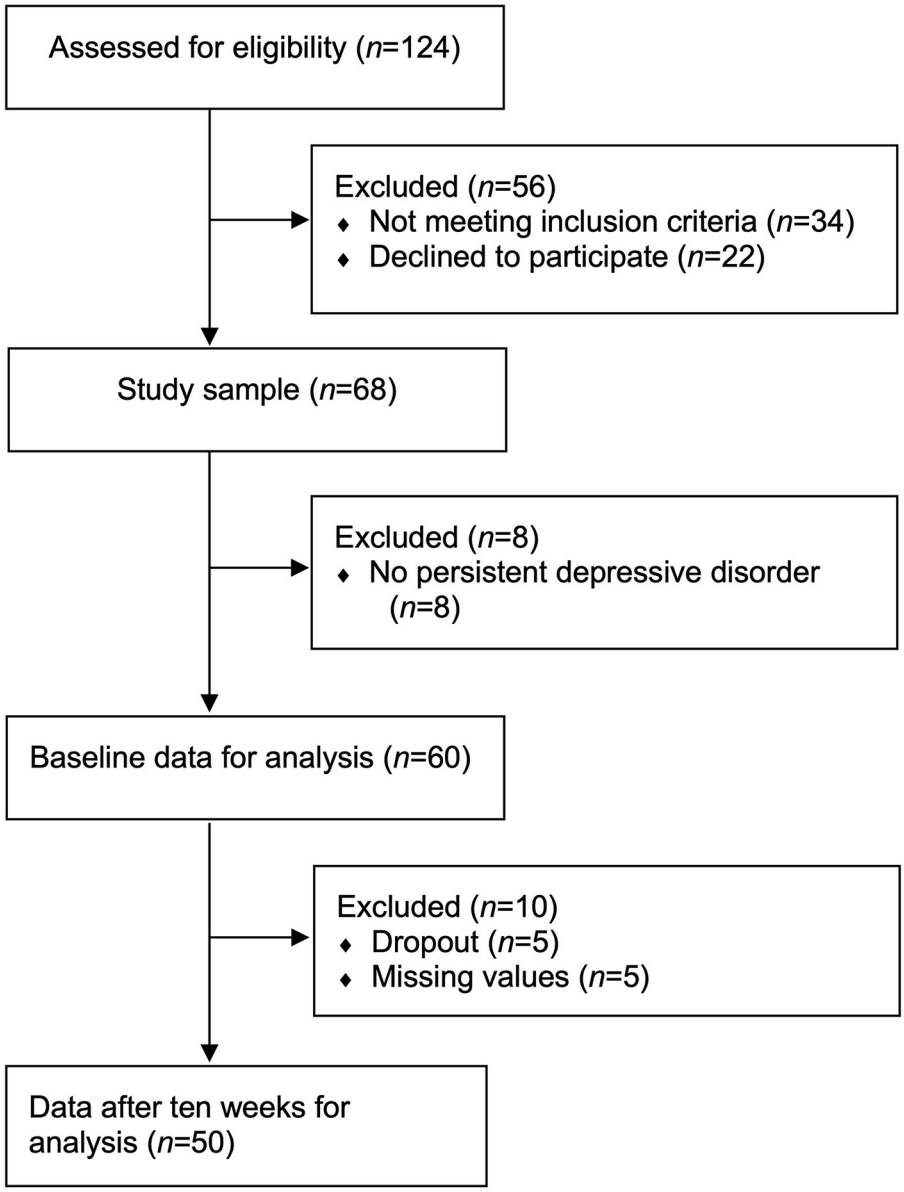

FIGURE 1 | Flow chart of study participants.

a clinician-based interview that assesses the severity of 10 depressive symptoms with a total score between 0 and 60. It has been found to have a high sensitivity to change (53). Interviews were conducted by the attending physicians that were trained in the Structured Interview Guide for the Montgomery-Asberg Depression Rating [SIGMA, (54)].

The Beck Depression Inventory [BDI-II, (55)] is a well-established 21-item self-report measure that assesses the severity of depressive symptoms within the last 14 days with a total score ranging from 0 to 63.

Borderline Personality Symptom Severity

BPD symptoms were also measured at baseline and post-treatment. The Borderline Personality Disorder Severity Index – Version IV (BPDSI-IV) is a clinician-based, semi-structured interview (56, 57). It provides a quantitative index of the severity of BPD manifestation by evaluating the frequency and intensity for BPD symptoms over the course of the last 3 months. The BPDSI-IV consists of 70 items organized in nine subscales according to DSM-IV criteria. Subscales range from 0 (never) to 10 (daily), except for the subscale identity disturbance. The sum of the means of each dimension form the total score ranging from 0 to 90. The BPDSI-IV has excellent psychometric characteristics [Cronbach's alpha = 0.96; interrater reliability: $r = 0.97$, high validity and sensitivity to change, (57)].

The Borderline Symptom List [BSL-23, (58)] is a self-rating questionnaire that assesses the subjective severity of 23 BPD

TABLE 1 | Frequency and percentage of prescribed drugs on admission and discharge ($N = 60$) and mean number of prescribed psychotropics; for CBASP dropouts medication at the date of dropout is reported.

		Admission *n*	Discharge *n*	*Z*	*P*
Any medication		54 (90.0%)	58 (96.7%)	2.0	0.04*
Psychotropic medication		40 (66.7%)	37 (61.7%)	1.7	0.08
Antidepressant drugs	SSRI	8 (13.3%)	6 (10.0%)	1.4	0.16
	SSNRI	12 (20.0%)	23 (38.3%)	3.3	0.001**
	Mirtazapine	6 (10.0%)	7 (11.7%)	1.0	0.32
	Bupropion	9 (15.0%)	11 (18.3%)	1.4	0.16
	Other	17 (28.3%)	10 (16.7%)	2.7	0.008**
Lithium		7 (11.7%)	6 (10.0%)	1.0	0.33
Quetiapine		12 (20.0%)	7 (11.7%)	2.2	0.03*
Aripiprazole		7 (11.7%)	11 (18.3%)	2.0	0.04*
Mean number of psychotropics		1.7 ± 1.4	1.6 ± 1.0	$t(59) = 0.4$	0.68

SSRI, selective serotonin reuptake inhibitor; SSNRI, selective serotonin noradrenaline reuptake inhibitor; Other, mainly Milnacipran, Tranylcypromine, different tricyclic antidepressants and Trazodone; p-values according to Wilcoxon rank test, (*) <0.05, (**) <0.01.

symptoms during the past week with a total score from 0 to 92. The BSL-23 has a high internal consistency (Cronbach's alpha = 0.93), high test-retest reliability ($r = 0.82$) and is very reliable in the diagnosis of BPD (58, 59).

Rejection Sensitivity Questionnaire

Rejection sensitivity was assessed at baseline with the rejection sensitivity questionnaire [RSQ, (26, 60)]. Participants are asked to rate both their anxiety and their expectation to be rejected in 20 scenarios on 6-point Likert scales. Scores for each scenario are multiplied. The total score ranges from 1 to 36, with higher scores indicating higher rejection sensitivity at beginning of treatment.

Childhood Maltreatment

The CTQ (61, 62) is a retrospective self-report measure that assesses CM on the subscales emotional abuse and neglect, physical abuse and neglect, and sexual abuse with 28 items. Participants rate whether different experiences were present during their childhood on Likert scales ranging from 1 (never true) to 5 (very often true). Subscale scores range from 5 to 25. For the German version of the CTQ a good internal consistency has been found for all subscales (alpha > 0.80) except for physical neglect (62).

Data Analysis

We used SPSS version 25 for statistical analyzes (https://www.ibm.com/de-de/products/spss-statistics). First, baseline values were analyzed: Intercorrelations between BPD features (i.e., SCID-5-PD score for BPD), BPD symptoms and depressive symptoms were calculated with Pearson or Spearman as appropriate. Furthermore, correlations with CM and rejection sensitivity were calculated and *p*-values were false discovery rate (FDR) corrected according to Benjamini and Hochberg (63) to correct for multiple correlations. Second, dependent *t*-tests were used to compare the differences of depressive symptoms before and after therapy. Patients that did not complete 10 weeks of CBASP or had missing values after 10 weeks were excluded from these analyses. The pre-post effect sizes were calculated using Cohen's d statistic. Linear regression analyses were performed to predict the change of depressive symptoms (delta) by the BPD dimensional score. Third, change of BPD symptoms was analyzed with dependent *t*-tests. Again, *p*-values were FDR corrected. Finally, the impact of skills training participation on BPD symptoms was analyzed with Mann-Whitney-*U*-Tests (participants vs. non-participants).

RESULTS

Sample

Baseline values of $n = 60$ patients were analyzed (37 females, 61.7%; mean age = 38.9, SD = 11.9). Demographic and clinical characteristics are presented in **Table 2**. Patients showed a variety of comorbidities including social phobia ($n = 19$, 31.7%), panic disorder/agoraphobia ($n = 16$, 26.7%), PTSD not as primary diagnosis ($n = 6$, 10.0%), pain disorder ($n = 6$, 10.0%), somatic symptom disorder ($n = 5$, 8.3%), alcohol abuse ($n = 5$, 8.3%) and binge eating disorder ($n = 3$, 5.0%). In addition, patients showed comorbidity for several PD including BPD ($n = 4$, 6.7%), avoidant ($n = 20$, 33.3%), dependent ($n = 1$, 1.7%), obsessive-compulsive ($n = 2$, 3.3%), paranoid ($n = 2$, 3.3%) and schizoid ($n = 2$, 3.3%) PD. After 10 weeks of CBASP, data from $n = 50$ patients were available (32 females, 64.0%; mean age = 39.3, SD = 12.0) because of dropouts ($n = 5$, 8.3%) and missing data ($n = 5$, 8.3%).

BPD Features and Symptoms at Baseline

Out of $n = 60$ patients with PDD, $n = 4$ (6.7%) fulfilled the diagnosis of BPD, i.e., ≥5 criteria according to DSM-5, $n = 3$ (5.0%) fulfilled four BPD criteria. The most frequently fulfilled criteria were emptiness (criterion 7: $n = 30$), affective instability (criterion 6: $n = 12$) and parasuicidal behavior (criterion 5: $n = 11$) (see **Figure 2**). Patients showed a mean of 1.5 (SD = 1.6) fulfilled BPD criteria and a mean SCID-5-PD BPD dimensional score of 3.8 (SD = 3.7). BPD symptoms were present in the observer-rating BPDSI-IV (mean total score

TABLE 2 | Demographic and clinical characteristics at baseline with mean and standard deviation (SD) or number of patients ($N = 60$) and percentages.

Demographic characteristics	
Age at admission, years	38.9 (SD 11.9)
Female sex	37 (61.7%)
Education, years	15.5 (SD 4.2)
No degree	1 (1.7%)
In Education	3 (5.0%)
Traineeship	43 (71.7%)
College/University	13 (21.7%)
Unemployed or early retirement	25 (41.7%)
Married/with partner	18 (30.0%)
Clinical characteristics	
Persistent major depressive episode	39 (65.0%)
Intermittent major depressive episode with current episode	12 (20.0%)
Intermittent major depressive episode without current episode	9 (15.0%)
Age at onset, years	17.1 (11.2)
At least one other Axis I disorder	36 (60.0%)
At least one other Axis II disorder	24 (40.0%)
Borderline personality disorder	4 (6.7%)
SCID-5-PD BPD D-score	3.8 (SD 3.7)
Suicide attempts in the past	16 (26.7%)
Self-injury behavior in the past	25 (41.7%)
MADRS	28.0 (SD 5.4)
BDI-II	31.0 (SD 10.9)
BPDSI-IV total	16.7 (SD 8.4)
BSL-23	1.4 (SD 0.8)
CTQ Emotional abuse	14.3 (SD 6.1)
CTQ Physical abuse	7.1 (SD 3.4)
CTQ Sexual abuse	6.3 (SD 2.9)
CTQ Emotional neglect	16.0 (SD 5.1)
CTQ Physical neglect	8.8 (SD 3.5)
Rejection sensitivity questionnaire	15.0 (SD 6.0)

SCID-5-PD BPD D-Score, SCID-5-PD dimensional score for borderline personality disorder; MADRS, Montgomery-Asberg Depression Rating Scale; BDI-II, Beck depression inventory; BPDSI-IV, borderline personality disorder severity index; BSL-23, borderline symptom list; CTQ, childhood trauma questionnaire.

= 16.7, SD = 8.4) and self-rating measure BSL-23 [mean = 1.4, SD = 0.8; moderate severity according to (59)]. Patients reported depressive symptoms at baseline (MADRS: mean = 28.0, SD = 5.4; BDI: mean = 31.0, SD = 10.9). Measurements for BPD features and symptoms showed a high intercorrelation of self- and observer-rating (see **Table 3**). Furthermore, total BPDSI-IV and BSL-23 correlated significantly with depressive symptoms.

Patients reported a history of CM including emotional abuse [mean = 14.3, SD = 6.1, 55.0% at least moderate to severe as defined by (61)], physical abuse (mean = 7.1, SD = 3.5, 20.0% at least moderate to severe), sexual abuse (mean = 6.2, SD = 2.9, 18.3% at least moderate to severe), emotional neglect (mean = 16.0, SD = 5.1, 66.7% at least moderate to severe) and physical neglect (mean = 8.8, SD = 3.5, 30.0% at least moderate to severe). Emotional abuse and physical neglect showed a significant correlation with BPD symptoms and subjective depressive symptoms at baseline (see **Table 4**). In addition, rejection sensitivity (mean = 15.0, SD = 6.0) was significantly correlated with self-reported BPD and depressive symptoms at baseline.

Effects of 10 Weeks CBASP and Impact of BPD Features

Depressive symptoms were reduced after 10 weeks of CBASP both on observer-rated (MADRS: $t(49) = 9.12$, $p_{FDR} = 0.007$, $d = -1.41$) and self-reported level (BDI-II: $t(49) = 5.59$, $p_{FDR} = .007$, $d = -0.90$; see **Table 5**). $N = 7$ patients (14.0%) showed a full MADRS response (Delta MADRS $\geq$ 50%) and $n = 22$ patients (44.0%) a partial response (Delta MADRS 25–50%). $N = 3$ patients (6.0%) reached remission on the MADRS whereas $n = 3$ (6.0%) showed a deterioration of symptoms. Regarding BDI-II, $n = 11$ patients (22.0%) showed a full response (Delta BDI-II $\geq$ 50%) and $n = 14$ (28.0%) patients showed a partial response (Delta BDI-II 25–50%). $N = 5$ patients (10.0%) reached remission (BDI-II $\leq$ 10) whereas $n = 11$ patients (22.0%) reported deterioration of symptoms (BDI-II increase). Baseline symptom severity of patients that dropped out or had missing data did not significantly differ from CBASP completers [MADRS: $t(58) = 0.27$, $p = 0.79$, $d = 0.10$; BDI-II: $t(58) = 0.76$, $p = 0.45$, $d = 0.26$; BPDSI-IV total: $t(58) = 1.47$, $p = 0.15$, $d = 0.51$; BSL-23: (58) = 0.91, $p = 0.37$, $d = -0.32$].

Linear regression analysis with the SCID-5-PD BPD dimensional score as independent variable and change of MADRS as dependent variable found that BPD features did not predict change of MADRS [Beta = −0.04, $t(47) = 0.24$, $p = 0.81$]. However, when using BDI-II as dependent variable, a trend was found for an association between BPD features at baseline and a smaller reduction of BDI-II scores after 10 weeks of CBASP treatment [Beta = 0.26, $t(47) = 1.85$, $p = 0.07$; see **Figure 3**].

Explorative Analysis of Change of BPD Symptoms

The total score of observer-rated BPD symptoms significantly decreased after 10 weeks [BPDSI-IV: $t(49) = 2.89$, $p_{FDR} = 0.02$, $d = -0.51$] with significant reductions in the subscales abandonment, impulsivity, affective instability, and a trend for emptiness (see **Table 5**). There was a statistical trend for a reduction of self-reported BPD symptoms after 10 weeks of CBASP [BSL-23: $t(49) = 1.96$, $p_{FDR} = 0.10$, $d = -0.31$]. When controlling for change of MADRS, the reduction of impulsivity remained significant ($p_{FDR} = 0.047$).

Thirty-nine out of 50 patients participated in at least one session of DBT skills training (mean session number = 5.2, SD = 3.4) that may have contributed to a reduction of BPD symptoms. Patients that attended DBT skills training did not differ from

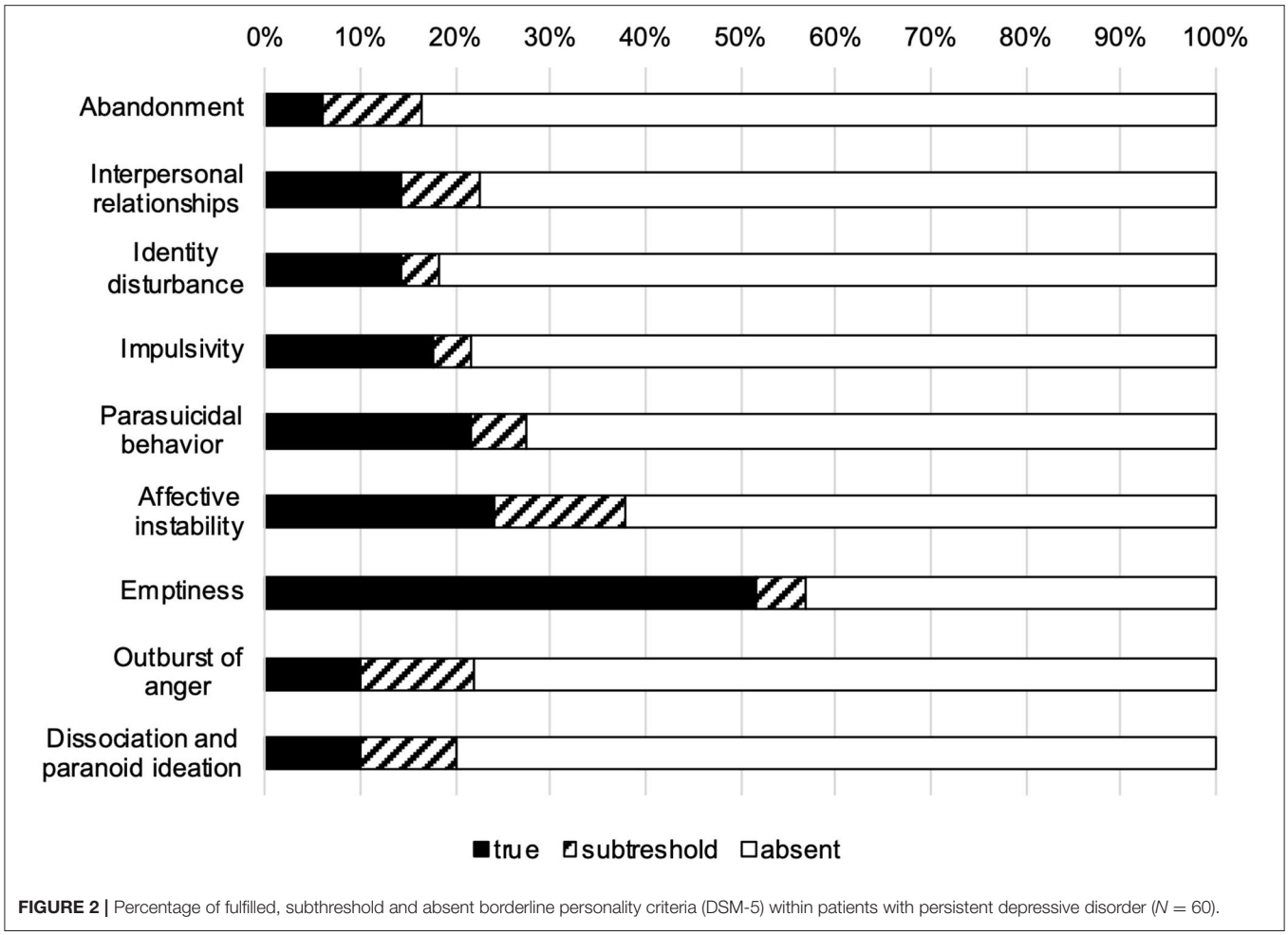

FIGURE 2 | Percentage of fulfilled, subthreshold and absent borderline personality criteria (DSM-5) within patients with persistent depressive disorder ($N = 60$).

TABLE 3 | Intercorrelation (Pearson or Spearman as appropriate) of borderline personality disorder (BPD) features, BPD symptoms and depressive symptoms at baseline, *p*-values are false discovery rate corrected (FDR).

	SCID-5-PD	BPDSI-IV total		BSL-23		MADRS		BDI-II	
	BPD D-score	*r*	p_{FDR}	*r*	p_{FDR}	*r*	p_{FDR}	*r*	p_{FDR}
SCID-5-PD BPD D-Score	–	0.53	0.001**	0.52	<0.001***	0.16	0.23	0.06	0.67
BPDSI-IV total	–	–	–	0.66	<0.001***	0.23	0.09	0.41	0.001**
BSL-23	–	–	–	–	–	0.42	0.04**	0.67	<0.001***
MADRS	–	–	–	–	–	–	–	0.48	<0.001***
BDI-II	–	–	–	–	–	–	–	–	–

SCID-5-PD BPD D-Score, SCID-5-PD dimensional score for borderline personality disorder; BPDSI-IV, borderline personality disorder severity index; BSL-23, borderline symptom list; MADRS, Montgomery-Asberg Depression Rating Scale; BDI-II, Beck depression inventory; (**) <0.01, (***) <0.001.

patients without DBT skills training regarding MADRS, BDI-II, or BSL-23 at baseline ($p > 0.10$). However, there was a trend that patients that participated in DBT skills training reported more BPD symptoms at baseline in the clinician-based interview (BPDSI-IV total: $Z = 1.91$, $p = 0.06$, $d = 0.64$). Furthermore, there was a trend that patients with DBT skills training showed a stronger BPDSI-IV reduction than patients without skills training ($Z = 1.72$, $p = 0.09$, $d = -0.58$).

DISCUSSION

The aim of this naturalistic study was the assessment of BPD features and symptoms in a sample of PDD inpatients undergoing a 10 weeks multimodal CBASP program and their impact on the therapeutic outcome. We found that BPD symptoms were prevalent in PDD patients and highly intertwined with self-reported depressive symptoms and a

TABLE 4 | Correlation (Pearson or Spearman as appropriate) of borderline personality disorder (BPD) features, BPD symptoms and depressive symptoms with trauma history and rejection sensitivity, *p*-values are false discovery rate corrected (FDR) for the number of subscales.

	SCID-5-PD BPD D-score		BPDSI-IV total		BSL-23		MADRS		BDI-II	
	r	p_{FDR}	*r*	p_{FDR}	*r*	p_{FDR}	*r*	p_{FDR}	*r*	p_{FDR}
CTQ										
Emotional abuse	0.29	0.31	0.35	0.009**	0.52	0.003**	0.05	0.69	0.49	0.003**
Physical abuse	0.14	0.35	0.19	0.23	0.35	0.02*	0.06	0.67	0.34	0.002**
Sexual abuse	0.06	0.81	0.04	0.78	0.22	0.40	0.13	0.40	0.14	0.40
Emotional neglect	0.12	0.37	0.11	0.40	0.21	0.27	0.18	0.27	0.20	0.27
Physical neglect	0.23	0.13	0.33	0.02*	0.37	0.02*	0.03	0.80	0.22	0.15
RSQ	0.23	0.14	0.22	0.09	0.51	0.003**	0.28	0.04*	0.53	0.003**

SCID-5-PD BPD D-Score, SCID-5-PD dimensional score for borderline personality disorder; BPDSI-IV, borderline personality disorder severity index; BSL-23, borderline symptom list; MADRS, Montgomery-Asberg Depression Rating Scale; BDI-II, Beck depression inventory; CTQ, childhood trauma questionnaire; RSQ, rejection sensitivity questionnaire; (*) <0.05, (**) <0.01.

TABLE 5 | Mean and standard deviation of depressive symptoms and borderline personality symptoms before and after 10 weeks of CBASP therapy for $n = 50$ patients (results of *t*-test or Wilcoxon as appropriate), *p*-values are false discovery rate (FDR) corrected.

	Before	After	*t(49), Z*	*p*	p_{FDR}	*d (CI95%)*
MADRS	27.9 (5.4)	19.6 (6.3)	9.12	<0.001***	0.007**	−1.41 (−1.84 to −0.97)
BDI-II	30.5 (11.0)	23.6 (13.3)	5.59	<0.001***	0.007**	−0.90 (−1.31 to −0.49)
BPDSI-IV total	15.3 (7.4)	13.0 (7.2)	2.89	0.006**	0.02*	−0.51 (−0.91 to −0.11)
1. Abandonment	1.4 (1.3)	0.9 (1.0)	−2.61	0.009**	0.02*	−0.34 (−0.74 to 0.05)
2. Interpersonal relationships	0.9 (0.8)	0.8 (0.9)	−0.077	0.94	0.94	−0.02 (−0.41 to 0.37)
3. Identity disturbance	1.1 (1.3)	0.9 (1.0)	−1.27	0.21	0.27	−0.19 (−0.58 to 0.20)
4. Impulsivity	0.5 (0.5)	0.2 (0.4)	−3.10	0.002**	0.009**	−0.43 (−0.83 to −0.04)
5. Parasuicidal behavior	0.7 (0.7)	0.6 (0.6)	−0.70	0.48	0.52	−0.08 (−0.47 to 0.32)
6. Affective instability	5.0 (2.4)	4.0 (2.2)	2.89	0.006**	0.02*	−0.40 (−0.79 to 0.00)
7. Emptiness	4.0 (2.4)	3.3 (2.5)	2.10	0.04*	0.07	−0.30 (−0.70 to 0.09)
8. Outburst of anger	1.1 (1.2)	1.0 (1.1)	−0.72	0.47	0.52	−0.12 (−0.51 to 0.27)
9. Dissociation and paranoid ideation	1.4 (1.0)	1.2 (1.4)	−1.52	0.13	0.19	−0.23 (−0.63 to 0.16)
BSL-23	1.3 (0.7)	1.2 (0.9)	1.96	0.06	0.10	−0.31 (−0.70 to 0.09)

MADRS, Montgomery-Asberg Depression Rating Scale; BDI-II, Beck depression inventory; BPDSI-IV, borderline personality disorder severity index; BSL-23, borderline symptom list; (*) <0.05, (**) <0.01, (***) <0.001.

history of emotional abuse. There was a trend that BPD features were associated with a smaller reduction of self-reported but not observer-rated depression scores after receiving CBASP. However, BPD features or symptoms did not evidently limit the effectiveness of the inpatient program, and BPD symptoms partially improved after 10 weeks. To our knowledge, this is the first study investigating the effect of BPD features on treatment outcome in patients with PDD.

At baseline, we found a particular high prevalence of emptiness and affective instability in PDD. Other typical BPD features like impulsive behavior, parasuicidal behavior and outbursts of anger were less prevalent, yet present. Naturally, prevalence of BPD features and symptoms was higher in our sample than the prevalence of fully diagnosed BPD due to the dimensional approach used here. Additionally, PDD patients showed a high rate of comorbidity with social phobia and avoidant PD. This finding corresponds with other results of PDD inpatients (9, 64) and outpatients (12) that showed a high comorbidity with anxiety disorders. However, these studies did not specifically assess BPD features and symptoms. BPD symptoms seem to be highly intertwined with depressive symptoms as the marked correlations between self-reported depression and self-reported BPD symptoms suggest. This result confirms previous findings that patients with BPD and depression tend to report higher depression scores than depressed patients without comorbid BPD (65). It has been suggested that the subjective experience of depression in BPD may be more severe and intense (65). However, BPD features (as measured by SCID-5-PD BPD dimensional score) did not correlate significantly with depressive symptoms in our sample whereas self-reported BPD symptoms did (as measured by BSL-23). This may be due to our small sample size and reduced

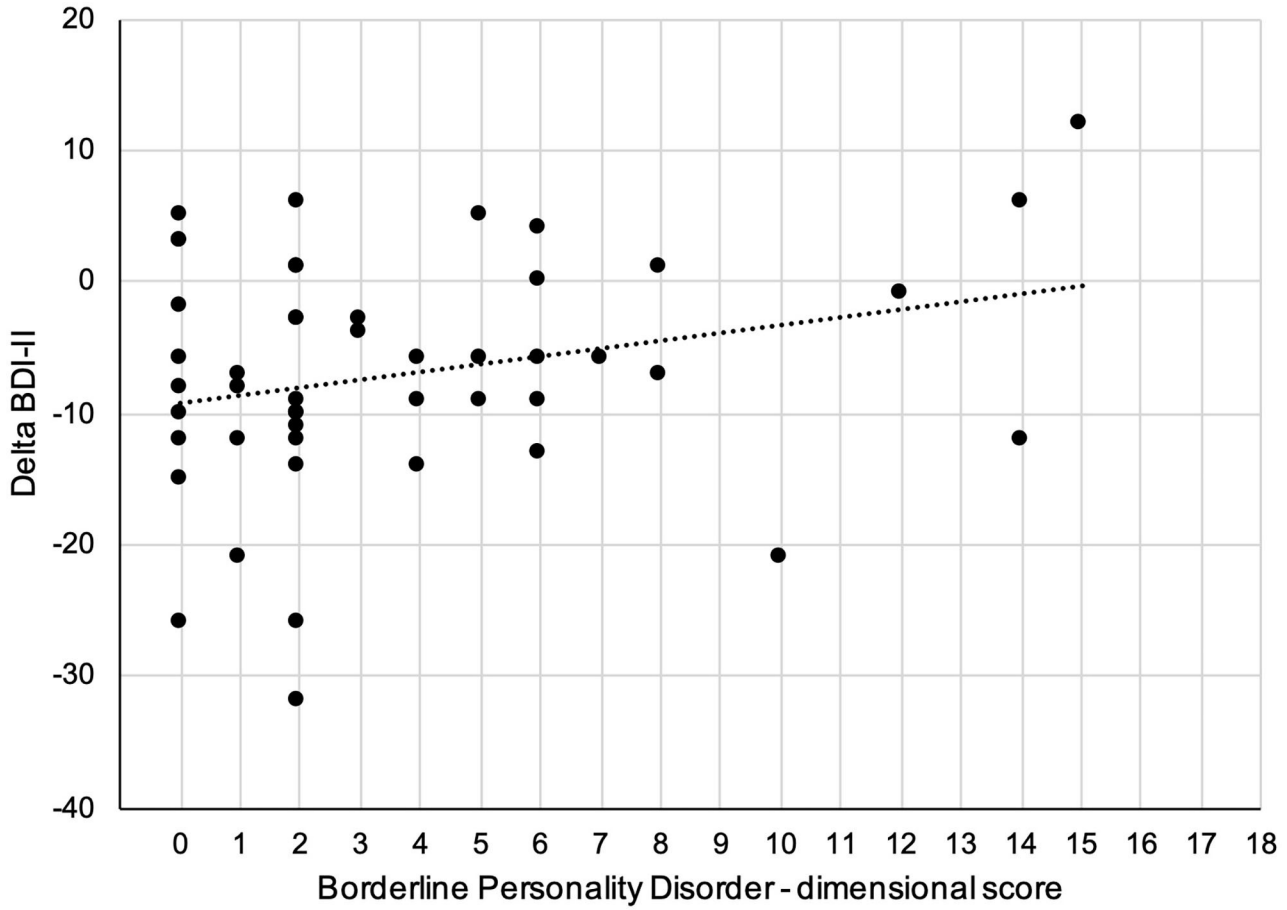

FIGURE 3 | Scatter plot of the relationship between dimensional assessed borderline personality features and change of self-rated depression scores (BDI-II: Beck depression inventory) after 10 weeks.

variance of the dimensional score. Interestingly, previous research found that patients with current depression showed more BPD features than patients with remitted depression (66) and BPD seemed to be associated with a longer persistence of depressive symptoms (16, 17). Taken together, BPD features and symptoms may augment the experience of depressive symptoms and contribute to a chronic course of depression.

In addition, BPD symptoms were associated with a history of emotional abuse in our sample. Indeed, CM has been found to be a risk factor for both PDD and BPD [e.g., (1, 24)]. Foxhall et al. (29) have proposed rejection sensitivity to be linked to both CM (i.e., particularly emotional abuse and neglect) and to BPD. Similarly, rejection sensitivity appears to be elevated in PDD compared to healthy controls (27, 28) and was correlated not only with BPD symptoms but also with self-reported depression. Rejection sensitivity may in fact be a mediating factor between childhood adversity and later psychopathology though this hypothesis still needs to be tested in larger cross-diagnostic studies (29).

Depressive symptoms were reduced after 10 weeks of CBASP in our sample. The general effectiveness of CBASP for PDD has been shown in numerous studies (31, 32, 34). However, our response and remission rates were lower than in comparable CBASP inpatient studies (9, 64, 67) with a longer treatment duration of 12 weeks compared to our program. As CBASP has been specifically developed for the treatment of PDD, there is basically no data on the effectiveness of CBASP in other psychiatric disorders including BPD. Patients with comorbid BPD have even been excluded in the majority of randomized controlled CBASP trials. From a practitioner's point of view, BPD features, like impulsivity and self-harm, could potentially interfere with CBASP as they shift the therapeutic focus away from CBASP toward emotion and impulse regulation. Indeed, our results suggest that the presence of BPD features may reduce the effectiveness of our inpatient program regarding self-reported depressive symptoms but not observer-rated depressive symptoms. The discrepancy of interview-based and self-report instruments for depression is well-known and clinician-rated instruments result in higher effect sizes for treatment outcome (68). It has been suggested that self-report instruments are less sensitive to change than observer-ratings (68) and that patients with BPD subjectively experience depression more

intensely (65). In general, this discrepancy of self and observer perception may lead to the problem that patients might perceive CBASP less effective than therapists do, which could result in misunderstandings and invalidating experiences for the patient. Yet, if therapists are aware of this issue, they could address and clarify this discrepancy.

Interestingly, we found a reduction of BPD symptoms in the subscales abandonment, impulsivity and affective instability. In addition, feelings of emptiness seemed to be reduced after 10 weeks. A reduction of depressive symptoms may lead to an alleviation of BPD symptoms due to the observed intercorrelation. However, the reduction of impulsivity remained significant when controlling for the change of MADRS. Another possible explanation for the reduction of BPD symptoms is the opportunity to attend DBT skills training in addition to the CBASP program. DBT skills training particularly addresses difficulties in emotion and stress regulation by teaching skills in stress tolerance, interpersonal behavior and mindfulness (47, 69). DBT has been shown to be effective in the treatment of patients with BPD (70). However, there was only a limited dosage of group sessions that patients could attend during their stay (with a maximum of 10 sessions) and it was not possible to undergo all the modules included in the DBT skills training (47). Also, most inpatients in our sample attended a limited number of group sessions. Another explanation for the reduction of some of the self-reported BPD symptoms could be that CBASP elements contributed to the reduction in a similar way as interventions from other evidence-based therapies for BPD do. Storebø et al. (70) state that the focus on the therapeutic relationship is a common element in all disorder-specific therapies addressing BPD. The therapeutic alliance is also one of the core elements of CBASP, as disciplined personal involvement (DPI) of the therapist through contingent personal responsivity (CPR) and the interpersonal discrimination exercise (IDE) gives the patient the opportunity to experience and perceive a new interpersonal reality within the session (30, 71).

Further studies are needed in order to disentangle specific actions and identify effective components across therapies. In fact, prospective trials investigating a specific psychotherapy in a cross-diagnostic spectrum are generally lacking. Thus, studies as ours investigating the efficacy of a distinct psychotherapeutic approach in a spectrum of the primary disorder and its comorbidity (e.g., PD features) may be an approximation toward this issue. Recent developments in psychotherapy research focus more and more on individually tailored treatments that address the individual patient's needs (72). Adjusting treatment via a modular approach bears the opportunity to combine evidence-based therapeutic strategies for PDD patients that show a great variety of comorbidities (1, 41). Future research is needed to investigate possible advantages of modular treatments.

This is, to our knowledge, the first study assessing the effect of BPD features on CBASP outcome in a naturalistic sample of PDD inpatient. Therefore, the lack of a control group and randomization are clear limitations of the study. Besides CBASP, patients may have had a benefit from a variety of unspecific factors (e.g., inpatient setting with daily routines, high amount of interpersonal support, medication, voluntary participation in DBT skills training). Furthermore, we assessed BPD features (i.e., DSM criteria) only at admission and we did not assess long-term outcome after discharge of a rather short treatment program of 10 weeks. BPD and PDD may show a conceptual overlap [e.g., (19, 73)] represented by a poor divergent validity and high intercorrelation of self-report instruments for depression and BPD [e.g., (58)]. Additionally, the sample of patients, which met the criteria for BPD, was small, i.e., on a case series level. Also, a (self-)selection bias may have occurred as patients with predominant BPD features and symptoms may either seek BPD directed therapy or have BPD directed treatment recommended by clinicians. Therefore, a randomized trial that compares CBASP with a BPD directed treatment in a larger sample and with patients suffering from higher severity of BPD features would be essential to support treatment decisions.

In sum, our clinical experience and the results of this study suggest a general feasibility of CBASP in patients with BPD features in an inpatient setting. Nevertheless, several requirements need to be met like a sufficient ability to regulate high-risk suicidal and self-injuring behavior that may disrupt the regular CBASP therapy process. Similarly, other therapy-hampering patterns as fluctuating motivation, difficulties in recall and sudden dissociative states may need to be addressed specifically. The use of a therapy contract (analogous to DBT) together with regular inter- and supervision in an interdisciplinary team with broad psychotherapeutic expertise has proven to be extremely valuable. Therefore, successively combined approaches, i.e., evidence-based treatment for BPD (such as DBT Stage 1) followed by CBASP, has been promising in our experience. A thorough investigation whether attending DBT or other evidence-based BPD therapies beforehand could increase the effectiveness of CBASP for those patients would be interesting.

CONCLUSION

Prevalent BPD features and BPD symptoms contribute to the symptom burden of patients with PDD and may affect the subjective CBASP outcome. Therefore, therapists should pay attention to the presence of subsyndromal BPD in PDD patients participating in a CBASP program. Nevertheless, CBASP has been found to be a feasible treatment option for PDD with BPD features. Our findings suggest that it might not be necessary to exclude these patients from receiving CBASP *per se* as there is a benefit in terms of reduction of depressive symptoms and even BPD symptoms. Strategies to regulate emotions and impulsivity may be necessary to enhance its therapeutic effectiveness. In order to even better tailor treatment to the individual PDD patient, future CBASP studies may include patients with comorbid subsyndromal and syndromal BPD.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethics committee Faculty of Medicine Ludwig Maximilian University Munich Munich, Germany EK-No. 713-15. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

MR, FK, BB, RM, AJ, and FP designed research. MR, FK, FG-W, TN-M, KF, BB, SG, and E-LB analyzed and interpreted data. MR, FK, and FP wrote first draft of manuscript. All authors revised the work critically and approved the final manuscript and agree to be accountable for the content of the work.

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REFERENCES

1. Schramm E, Klein DN, Elsaesser M, Furukawa TA, Domschke K. Review of dysthymia and persistent depressive disorder: history, correlates, and clinical implications. *Lancet Psychiatry.* (2020) 7:801–12. doi: 10.1016/S2215-0366(20)30099-7
2. Köhler S, Chrysanthou S, Guhn A, Sterzer P. Differences between chronic and nonchronic depression: systematic review and implications for treatment. *Depress Anxiety.* (2019) 36:18–30. doi: 10.1002/da.22835
3. Murphy JA, Byrne GJ. Prevalence and correlates of the proposed DSM-5 diagnosis of chronic depressive disorder. *J Affect Disord.* (2012) 139:172–80. doi: 10.1016/j.jad.2012.01.033
4. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders (DSM-5®)*. Washington, DC: American Psychiatric Pub (2013).
5. Nübel J, Guhn A, Müllender S, Le HD, Cohrdes C, Köhler S. Persistent depressive disorder across the adult lifespan: results from clinical and population-based surveys in Germany. *BMC Psychiatry.* (2020) 20:58. doi: 10.1186/s12888-020-2460-5
6. Satyanarayana S, Enns MW, Cox BJ, Sareen J. Prevalence and correlates of chronic depression in the canadian community health survey: mental health and well-being. *Can J Psychiatry.* (2009) 54:389–98. doi: 10.1177/070674370905400606
7. Riso LP, du Toit PL, Blandino JA, Penna S, Dacey S, Duin JS, et al. Cognitive aspects of chronic depression. *J Abnorm Psychol.* (2003) 112:72–80. doi: 10.1037/0021-843X.112.1.72
8. Garyfallos G, Adamopoulou A, Karastergiou A, Voikli M, Sotiropoulou A, Donias S, et al. Personality disorders in dysthymia and major depression. *Acta Psychiatr Scand.* (1999) 99:332–40. doi: 10.1111/j.1600-0447.1999.tb07238.x
9. Brakemeier EL, Radtke M, Engel V, Zimmermann J, Tuschen-Caffier B, Hautzinger M, et al. Overcoming treatment resistance in chronic depression: a pilot study on outcome and feasibility of the cognitive behavioral analysis system of psychotherapy as an inpatient treatment program. *Psychother Psychosom.* (2015) 84:51–6. doi: 10.1159/000369586
10. Rothschild L, Zimmerman M. Personality disorders and the duration of depressive episode: a retrospective study. *J Pers Disord.* (2002) 16:293–303. doi: 10.1521/pedi.16.4.293.24129
11. Klein DN, Schatzberg AF, McCullough JP, Dowling F, Goodman D, Howland RH, et al. Age of onset in chronic major depression: relation to demographic and clinical variables, family history, and treatment response. *J Affect Disord.* (1999) 55:149–57. doi: 10.1016/S0165-0327(99)00020-8
12. Erkens N, Schramm E, Kriston L, Hautzinger M, Harter M, Schweiger U, et al. Association of comorbid personality disorders with clinical characteristics and outcome in a randomized controlled trial comparing two psychotherapies for early-onset persistent depressive disorder. *J Affect Disord.* (2018) 229:262–8. doi: 10.1016/j.jad.2017.12.091
13. Klein JP, Fassbinder E, Schweiger U. [Chronic depression and personality disorder: one and the same? Scientific evidence and its implication for psychotherapy]. *Die Psychiatrie.* (2014) 11:94–103. doi: 10.1055/s-0038-1670750
14. Grant BF, Chou SP, Goldstein RB, Huang B, Stinson FS, Saha TD, et al. Prevalence, correlates, disability, and comorbidity of DSM-IV borderline personality disorder: results from the Wave 2 National Epidemiologic Survey on alcohol and related conditions. *J Clin Psychiatry.* (2008) 69:533–45. doi: 10.4088/JCP.v69n0404
15. Zanarini MC, Frankenburg FR, Dubo ED, Sickel AE, Trikha A, Levin A, et al. Axis I comorbidity of borderline personality disorder. *Am J Psychiatry.* (1998) 155:1733–9. doi: 10.1176/ajp.155.12.1733
16. Joyce PR, Mulder RT, Luty SE, McKenzie JM, Sullivan PF, Cloninger RC. Borderline personality disorder in major depression: symptomatology, temperament, character, differential drug response, and 6-month outcome. *Compr Psychiatry.* (2003) 44:35–43. doi: 10.1053/comp.2003.50001
17. Skodol AE, Grilo CM, Keyes KM, Geier T, Grant BF, Hasin DS. Relationship of personality disorders to the course of major depressive disorder in a nationally representative sample. *Am J Psychiatry.* (2011) 168:257–64. doi: 10.1176/appi.ajp.2010.10050695
18. Gunderson JG, Morey LC, Stout RL, Skodol AE, Shea MT, McGlashan TH, et al. Major depressive disorder and borderline personality disorder revisited: longitudinal interactions. *J Clin Psychiatry.* (2004) 65:1049–56. doi: 10.4088/JCP.v65n0804
19. Klein DN, Schwartz JE. The relation between depressive symptoms and borderline personality disorder features over time in dysthymic disorder. *J Pers Disord.* (2002) 16:523–35. doi: 10.1521/pedi.16.6.523.22143
20. Struck N, Krug A, Yuksel D, Stein F, Schmitt S, Meller T, et al. Childhood maltreatment and adult mental disorders - the prevalence of different types of maltreatment and associations with age of onset and severity of symptoms. *Psychiatry Res.* (2020) 293:113398. doi: 10.1016/j.psychres.2020.113398
21. Nelson J, Klumparendt A, Doebler P, Ehring T. Childhood maltreatment and characteristics of adult depression: meta-analysis. *Br J Psychiatry.* (2017) 210:96–104. doi: 10.1192/bjp.bp.115.180752
22. Struck N, Krug A, Feldmann M, Yuksel D, Stein F, Schmitt S, et al. Attachment and social support mediate the association between childhood maltreatment and depressive symptoms. *J Affect Disord.* (2020) 273:310–7. doi: 10.1016/j.jad.2020.04.041
23. Crowell SE, Beauchaine TP, Linehan MM. A biosocial developmental model of borderline personality: elaborating and extending linehan's theory. *Psychol Bull.* (2009) 135:495–510. doi: 10.1037/a0015616
24. Stepp SD, Lazarus SA, Byrd AL. A systematic review of risk factors prospectively associated with borderline personality disorder: taking stock and moving forward. *Personal Disord.* (2016) 7:316–23. doi: 10.1037/per0000186
25. Brakemeier EL, Dobias J, Hertel J, Bohus M, Limberger MF, Schramm E, et al. Childhood maltreatment in women with borderline personality disorder, chronic depression, and episodic depression, and in healthy controls. *Psychother Psychosom.* (2018) 87:49–51. doi: 10.1159/000484481

26. Downey G, Feldman SI. Implications of rejection sensitivity for intimate relationships. *J Pers Soc Psychol.* (1996) 70:1327–43. doi: 10.1037/0022-3514.70.6.1327
27. Nenov-Matt T, Barton BB, Dewald-Kaufmann J, Goerigk S, Rek S, Zentz K, et al. Loneliness, social isolation and their difference: a cross-diagnostic study in persistent depressive disorder and borderline personality disorder. *Front Psychiatry.* (2020) 11:608476. doi: 10.3389/fpsyt.2020.608476
28. Seidl E, Padberg F, Bauriedl-Schmidt C, Albert A, Daltrozzo T, Hall J, et al. Response to ostracism in patients with chronic depression, episodic depression and borderline personality disorder a study using cyberball. *J Affect Disord.* (2020) 260:254–62. doi: 10.1016/j.jad.2019.09.021
29. Foxhall M, Hamilton-Giachritsis C, Button K. The link between rejection sensitivity and borderline personality disorder: a systematic review and meta-analysis. *Br J Clin Psychol.* (2019) 58:289–326. doi: 10.1111/bjc.12216
30. McCullough J. *Treatment for Chronic Depression: Cognitive Behavioral Analysis System of Psychotherapy (CBASP)*. New York, NY: Guilford Press (2000).
31. Kriston L, von Wolff A, Westphal A, Holzel LP, Harter M. Efficacy and acceptability of acute treatments for persistent depressive disorder: a network meta-analysis. *Depress Anxiety.* (2014) 31:621–30. doi: 10.1002/da.22236
32. Negt P, Brakemeier EL, Michalak J, Winter L, Bleich S, Kahl KG. The treatment of chronic depression with cognitive behavioral analysis system of psychotherapy: a systematic review and meta-analysis of randomized-controlled clinical trials. *Brain Behav.* (2016) 6:e00486. doi: 10.1002/brb3.486
33. Jobst A, Brakemeier EL, Buchheim A, Caspar F, Cuijpers P, Ebmeier KP, et al. European psychiatric association guidance on psychotherapy in chronic depression across Europe. *Eur Psychiatry.* (2016) 33:18–36. doi: 10.1016/j.eurpsy.2015.12.003
34. Schramm E, Kriston L, Zobel I, Bailer J, Wambach K, Backenstrass M, et al. Effect of disorder-specific vs. nonspecific psychotherapy for chronic depression: a randomized clinical trial. *JAMA Psychiatry.* (2017) 74:233–42. doi: 10.1001/jamapsychiatry.2016.3880
35. Nemeroff CB, Heim CM, Thase ME, Klein DN, Rush AJ, Schatzberg AF, et al. Differential responses to psychotherapy versus pharmacotherapy in patients with chronic forms of major depression and childhood trauma. *Proc Natl Acad Sci USA.* (2003) 100:14293–6. doi: 10.1073/pnas.2336126100
36. Klein JP, Erkens N, Schweiger U, Kriston L, Bausch P, Zobel I, et al. Does childhood maltreatment moderate the effect of the cognitive behavioral analysis system of psychotherapy versus supportive psychotherapy in persistent depressive disorder? *Psychother Psychosom.* (2018) 87:46–8. doi: 10.1159/000484412
37. Maddux RE, Riso LP, Klein DN, Markowitz JC, Rothbaum BO, Arnow BA, et al. Select comorbid personality disorders and the treatment of chronic depression with nefazodone, targeted psychotherapy, or their combination. *J Affect Disord.* (2009) 117:174–9. doi: 10.1016/j.jad.2009.01.010
38. Schramm E, Zobel I, Schoepf D, Fangmeier T, Schnell K, Walter H, et al. Cognitive behavioral analysis system of psychotherapy versus escitalopram in chronic major depression. *Psychother Psychosom.* (2015) 84:227–40. doi: 10.1159/000381957
39. Keller MB, McCullough JP, Klein DN, Arnow B, Dunner DL, Gelenberg AJ, et al. A comparison of nefazodone, the cognitive behavioral-analysis system of psychotherapy, and their combination for the treatment of chronic depression. *N Engl J Med.* (2000) 342:1462–70. doi: 10.1056/NEJM200005183422001
40. Klein JP, Belz M. *Psychotherapie Chronischer Depression: Praxisleitfaden CBASP*. Göttingen: Hogrefe Verlag (2014).
41. Brakemeier EL, Guhn A, Normann C. *Praxisbuch CBASP. Behandlung chronischer Depression und Modifikationen für weitere interpersonelle Störungen*. 2nd ed. Weinheim: Beltz Verlag (2021).
42. Levenson JC, Wallace ML, Fournier JC, Rucci P, Frank E. The role of personality pathology in depression treatment outcome with psychotherapy and pharmacotherapy. *J Consult Clin Psychol.* (2012) 80:719–29. doi: 10.1037/a0029396
43. Krueger RF, Hobbs KA. An overview of the DSM-5 alternative model of personality disorders. *Psychopathology.* (2020) 53:126–32. doi: 10.1159/000508538
44. Verheul R. Clinical utility of dimensional models for personality pathology. *J Pers Disord.* (2005) 19:283–302. doi: 10.1521/pedi.2005.19.3.283
45. Zimmerman M, Chelminski I, Young D, Dalrymple K, Martinez J. Does the presence of one feature of borderline personality disorder have clinical significance? Implications for dimensional ratings of personality disorders. *J Clin Psychiatry.* (2012) 73:8–12. doi: 10.4088/JCP.10m06784
46. Schneider F, Härter M, Schorr S. *S3-Leitlinie/Nationale VersorgungsLeitlinie Unipolare Depression*. Heidelberg: Springer-Verlag (2017).
47. Bohus M, Wolf-Arehult M. *Interaktives Skillstraining für Borderline-Patienten*. Stuttgart: Schattauer Verlag (2013).
48. First MB, Spitzer RL, Gibbon M, Williams JB. *Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I)*. New York, NY: Biometrics Research Department, New York State Psychiatric Institute (1995).
49. Wittchen H, Zaudig M, Fydrich T. *SKID-I und SKID-II. Strukturiertes Klinisches Interview Für DSM-IV*. Göttingen: Hogrefe-Verlag (1997).
50. Beesdo-Baum K, Zaudig M, Wittchen H-U. *SCID-5-CV Strukturiertes Klinisches Interview für DSM-5-Störungen- Klinische Version: Deutsche Bearbeitung des Structured Clinical Interview for DSM-5 Disorders -Clinician Version.* First MB, Williams JBW, Karg RS, Spitzer RL, editors. Göttingen: Hogrefe Verlag (2019).
51. Beesdo-Baum K, Zaudig M, Wittchen H-U. *SCID-5-PD Strukturiertes Klinisches Interview für DSM-5 Persönlichkeitsstörungen: Deutsche Bearbeitung des Structured Clinical Interview for DSM-5- Personality Disorders.* First MB, Williams JBW, Benjamin LS, Spitzer RL, editors. Göttingen: Hogrefe Verlag (2019).
52. Montgomery SA, Asberg M. A new depression scale designed to be sensitive to change. *Br J Psychiatry.* (1979) 134:382–9. doi: 10.1192/bjp.134.4.382
53. Schmidtke A, Fleckenstein P, Moises W, Beckmann H. [Studies of the reliability and validity of the German version of the montgomery-asberg depression rating scale (MADRS)]. *Schweiz Arch Neurol Psychiatr 1985.* (1988) 139:51–65.
54. Williams JB, Kobak KA. Development and reliability of a structured interview guide for the montgomery asberg depression rating scale (SIGMA). *Br J Psychiatry.* (2008) 192:52–8. doi: 10.1192/bjp.bp.106.032532
55. Beck AT, Steer RA, Ball R, Ranieri W. Comparison of beck depression inventories -IA and -II in psychiatric outpatients. *J Pers Assess.* (1996) 67:588–97. doi: 10.1207/s15327752jpa6703_13
56. Giesen-Bloo JH, Wachters LM, Schouten E, Arntz A. The borderline personality disorder severity index-IV: psychometric evaluation and dimensional structure. *Pers Individ Differ.* (2010) 49:136–41. doi: 10.1016/j.paid.2010.03.023
57. Kroger C, Vonau M, Kliem S, Roepke S, Kosfelder J, Arntz A. Psychometric properties of the German version of the borderline personality disorder severity index–version IV. *Psychopathology.* (2013) 46:396–403. doi: 10.1159/000345404
58. Bohus M, Kleindienst N, Limberger MF, Stieglitz RD, Domsalla M, Chapman AL, et al. The short version of the borderline symptom list (BSL-23): development and initial data on psychometric properties. *Psychopathology.* (2009) 42:32–9. doi: 10.1159/000173701
59. Kleindienst N, Jungkunz M, Bohus M. A proposed severity classification of borderline symptoms using the borderline symptom list (BSL-23). *Borderline Personal Disord Emot Dysregul.* (2020) 7:11. doi: 10.1186/s40479-020-00126-6
60. Staebler K, Helbing E, Rosenbach C, Renneberg B. Rejection sensitivity and borderline personality disorder. *Clin Psychol Psychother.* (2011) 18:275–83. doi: 10.1002/cpp.705
61. Bernstein DP, Fink L. *Childhood Trauma Questionnaire: A retrospective Self-Report: Manual*. San Antonio, TX: Harcourt Brace & Company (1998).
62. Klinitzke G, Romppel M, Hauser W, Brahler E, Glaesmer H. [The German version of the childhood trauma questionnaire (CTQ): psychometric characteristics in a representative sample of the general population]. *Psychother Psychosom Med Psychol.* (2012) 62:47–51. doi: 10.1055/s-0031-1295495
63. Benjamini Y, Hochberg Y. Controlling the false discovery rate: a practical and powerful approach to multiple testing. *J R Stat Soc Series B Stat Methodol.* (1995) 57:289–300. doi: 10.1111/j.2517-6161.1995.tb02031.x
64. Sabass L, Padberg F, Normann C, Engel V, Konrad C, Helmle K, et al. Cognitive behavioral analysis system of psychotherapy as group psychotherapy for chronically depressed inpatients: a naturalistic multicenter

feasibility trial. *Eur Arch Psychiatry Clin Neurosci.* (2018) 268:783–96. doi: 10.1007/s00406-017-0843-5
65. Stanley B, Wilson ST. Heightened subjective experience of depression in borderline personality disorder. *J Pers Disord.* (2006) 20:307–18. doi: 10.1521/pedi.2006.20.4.307
66. Distel MA, Smit JH, Spinhoven P, Penninx BW. Borderline personality features in depressed or anxious patients. *Psychiatry Res.* (2016) 241:224–31. doi: 10.1016/j.psychres.2016.05.007
67. Guhn A, Köhler S, Brakemeier EL, Sterzer P. Cognitive behavioral analysis system of psychotherapy for inpatients with persistent depressive disorder: a naturalistic trial on a general acute psychiatric unit. *Eur Arch Psychiatry Clin Neurosci.* (2019) 1–11. doi: 10.1007/s00406-019-01038-5
68. Cuijpers P, Li J, Hofmann SG, Andersson G. Self-reported versus clinician-rated symptoms of depression as outcome measures in psychotherapy research on depression: a meta-analysis. *Clin Psychol Rev.* (2010) 30:768–78. doi: 10.1016/j.cpr.2010.06.001
69. Linehan MM. *Skills Training Manual for Treating Borderline Personality Disorder*. New York, NY: Guilford Press. (1993).
70. Storebo OJ, Stoffers-Winterling JM, Vollm BA, Kongerslev MT, Mattivi JT, Jorgensen MS, et al. Psychological therapies for people with borderline personality disorder. *Cochrane Database Syst Rev.* (2020) 5:CD012955. doi: 10.1002/14651858.CD012955.pub2
71. Köhler S, Guhn A, Betzler F, Stiglmayr C, Brakemeier E-L, Sterzer P. Therapeutic self-disclosure within DBT, schema therapy, and CBASP: opportunities and challenges. *Front Psychol.* (2017) 8:2073. doi: 10.3389/fpsyg.2017.02073
72. Brakemeier EL, Herpertz S. [Innovative psychotherapy research: towards an evidence-based and process-based individualized and modular psychotherapy]. *Der Nervenarzt.* (2019) 90:1125–34. doi: 10.1007/s00115-019-00808-9
73. Rao S, Broadbear J. Borderline personality disorder and depressive disorder. *Australas Psychiatry.* (2019) 27:573–7. doi: 10.1177/1039856219878643

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BRIEF RESEARCH REPORT
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Reduced Social Connectedness and Compassion Toward Close Others in Patients With Chronic Depression Compared to a Non-clinical Sample

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Reduced social functioning in depression has been explained by different factors. Reduced social connectedness and prosocial motivation may contribute to interpersonal difficulties, particularly in chronic depression. In the present study, we tested whether social connectedness and prosocial motivation are reduced in chronic depression. Forty-seven patients with persistent depression and 49 healthy controls matched for age and gender completed the Inclusion of the Other in the Self Scale (IOS), the Compassionate Love Scale (CLS), the Beck Depression Inventory-II, and the Childhood Trauma Questionnaire. A Multivariate analysis of variance (MANOVA) with IOS and CLS as dependent variables revealed a highly significant difference between both groups. The IOS and the CLS-subscale Close Others were lower in persistent depression, whereas there was no difference in the CLS-subscale Strangers/Humanity. IOS and CLS-Close Others showed significant negative correlations with depressive symptoms. Connectedness to family members as measured by the IOS was negatively correlated with childhood trauma in patients with chronic depression. The results indicate that compassion and perceived social connection are reduced in depressed patients toward close others, but not to others in general. Implications for the treatment of depression are discussed.

Keywords: social connectedness, interpersonal closeness, prosocial motivation, compassion, compassionate love, chronic depression, persistent depressive disorder

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INTRODUCTION

Depression is associated with a low level of social integration and connectedness (1) and reduced social functioning (2). Possible explanations for the social retreat of depressed patients refer to decreased pleasure from social interactions due to reduced response from the social reward system [social anhedonia, (3)] and hypersensitivity to social rejection (4), or dysfunctional interpersonal behaviors, such as excessive reassurance seeking or negative feedback seeking (5).

According to the social identity theory, the impairment of interpersonal relationships and social isolation affects the attachment to close others as well as the belonging to groups, resulting in a loss of social connectedness (6, 7). A recent longitudinal study which used objective indicators of social connectedness demonstrated that there are strong bidirectional associations between

social disconnectedness and symptoms of depression (8). However, the perception of belonging to others, rather than objective social interaction, may be the component of social connectedness most relevant to the development and maintenance of depression (1, 7). For example, social connectedness is associated with increased motivation to make contact with other people (9) and may be a mediator of the positive effects of social competence and social support on mental health (10).

In addition, impairment of prosocial motivation may also affect social functioning in depressed individuals. This may be closely related to the reduction of perceived social connectedness. According to Batson et al. (11), prosocial motivation can be based on altruistic motives such as empathic concern or compassion. For instance, there is evidence that empathy is reduced during major depressive episodes (12). However, mixed results have been found with respect to prosocial motivation when using the Prisoner's Dilemma to investigate the link between depression and prosocial motivation (13).

A prominent feature of depression, although not specific to depression alone, is a self-critical attitude (14). Opposed to self-criticism is self-compassion, which entails the attitude to be "open to and moved by one's own suffering, experiencing feelings of caring and kindness toward oneself and taking an understanding non-judgmental attitude toward one's inadequacies and failures, and recognizing that one's experience is part of the common human experience" (15). A lack of self-compassion is a strong predictor of depressive symptoms in the general population (16) and in depressed patients (17), and self-compassion is significantly reduced in individuals with current (18, 19) as well as remitted depression (19). However, these studies have focused on major depressive disorder.

Although previous research demonstrated that *self*-compassion is reduced in depression, research on the role of compassion *toward others* in depression is sparse. A recent longitudinal study on the relationship between dispositional compassion and depressive symptoms found that among adolescents and young adults, high levels of dispositional compassion predicted lower depression, whereas conversely, depression was not likely to influence compassion (20). However, depressive symptoms were only mild and non-clinical in the sample studied. Another recent longitudinal study indicated that the experience of depressive episodes may even trigger increased compassion at a later time (21), possibly by inducing posttraumatic growth and compassionate identification with the suffering of others. However, during an acute depressive episode, prosocial constructs such as empathy appear to be impaired compared with healthy control subjects (22). So far, it is unclear whether dispositional compassion is altered in chronically depressed patients. According to the above-mentioned studies, on the one hand it could be assumed that patients with chronic depression develop a stronger dispositional compassion in the sense of posttraumatic growth due to their often long history of depression. On the other hand, it could be speculated that the acute symptoms during chronic depression tend to reduce compassion.

As compared to the episodic form of depression, Persistent Depressive Disorder (PDD) is associated with stronger impairment in life and higher social and economic costs (23). Although it has often been hypothesized that a chronic course of depression may be explained by dysfunctional interpersonal patterns, there is a lack of research supporting this assumption. Previous studies indicate, however, that chronic depression is characterized by a dysfunctional interpersonal style, as compared to patients with episodic depression (24, 25). Impaired social cognition, either in terms of a mood-congruent interpretive bias (26) or in terms of preoperational thinking (27), has been highlighted as a risk factor for the development of depressive symptomatology. In this context, indirect evidence for a relationship between impaired social cognition and a hostile and overly submissive interpersonal style has been discussed (26). Furthermore, preoperational thinking appears to mediate the association between adverse childhood experiences and a hostile interpersonal style in depressed patients (28). In particular, it has been shown that early emotional neglect, abuse, and rejection during childhood are important risk factors to interpersonal difficulties in chronic depression (29). However, up to now there is little research on the role of social connectedness and compassion in chronic depression. The present study aims at reducing this gap. We hypothesized that compared to healthy controls, patients with chronic depression report significantly lower social connectedness and less compassion. Since there is some evidence for gender differences in prosociality (13, 30, 31) and social connectedness (32), we hypothesized that women report higher compassion than men, and differ from men with respect to social connectedness. In addition, we explored whether social connectedness and compassion are significantly correlated, and whether both are related to severity of depressive symptoms and self-reported childhood adversity.

MATERIALS AND METHODS

Participants and Recruitment

As part of the *MeCBT* study (33) we recruited 47 patients with PDD according to the DSM 5. These patients were compared to 49 control subjects without mental disorders who were recruited outside the project. A total of 35 women and 12 men aged 25–69 ($M = 50.34$; $SD = 11.39$) were in the group of chronically depressive patients, and 34 women and 15 men aged 27–69 ($M = 50.06$; $SD = 12.81$) were in the healthy control sample (see **Supplementary Table 1** for more details). Healthy control subjects were recruited via public social media as well as via notices in public places. Interested participants registered by e-mail. If participants gave their written informed consent, a screening interview was conducted by telephone using the *Patient Health Questionnaire* [German version by Löw et al. (34)] to check for a current mental disorder. The interview was conducted by psychology master's degree candidates who had received specific training. If participants met inclusion criteria, they were

Abbreviations: BDI-II, Beck Depression Inventory II; CLS, Compassionate Love Scale; CTQ, Childhood Trauma Questionnaire; DSM-5, Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition; IOS, Inclusion of Other in the Self scale; MANOVA, Multivariate analysis of variance; PDD, Persistent depressive disorder.

provided a link to an online survey in which they filled out demographic information and completed the *Beck Depression Inventory-II* [BDI-II; German version by Hautzinger et al. (35)] and the questionnaires on compassion and social connectedness. The same questionnaires had been filled out on the same platform by the chronically depressed participants of the MeCBT study at baseline assessment. The survey included a mechanism to check for completion of the survey. The IOS-Item *romantic partner* was an exception and participants could leave this item blank if they currently had no romantic partner. The participants of the healthy control group received a compensation of €40 for participation. The two samples were matched for age and gender.

Outcome Measures

Social Connectedness

As a proxy to social connectedness in the sense of *interpersonal closeness*, we used the *Inclusion of Other in the Self Scale* (IOS) developed by Aron et al. (36). The IOS is a pictorial measure that provides seven images showing two circles overlapping to different degrees, and the participant is asked to select the one image that best represents the relationship between him- or herself and a specified other person. It shows good psychometric properties, including convergent, discriminant and predictive validity (36). Aron et al. reported an overall retest-reliability of $r = 0.83$, and retest-reliabilities between $r = 0.85$ and $r = 0.87$ for single items (36). The IOS is efficient and valid in measuring relationship quality (37) and has been shown to predict helping behavior better than empathy (38). In the present study, the IOS was used to assess the extent of connectedness to five different groups of people: With (1) a partner, (2) family, (3) friends, (4) acquaintances, and (5) people in general.

Compassion

We used the *Compassionate Love Scale* (CLS) by Sprecher and Fehr (39) to assess compassion for others. According to Sprecher and Fehr, the construct *Compassionate Love* refers to *Agape*, one of the six love styles described by J. A. Lee (40). Agape is rooted in the occidental philosophy and is defined as altruistic love directed toward others. The CLS contains 21 items to be rated on a seven-point Likert scale ranged from 1 (not at all true of me) to 7 (very true of me). It exists in two versions: (a) compassion toward close others (friends, family) and (b) compassion toward strangers or all humanity. In the present study both versions were used. The CLS showed high internal consistency of $\alpha = 0.95$ for both versions (39). However, no retest-reliability has been reported for the CLS and convergent validity has not yet been researched extensively. Moreover, the content validity, at least of a part of the scale, has been questioned recently (41, 42).

Childhood Adversity

The *Childhood Trauma Questionnaire* [CTQ; German version by Klinitzke et al. (43)] was used to assess childhood adversity in depressed patients. The CTQ is a self-report measure with good internal consistency and construct validity (43). Due to organizational restrictions, we did not administer the CTQ in the healthy control group. We added data from other studies for a representative sample as well as for a healthy sample in the Methods section to interpret the results for the chronically depressed patients (see also **Supplementary Table 2** for more details).

Depressive Symptoms

The German version of the BDI-II (35) was used for the assessment of self-reported severity of depressive symptoms. The BDI-II has been shown to be a largely objective, reliable (internal consistency $\alpha \geq 0.84$), and valid instrument for assessing depressive symptoms (44).

Statistical Analysis

For the main statistical analysis, we employed a two-factorial MANOVA. Factor 1 was *Group* and consisted of two levels (mentally healthy vs. PDD affected participants), factor two was *Gender*. The dependent variables were the scores in the Compassionate Love Scale - Close others, the Compassionate Love Scale - Strangers/All of Humanity, and the IOS-Items *family*, *friends*, *acquaintances* and *people in general*. IOS connectedness to a *romantic partner* was analyzed in a separate analysis of variance for all participants who filled out the item (i.e., were in a partnership, $N = 75$). The IOS item "romantic partner" was completed less frequently by the chronically depressed patients ($N = 30$) than by healthy controls ($N = 45$). We think that the reduced number of romantic partners may be representative for patients with chronic depression. However, due to this difference it is difficult to compare both groups with respect to the "romantic partner" item and results regarding this item should be considered with more caution than the other analyses. Bivariate correlations (*Pearson's r)* between age, BDI-II, CLS, and IOS scales were exploratively analyzed separately for the two groups. Additionally, among the group of chronically depressed patients, we examined the correlations between the above variables and the CTQ.

RESULTS

The MANOVA test using Pillai's Trace showed significant main effects of Group ($F_{(6,87)} = 12.05$, $p < 0.001$, $\eta^2_p = 0.29$) and Gender ($F_{(6,87)} = 3.43$, $p = 0.004$, $\eta^2_p = 0.19$) and a significant interaction effect of Group*Gender ($F_{(6,87)} = 2.41$, $p = 0.034$, $\eta^2_p = 0.14$) on CLS and IOS scales.

Univariate analyses (**Table 1**) showed no significant main Group effect (healthy controls: $M = 4.28$, $SD = 1.05$; patients with PDD: $M = 4.19$, $SD = 1.18$) or interaction effect of Gender by Group on compassion toward strangers/all humanity, as reflected in the CLS scores (see **Figure 1** for CLS means by Group and Gender). However, compared to the chronically depressed patients ($M = 5.41$, $SD = 1.05$), healthy individuals ($M = 5.96$, $SD = 0.74$) had significantly higher compassion toward close others on the CLS scale, and significantly higher social connectedness on the IOS scale with their romantic partners ($M = 4.98$, $SD = 1.63$ vs. $M = 3.43$, $SD = 1.83$), family members ($M = 5.06$, $SD = 1.23$ vs. $M = 3.15$, $SD = 1.84$), friends ($M = 4.00$, $SD = 1.14$ vs. $M = 3.36$, $SD = 1.57$), acquaintances ($M = 2.92$, $SD = 1.06$ vs. $M = 2.32$, $SD = 1.09$), and people in general ($M = 2.59$,

TABLE 1 | Results of main and interaction effects of Group and Gender using univariate Analyses of Variance.

	Group		Gender		Group*Gender	
	F	η_p^2	*F*	η_p^2	*F*	η_p^2
CLS strangers/humanity[a]	0.11	<0.01	1.34	0.01	0.02	<0.01
CLS close others[a]	8.48**	0.08	8.82**	0.09	0.00	0.01
IOS romantic partner[b]	18.85**	0.21	1.85	0.03	3.67	0.05
IOS family[a]	32.09**	0.26	1.70	0.02	0.27	<0.01
IOS friends[a]	14.34**	0.14	6.94*	0.07	10.88**	0.11
IOS acquaintances[a]	16.98**	0.16	0.71	0.01	11.66**	0.11
IOS people in general[a]	6.45*	0.07	2.19	0.02	6.72*	0.07

[a]*F(1, 92),* [b]*F(1, 71); *p <0.05; **p <0.01;* η_p^2 *= partial eta-squared.*

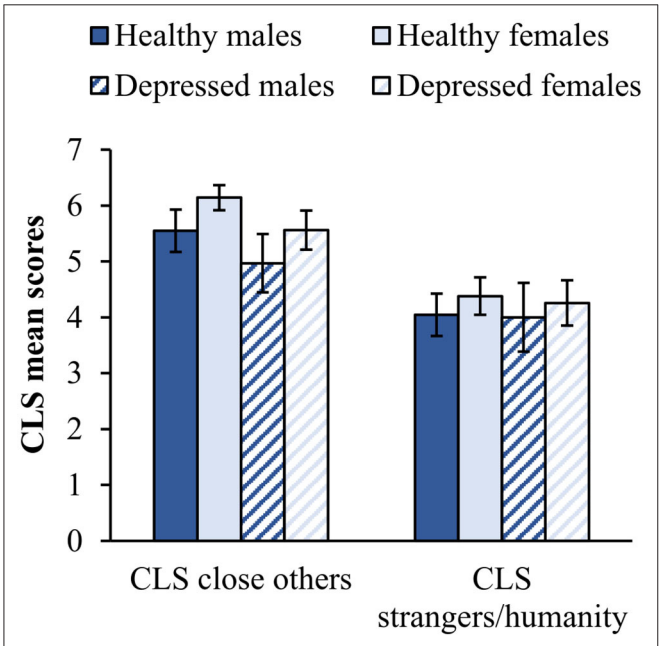

FIGURE 1 | Mean CLS scores by Group and Gender. Error bars represent 95% confidence intervals. Healthy males *N* = 15, Healthy females *N* = 34, Depressed males *N* = 12, and Depressed females *N* = 35.

SD = 1.08 vs. *M* = 2.23, *SD* = 1.36; see **Table 1** for *F*-values and effect sizes).

In the total sample, women (*M* = 5.85, *SD* = 1.05) reported significantly more compassion toward close others than men on the CLS scale (*M* = 5.26, *SD* = 1.70), and higher connectedness with friends on the IOS scale (*M* = 3.87, *SD* = 1.33 vs. *M* = 3.22, *SD* = 1.48; see **Table 1** for *F*-values and effect sizes). With regards to the latter, there was also a significant interaction effect of Group by Gender on social connectedness toward friends, acquaintances, and people in general (see **Table 1** for *F*-values, **Figure 2** for means and **Supplementary Table 1** for details on descriptive statistics). Healthy men reported slightly higher values than healthy women for friends, acquaintances, and people in general, but depressed men reported significantly lower values than depressed women. Furthermore, while depressed women reported approximately the same level of social connectedness toward friends, acquaintances, and people in general as their healthy counterparts, depressed men reported significantly less social connectedness to all groups of people than healthy men. However, both, depressed women and men reported reduced social connectedness toward romantic partners and family members compared to their healthy counterparts (**Figure 2**).

Patients with PDD reported higher levels of childhood adversity (CTQ total score: *M* = 53.17, *SD* = 16.36) compared to a representative sample (43) as well as a healthy control group from a recent other study (45), especially regarding emotional abuse [*M* = 13.72, *SD* = 5.77 vs. *M* = 6.49, *SD* = 2.60 (43) and *M* = 7.0, *SD* = 3.5 (45), respectively] and emotional neglect *M* = 16.40, *SD* = 5.34 vs. *M* = 10.05, *SD* = 4.23 (43) and *M* = 8.3, *SD* = 3.1 (45), respectively; see **Supplementary Table 2** for details]. Overall childhood adversity was significantly negatively correlated with connectedness to family members (**Table 2**). On the CTQ subscale level, IOS family correlated most strongly with emotional neglect, $r(45) = -0.541$, $p < 0.001$, emotional abuse, $r(45) = -0.409$, $p < 0.01$, and physical abuse, $r(45) = -0.380$, $p < 0.01$ (for details see **Supplementary Table 3**). Among the chronically depressed, compassion toward close others was significantly positively correlated with connectedness toward all groups of people except romantic partners. Compassion toward people in general was slightly positively correlated with connectedness toward more distant groups of people (friends, acquaintances, people in general). In the healthy control group, there was only a significant positive correlation between compassion toward close others and connectedness with family members, as wells as a significant negative correlation between compassion toward people in general and connectedness with a partner (**Table 2**). In the group of chronically depressed patients (BDI-II: *M* = 29.94, *SD* = 9.17; in total sample: *M* = 16.36, *SD* = 14.97), there was no correlation between severity of depressive symptomatology and connectedness or compassion. However, within the healthy control group (BDI-II: *M* = 3.35, *SD* = 3.14), there were a significant negative correlation between depression and connectedness with a romantic partner, and low or non-significant negative correlations between depression and connectedness with the other groups of people (**Table 2**).

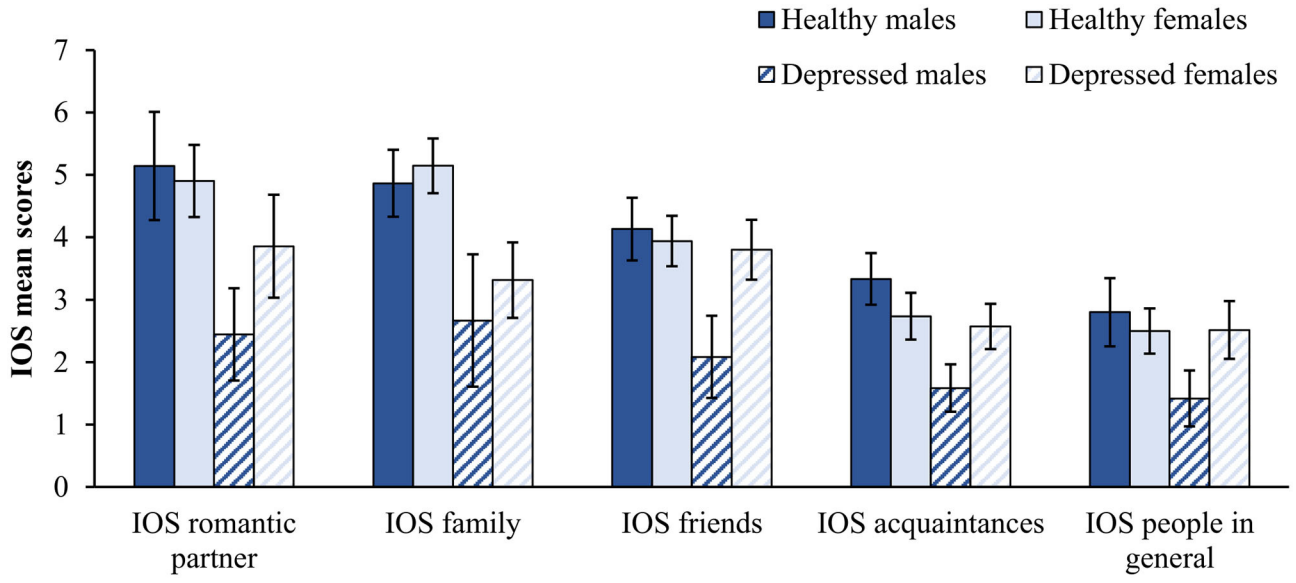

FIGURE 2 | Mean IOS scores by Group and Gender. Error bars represent 95% confidence intervals. IOS romantic partner: Healthy males $N = 14$, Healthy females $N = 31$, Depressed males $N = 9$, Depressed females $N = 21$. Other IOS scales: Healthy males $N = 15$, Healthy females $N = 34$, Depressed males $N = 12$, and Depressed females $N = 35$.

TABLE 2 | Bivariate correlations (Pearson's r) between childhood adversity (depression group only), age severity of depression, compassion and social connectedness in the healthy control group (above the diagonal) and in the group of chronically depressed patients (below the diagonal).

	CTQ	Age (years)	BDI-II	CLS CO	CLS S/H	IOS RP	IOS FAM	IOS FR	IOS ACQ	IOS PG
Age (years)	0.118	.	0.043	0.261	0.362*	−0.297*	−0.107	−0.209	−0.241	−0.040
BDI-II	0.239	−0.078	.	0.156	0.089	−0.385**	−0.103	−0.187	−0.161	−0.148
CLS CO	−0.053	−0.098	−0.133	.	0.547**	−0.083	0.299*	0.119	0.108	0.104
CLS S/H	0.168	−0.172	0.128	0.657**	.	−0.341*	−0.137	−0.112	−0.096	0.157
IOS RP	−0.017	0.167	−0.129	0.249	0.062	.	0.477**	0.584**	0.587**	0.245
IOS FAM	−0.470**	−0.216	−0.090	0.306*	0.071	0.337	.	0.551**	0.468**	0.349*
IOS FR	−0.058	−0.131	0.082	0.350*	0.223	0.400*	0.395**	.	0.867**	0.612**
IOS ACQ	−0.035	0.147	0.022	0.428**	0.330*	0.407*	0.356*	0.749**	.	0.737**
IOS PG	−0.003	0.138	−0.114	0.312*	0.220	0.396*	0.265	0.492**	0.658**	.

*$p < 0.05$; **$p < 0.01$; CTQ, Childhood Trauma Questionnaire; BDI-II, Beck Depression Inventory II; CLS CO, close others; CLS S/H, CLS strangers/humanity; IOS RP, IOS romantic partner; IOS FAM, IOS family; IOS FR, IOS friends; IOS ACQ, IOS acquaintances; IOS PG, IOS people in general.*
N = 30 for IOS romantic partner and N = 47 for all other variables in the chronic depression group; N = 45 for IOS romantic partner and N = 49 for all other variables in the healthy control group.

The lack of correlations between depression severity and social connectedness encouraged us to explore possible interactions with gender (see **Supplementary Table 1** for details on descriptive statistics). In depressed men, severity of depression was correlated only with connectedness with a romantic partner ($r(7) = 0.681$, $p < 0.05$), whereas there were no significant correlations in depressed women. No significant correlations were also found in healthy men, while there was a significant moderate correlation between severity of depression and connectedness with a romantic partner in healthy women ($r(29) = 0.413$, $p < 0.05$). However, due to the small number of participants within the subsamples, these results should be interpreted with great caution.

DISCUSSION

Our hypothesis that patients with chronic depression would report lower perception of social connectedness as compared to healthy controls was supported by significant differences in the IOS scale. This is consistent with longitudinal data indicating bi-directional correlations between depressive symptoms and objective indicators of social disconnectedness, such as the frequency of social interactions, as well as the perception of social isolation during episodes of major depression (8). Although our cross-sectional design does not allow for causal conclusions, the results confirm the importance of perceived social disconnectedness and severe social impairment in social functioning among chronically depressed patients (2). Within the

context of social identity theory, social relationships structure the individuals' self-concept and behavior (7). Thus, the perception of distorted relationships to others, low self-esteem, and reduced motivation to sustain social relationships may build a negative spiral (46), which may also contribute to the maintenance of depressed mood in persistent depressive disorder.

Contrary to our expectations and inconsistent with results from the longitudinal study by Santini et al. (8), social connectedness was not related to the severity of depressive symptoms within depressed patients. A possible reason for this may be the relatively high homogeneity of depression scores within the chronic depression group. Studies with larger samples are needed to provide more conclusive evidence. Furthermore, the link between social connectedness and depressive symptoms may be complicated by moderating variables such as prosocial behavior, in the sense that positively valued social interactions may be required to maintain interpersonal connectedness.

While we found significant differences between chronically depressed patients and healthy controls in all IOS subscales (i.e., romantic partner, family, friends, acquaintances, and people in general), a differential pattern occurred with respect to compassion. On the one hand, patients with chronic depression also reported significantly reduced compassion to close others. This result is consistent with findings of reduced dispositional compassion (20) and reduced empathy - as an integral part of compassion - in depression (12). On the other hand, and contrary to our expectations, compassion was not impaired toward strangers or other humans in general. A possible explanation of this discrepancy may be that compassion, as defined by "the sensitivity to suffering in self and others with a commitment to try to alleviate and prevent it" [(47), p. 2260], may affect the perception of social connectedness more in relationships to close others than to strangers.

Given the relationship between compassion and empathy, especially *empathic concern* (48), our findings can be related - with some caution - to existing research on the relationship between depression and empathy. *Distress tolerance*, the "ability to tolerate difficult emotions in oneself when confronted with someone else's suffering" is considered an aspect of compassion (41) and may reflect low trait *personal distress*, another facet of empathy. Considering previous findings of increased personal distress (49, 50) and our present findings of reduced compassion in patients with PDD, it could be hypothesized that patients with PDD experience other people's negative experiences as distressing rather than responding to them compassionately (i.e., with emotional concern). However, the assumption of reduced empathic concern would be in contrast to findings that suggest that empathic concern is either not reduced (49, 51) or is even increased (50) in patients with PDD. Moreover, our findings of reduced compassion in PDD cannot be validly reconciled with other studies' findings of increased personal distress (as a correlate of reduced compassion) because the CLS contains few items regarding distress tolerance (41) and correlates only weakly with personal distress (48). Yet, our results may be regarded consistent with Guhn et al. (52), who found markedly blunted emotional reactivity toward negative stimuli, such as others' suffering, in patients with PDD as compared with patients with recurrent depression or healthy controls.

It should be noted that Neugebauer et al. (21) observed in a longitudinal study that episodes of major depression were subsequently followed by increased altruism as assessed by a scale comprising compassion, social love, and human engagement. Interestingly, in our patient sample, reduced social connectedness was significantly correlated with reduced compassion toward close others, but not toward strangers or other humans in general. Importantly, reduced connectedness toward family members was also associated with self-reported childhood adversity, in particular with emotional abuse and emotional neglect. Thus, it is possible that the effect of childhood adversity as a risk factor for chronic depression may be meditated by the impairment of social connectedness in close relationships, rather than in relationships to others in general (53). By contrast, in chronically depressed patients, compassion toward close others or strangers was unrelated to childhood adversity. Thus, we could not confirm the findings of Lim and DeSteno (54), who found a significant positive correlation of life adversity with compassion toward others. However, it should be noted that we assessed severe and traumatic adversities in childhood, which may not have the same beneficial effects on prosocial attitudes and motivation in terms of posttraumatic growth. Further, our findings are consistent with a recent study that found an association between emotional abuse with loneliness, with the association mediated by increased rejection sensitivity (45).

There was a significant difference between chronically depressed patients and healthy controls with respect to gender effects on social connectedness. For both genders, depression was associated with a reduced degree of social connectedness, but the difference was significantly greater for men than for women. Thus, chronic depression was stronger associated with reduced social connectedness in men than in women. This may relate to the findings that men have less stable relationships with friends and acquaintances (55), weaker networks of social support (56) and less resources of emotional support in their social environment (57) than women. Following a divorce, men experience longer phases of psychological distress (58) and are at greater risk of suicide (59). Thus, although the risk of developing depression is higher in women (60), the effect of depression on social connectedness may be more serious in men.

There are several limitations to be noted. First, the use of cross-sectional data does not allow to make statements about the causality of the findings. Further studies with longitudinal study designs would be necessary to investigate possible causalities and, if applicable, their direction. Second, the reduced statistical power due to the small sample may increase the likelihood of false negative results. Thus, our findings warrant a replication in a larger sample. Third, the specificity of the results for chronic depression needs to be tested in future studies by including patients with major depressive disorder and other clinical conditions. Fourth, a multi-method approach using clinical ratings in addition to self-report measures may increase the validity of the findings. While the validity of the IOS has been repeatedly demonstrated (37), the compassionate love scale needs

further testing. Hence, findings regarding compassion should be interpreted with caution.

To conclude, we found evidence for reduced social connectedness and compassion toward close others in chronically depressed patients, which should be addressed in the treatment. Based on findings that patients with chronic depression experience lower social integration, less social support (61), and smaller social networks (62), it can be speculated that social connectedness and belongingness are particularly impaired in patients with chronic depression, as compared to episodic depression. As for depressed patients in general, reduced social connectedness may also correspond with reduced empathic response to positive affect (51), impaired social cognition (26, 27), and social anhedonia (3). Psychological interventions for chronic depression should therefore target interpersonal problems. In line with this recommendation, Cognitive Behavioral Analysis System of Psychotherapy (CBASP) has proven to be effective in the treatment of chronic depression (63). In addition, meditation techniques focusing on loving kindness (64, 65) have also shown promising results. Thus, besides using cognitive and behavioral interventions focusing of specific interpersonal deficits, the enhancement of prosocial motivation and positive affect by combining CBT with metta meditation may also be an effective approach in the treatment of chronic depression (33).

DATA AVAILABILITY STATEMENT

The datasets presented in this article are not readily available because of patient confidentiality and participant privacy. Requests to access the datasets should be directed to frick@psych.uni-frankfurt.de.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethics Committee of the Faculty of Medicine at Goethe University Frankfurt (MeCBT study, chronically depressed patients); Ethics Committee of the Faculty of Psychology and Sports Sciences at Goethe University Frankfurt (healthy control group). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

US conceived the study and obtained ethical approval. AF, IT, SH, and SW contributed to conception and design of the study. IT and AF coordinated recruitment and data collection. AF performed the statistical analysis. AF and US drafted the article. SH and SW contributed to the review of literature and proofread the manuscript. AF edited the final manuscript. All authors contributed to manuscript revision, read, and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2021.608607/full#supplementary-material

REFERENCES

1. Santini ZI, Koyanagi A, Tyrovolas S, Mason C, Haro JM. The association between social relationships and depression: a systematic review. *J Affect Disord*. (2015) 175:53–65. doi: 10.1016/j.jad.2014.12.049
2. Kupferberg A, Bicks L, Hasler G. Social functioning in major depressive disorder. *Neurosci Biobehav Rev*. (2016) 69:313–32. doi: 10.1016/j.neubiorev.2016.07.002
3. Atherton BD, Nevels RM, Moore MT. Predicting symptoms of depression from social anhedonia and emotion regulation. *J Nerv Ment Dis*. (2015) 203:170–4. doi: 10.1097/NMD.0000000000000262
4. Gao S, Assink M, Cipriani A, Lin K. Associations between rejection sensitivity and mental health outcomes: a meta-analytic review. *Clin Psychol Rev*. (2017) 57:59–74. doi: 10.1016/j.cpr.2017.08.007
5. Hames JL, Chiurliza B, Podlogar MC, Smith AR, Selby EA, Anestis MD, et al. Perceived burdensomeness and thwarted belongingness predict excessive reassurance seeking among clinical outpatients. *J Clin Psychol*. (2015) 71:597–605. doi: 10.1002/jclp.22158
6. Haslam SA, Jetten J, Postmes T, Haslam C. Social identity, health and well-being: an emerging agenda for applied psychology. *Appl Psychol*. (2009) 58:1–23. doi: 10.1111/j.1464-0597.2008.00379.x
7. Cruwys T, Haslam SA, Dingle GA, Haslam C, Jetten J. Depression and social identity: an integrative review. *Pers Soc Psychol Rev*. (2014) 18:215–38. doi: 10.1177/1088868314523839
8. Santini ZI, Jose PE, York Cornwell E, Koyanagi A, Nielsen L, Hinrichsen C, et al. Social disconnectedness, perceived isolation, and symptoms of depression and anxiety among older Americans (NSHAP): a longitudinal mediation analysis. *Lancet Public Health*. (2020) 5:e62–e70. doi: 10.1016/S2468-2667(19)30230-0
9. Lee RM, Robbins SB. The relationship between social connectedness and anxiety, self-esteem, and social identity. *J Couns Psychol*. (1998) 45:338–45. doi: 10.1037/0022-0167.45.3.338
10. Williams KL, Galliher RV. Predicting depression and self–esteem from social connectedness, support, and competence. *J Soc Clin Psychol*. (2006) 25:855–74. doi: 10.1521/jscp.2006.25.8.855

11. Batson CD, Ahmad N, Powell AA, Stocks EL, Shah J, Gardner WL. Prosocial motivation. In: Shah JY, Gardner WL, editors. *Handbook of Motivation Science*. New York, NY: Guilford Press (2008). p. 135–49.
12. Cusi AM, MacQueen GM, Spreng RN, McKinnon MC. Altered empathic responding in major depressive disorder: relation to symptom severity, illness burden, and psychosocial outcome. *Psychiatry Res*. (2011) 188:231–6. doi: 10.1016/j.psychres.2011.04.013
13. Alarcón G, Forbes EE. Prosocial behavior and depression: a case for developmental gender differences. *Curr Behav Neurosci Rep*. (2017) 4:117–27. doi: 10.1007/s40473-017-0113-x
14. Werner AM, Tibubos AN, Rohrmann S, Reiss N. The clinical trait self-criticism and its relation to psychopathology: a systematic review - Update. *J Affect Disord*. (2019) 246:530–47. doi: 10.1016/j.jad.2018.12.069
15. Neff KD. The development and validation of a scale to measure self-compassion. *Self Identity*. (2003) 2:223–50. doi: 10.1080/15298860309027
16. López A, Sanderman R, Schroevers MJ. A close examination of the relationship between self-compassion and depressive symptoms. *Mindfulness (N Y)*. (2018) 9:1470–8. doi: 10.1007/s12671-018-0891-6
17. Krieger T, Berger T, Holtforth MG. The relationship of self-compassion and depression: cross-lagged panel analyses in depressed patients after outpatient therapy. *J Affect Disord*. (2016) 202:39–45. doi: 10.1016/j.jad.2016.05.032
18. Krieger T, Altenstein D, Baettig I, Doerig N, Holtforth MG. Self-compassion in depression: associations with depressive symptoms, rumination, and avoidance in depressed outpatients. *Behav Ther*. (2013) 44:501–13. doi: 10.1016/j.beth.2013.04.004
19. Ehret AM, Joormann J, Berking M. Examining risk and resilience factors for depression: the role of self-criticism and self-compassion. *Cogn Emot*. (2015) 29:1496–504. doi: 10.1080/02699931.2014.992394
20. Saarinen A, Keltikangas-Järvinen L, Cloninger CR, Veijola J, Elovainio M, Lehtimäki T, et al. The relationship of dispositional compassion for others with depressive symptoms over a 15-year prospective follow-up. *J Affect Disord*. (2019) 250:354–62. doi: 10.1016/j.jad.2019.03.029
21. Neugebauer R, Wickramaratne P, Svob C, McClintock CH, Gameroff MJ, Miller L, et al. Contribution of religion/spirituality and major depressive disorder to altruism. *J Affect Disord*. (2020) 262:16–22. doi: 10.1016/j.jad.2019.10.031
22. Schreiter S, Pijnenborg GH, Rot M. Empathy in adults with clinical or subclinical depressive symptoms. *J Affect Disord*. (2013) 150:1–16. doi: 10.1016/j.jad.2013.03.009
23. Nübel J, Guhn A, Müllender S, Le HD, Cohrdes C, Köhler S. Persistent depressive disorder across the adult lifespan: results from clinical and population-based surveys in Germany. *BMC Psychiatry*. (2020) 20:58. doi: 10.1186/s12888-020-2460-5
24. Bird T, Tarsia M, Schwannauer M. Interpersonal styles in major and chronic depression: a systematic review and meta-analysis. *J Affect Disord*. (2018) 239:93–101. doi: 10.1016/j.jad.2018.05.057
25. Köhler S, Chrysanthou S, Guhn A, Sterzer P. Differences between chronic and nonchronic depression: systematic review and implications for treatment. *Depress Anxiety*. (2019) 36:18–30. doi: 10.1002/da.22835
26. Weightman MJ, Knight MJ, Baune BT. A systematic review of the impact of social cognitive deficits on psychosocial functioning in major depressive disorder and opportunities for therapeutic intervention. *Psychiatry Res*. (2019) 274:195–212. doi: 10.1016/j.psychres.2019.02.035
27. Sondermann S, Stahl J, Grave U, Outzen J, Moritz S, Klein JP. Preoperational thinking as a measure of social cognition is associated with long-term course of depressive symptoms. a longitudinal study involving patients with depression and healthy controls. *Front Psychiatry*. (2020) 11:652. doi: 10.3389/fpsyt.2020.00652
28. Klein JP, Grasshoff L, Hermanns R, Haeger S, Sondermann S, Kühnen T, et al. Präoperatorisches Denken bei verschiedenen psychischen Störungen: Zwei Querschnittsstudien zum besseren Verständnis des CBASP. *Zeitschrift für Psychiatrie, Psychologie und Psychotherapie*. (2020) 68:191–9. doi: 10.1024/1661-4747/a000418
29. Wiersma JE, Hovens JG, van Oppen P, Giltay EJ, van Schaik DJ, Beekman AT, et al. The importance of childhood trauma and childhood life events for chronicity of depression in adults. *J Clin Psychiatry*. (2009) 70:983–9. doi: 10.4088/JCP.08m04521
30. Soutschek A, Burke CJ, Raja Beharelle A, Schreiber R, Weber SC, Karipidis II, et al. The dopaminergic reward system underpins gender differences in social preferences. *Nat Hum Behav*. (2017) 1:819–27. doi: 10.1038/s41562-017-0226-y
31. Brañas-Garza P, Capraro V, Rascón-Ramírez E. Gender differences in altruism on Mechanical Turk: expectations and actual behaviour. *Econ Lett*. (2018) 170:19–23. doi: 10.1016/j.econlet.2018.05.022
32. Kawachi I, Berkman LF. Social ties and mental health. *J Urban Health*. (2001) 78:458–67. doi: 10.1093/jurban/78.3.458
33. Frick A, Thinnes I, Stangier U. Metta-based group meditation and individual cognitive behavioral therapy (MeCBT) for chronic depression: study protocol for a randomized controlled trial. *Trials*. (2020) 21:20. doi: 10.1186/s13063-019-3815-4
34. Löw B, Zipfel S, Herzog W. *Deutsche Übersetzung und Validierung des Patient Health Questionnaire (PHQ) von Spitzer, Kroenke u. Williams*. Heidelberg: Medizinische Universitätsklinik Heidelberg (2002).
35. Hautzinger M, Keller F, Kühner C. *Beck Depressions-Inventar (BDI-II)*. Frankfurt: Harcourt Test Services (2006).
36. Aron A, Aron EN, Smollan D. Inclusion of other in the self scale and the structure of interpersonal closeness. *J Pers Soc Psychol*. (1992) 63:596–612. doi: 10.1037/0022-3514.63.4.596
37. Gächter S, Starmer C, Tufano F. Measuring the closeness of relationships: a comprehensive evaluation of the 'inclusion of the other in the self' scale. *PLoS ONE*. (2015) 10:e0129478. doi: 10.1371/journal.pone.0129478
38. Cialdini RB, Brown SL, Lewis BP, Luce C, Neuberg SL. Reinterpreting the empathy-altruism relationship: when one into one equals oneness. *J Pers Soc Psychol*. (1997) 73:481–94. doi: 10.1037/0022-3514.73.3.481
39. Sprecher S, Fehr B. Compassionate love for close others and humanity. *J Soc Pers Relat*. (2005) 22:629–51. doi: 10.1177/0265407505056439
40. Lee JA. *Colours of Love: An Exploration of the Ways of Loving*. Toronto: New Press (1973). p. 294.
41. Strauss C, Lever Taylor B, Gu J, Kuyken W, Baer R, Jones F, et al. What is compassion and how can we measure it? A review of definitions and measures. *Clin Psychol Rev*. (2016) 47:15–27. doi: 10.1016/j.cpr.2016.05.004
42. Gu J, Cavanagh K, Baer R, Strauss C. An empirical examination of the factor structure of compassion. *PLoS ONE*. (2017) 12:e0172471. doi: 10.1371/journal.pone.0172471
43. Klinitzke G, Romppel M, Häuser W, Brähler E, Glaesmer H. Die deutsche Version des Childhood Trauma Questionnaire (CTQ) - psychometrische Eigenschaften in einer bevölkerungsrepräsentativen Stichprobe. *Psychother Psychosom Med Psychol*. (2012) 62:47–51. doi: 10.1055/s-0031-1295495
44. Kühner C, Bürger C, Keller F, Hautzinger M. Reliabilität und Validität des revidierten Beck-Depressionsinventars (BDI-II). *Nervenarzt*. (2007) 78:651–6. doi: 10.1007/s00115-006-2098-7
45. Nenov-Matt T, Barton BB, Dewald-Kaufmann J, Goerigk S, Rek S, Zentz K, et al. Loneliness, social isolation and their difference: a cross-diagnostic study in persistent depressive disorder and borderline personality disorder. *Front. Psychiatry*. (2020) 11:608476. doi: 10.3389/fpsyt.2020.608476
46. Waugh CE, Fredrickson BL. Nice to know you: positive emotions, self-other overlap, and complex understanding in the formation of a new relationship. *J Posit Psychol*. (2006) 1:93–106. doi: 10.1080/17439760500510569
47. Gilbert P, Basran J, MacArthur M, Kirby JN. Differences in the semantics of prosocial words: an exploration of compassion and kindness. *Mindfulness (N Y)*. (2019) 10:2259–71. doi: 10.1007/s12671-019-01191-x
48. Schlosser M, Pfaff NG, Schweinberger SR, Marchant NL, Klimecki O. The psychometric properties of the Compassionate Love Scale and the validation of the English and German 7-item Compassion for Others Scale (COS-7). *MindRxiv Papers [Preprint]*. (2020). Available online at: https://mindrxiv.org/z4ngy/ (accessed 01 February, 2021).
49. Domes G, Spenthof I, Radtke M, Isaksson A, Normann C, Heinrichs M. Autistic traits and empathy in chronic vs. episodic depression. *J Affect Disord*. (2016) 195:144–7. doi: 10.1016/j.jad.2016.02.006
50. Struck N, Gärtner T, Kircher T, Brakemeier E-L. Social cognition and interpersonal problems in persistent depressive disorder vs. episodic depression: the role of childhood maltreatment. *Front. Psychiatry*. (2021) 11:608795. doi: 10.3389/fpsyt.2020.608795
51. Guhn A, Merkel L, Hübner L, Dziobek I, Sterzer P, Köhler S. Understanding versus feeling the emotions of others: how persistent

and recurrent depression affect empathy. *J Psychiatr Res*. (2020) 130:120–7. doi: 10.1016/j.jpsychires.2020.06.023
52. Guhn A, Steinacher B, Merkl A, Sterzer P, Köhler S. Negative mood induction: affective reactivity in recurrent, but not persistent depression. *PLoS ONE*. (2019) 14:e0208616. doi: 10.1371/journal.pone.0208616
53. Liu RT. Childhood adversities and depression in adulthood: current findings and future directions. *Clin Psychol (New York)*. (2017) 24:140–53. doi: 10.1111/cpsp.12190
54. Lim D, DeSteno D. Suffering and compassion: the links among adverse life experiences, empathy, compassion, and prosocial behavior. *Emotion*. (2016) 16:175–82. doi: 10.1037/emo0000144
55. van Daalen G, Sanders K, Willemson TM. Sources of social support as predictors of health, psychological well-being and life satisfaction among Dutch male and female dual-earners. *Women Health*. (2005) 41:43–62. doi: 10.1300/J013v41n02_04
56. Fischer CS, Beresford L. Changes in support networks in late middle age: the extension of gender and educational differences. *J Gerontol Ser B Psychol Sci Soc Sci*. (2015) 70:123–31. doi: 10.1093/geronb/gbu057
57. Matud MP, Ibáñez I, Bethencourt JM, Marrero R, Carballeira M. Structural gender differences in perceived social support. *Pers Individ Dif*. (2003) 35:1919–29. doi: 10.1016/S0191-8869(03)00041-2
58. Gähler M. "To Divorce Is to Die a Bit…": a longitudinal study of marital disruption and psychological distress among swedish women and men. *Family J*. (2006) 14:372–82. doi: 10.1177/1066480706290145
59. Kõlves K, Ide N, Leo DD. Suicidal ideation and behaviour in the aftermath of marital separation: gender differences. *J Affect Disord*. (2010) 120:48–53. doi: 10.1016/j.jad.2009.04.019
60. Kuehner C. Why is depression more common among women than among men? *Lancet Psychiatry*. (2017) 4:146–58. doi: 10.1016/S2215-0366(16)30263-2
61. Hölzel L, Härter M, Reese C, Kriston L. Risk factors for chronic depression–a systematic review. *J Affect Disord*. (2011) 129:1–13. doi: 10.1016/j.jad.2010.03.025
62. Visentini C, Cassidy M, Bird VJ, Priebe S. Social networks of patients with chronic depression: a systematic review. *J Affect Disord*. (2018) 241:571–8. doi: 10.1016/j.jad.2018.08.022
63. Negt P, Brakemeier E-L, Michalak J, Winter L, Bleich S, Kahl KG. The treatment of chronic depression with cognitive behavioral analysis system of psychotherapy: a systematic review and meta-analysis of randomized-controlled clinical trials. *Brain Behav*. (2016) 6:e00486. doi: 10.1002/brb3.486
64. Graser J, Höfling V, Weßlau C, Mendes A, Stangier U. Effects of a 12-week mindfulness, compassion, and loving kindness program on chronic depression: a pilot within-subjects wait-list controlled trial. *J Cogn Psychother*. (2016) 30:35–49. doi: 10.1891/0889-8391.30.1.35
65. Hofmann SG, Petrocchi N, Steinberg J, Lin M, Arimitsu K, Kind S, et al. Loving-kindness meditation to target affect in mood disorders: a proof-of-concept study. *Evid Based Complement Alternat Med*. (2015) 2015:1–11. doi: 10.1155/2015/269126

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BRIEF RESEARCH REPORT
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Negative Effects of a Multimodal Inpatient CBASP Program: Rate of Occurrence and Their Impact on Treatment Outcome in Chronic and Treatment-Resistant Depression

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Background: A growing number of studies indicate that the Cognitive Behavioral Analysis System of Psychotherapy (CBASP) is effective in treating chronic depression. However, there is no systematic research into possible negative effects. Therefore, the objectives of the study were to investigate the rate of occurrence of negative effects of an inpatient CBASP program and their impact on treatment response.

Methods: Patients with chronic depression and treatment resistance who completed the 12-week multimodal inpatient CBASP treatment program in an open trial ($N = 52$) retrospectively completed the Inventory for the Assessment of Negative Effects of Psychotherapy (INEP) during follow-up data collection. Severity of depressive symptoms was assessed self- and observer-rated at admission, discharge, and 6 months follow-up. Rates of occurrence of negative effects were calculated and binary logistic regression analyses were conducted to determine the relationship to treatment outcome.

Results: The results indicate that 92.3% of patients reported having experienced at least one negative effect and 45.2% indicated dependence on their therapist. Stigmatization and financial concerns as well as intrapersonal changes were reported by about one-third. Only dependence on the therapist negatively impacted treatment outcome in both outcome measures.

Conclusions: While almost all patients reported at least one negative effect of a multimodal inpatient CBASP treatment program, most of the reported negative effects appear to be benign. However, dependence on the therapist seems to have a negative impact on treatment outcome. If these results can be replicated in future large-scale, randomized controlled prospective studies, CBASP therapists should be aware of possible dependence and consciously address it during treatment.

Keywords: negative effects, inpatient psychotherapy, chronic depression, cognitive behavioral analysis system of psychotherapy, treatment outcome, dependence, CBASP

INTRODUCTION

Systematic research to assess and report negative effects such as side effects and other unwanted effects of psychotherapy is lacking (1). By definition, negative effects of psychotherapy can be divided into unwanted effects caused by malpractice or unethical behavior and unwanted effects caused by correct treatment (referred to as side or adverse effects) (2). The relevance of negative effects depends on the severity and duration and should therefore be considered in relation to the short- and long-term treatment outcome: Negative effects are considered relevant, in case they negatively relate to treatment outcome; and irrelevant, if there is no or a positive association to treatment outcome (2).

Over the past 10 years, several instruments for assessing negative effects of psychotherapy have been developed and partially validated, notably the Inventory for the Assessment of Negative Effects of Psychotherapy [INEP; (3)] and the Negative Effect Questionnaire [NEQ; (4)]. According to the INEP, a recent study reveals that 58.7% of patients from a psychiatric hospital and 45.2% of patients from a psychosomatic hospital reported to have experienced at least one negative effect during therapy (5). Another INEP study indicates that 93.8% of former psychotherapy patients reported having experienced at least one negative effect during or after psychotherapy, with the highest rates concerning intrapersonal changes, stigmatization, and relationships (3). In a recent inpatient study, which did not use INEP to measure negative effects, 60–65% of psychiatric inpatients reported deterioration of mood state and unwanted treatment reactions; unwanted treatment reactions decreased in the course of treatment but were negatively associated with the treatment outcome (6). In addition, first research data indicate that negative effects have a negative impact on the outcome of treatment for obsessive–compulsive disorder (7). Overall, knowledge about the occurrence of specific negative effects in different treatment settings and their effects on treatment outcomes is too limited to determine the relevance of the negative effects. However, these reported high rates of occurrence of negative effects of psychotherapy in different treatment settings and mental disorders underline the importance of further investigations of negative effects, especially in seriously burdened patients like those suffering from treatment-resistant chronic depression (CD).

The Cognitive Behavioral Analysis System of Psychotherapy [CBASP; (8, 9)] is a disorder-specific treatment for patients with CD. Since chronically depressed patients have often experienced childhood maltreatment (10), the main goal of therapy is to enable patients to experience healing relationships. Through disciplined personal involvement, the therapist discloses her/his positive and negative personal feelings and reactions that the patient triggers in her/him, to teach the patient that people today respond to him differently than she/he expected or feared, supported by interpersonal discrimination exercises (11). CBASP can therefore be described as an interpersonal learning therapy. Several research studies indicate the efficacy of CBASP as an outpatient treatment for CD (12, 13) and CBASP as an inpatient treatment program (14).

In general, a strong therapeutic alliance has consistently been associated with positive treatment outcomes: Meta-analyses revealed a positive alliance–outcome association for face-to-face and internet-based psychotherapy with a medium and significant effect, explaining about 8% of the variability in treatment outcome (15, 16). More specifically, a relationship between the therapeutic alliance and outcome in CBASP has also been well-documented in literature (17, 18). Indeed, an early positive therapeutic alliance predicted favorable outcomes in CBASP (19) and independently contributed to specific CBASP elements to depressive symptom improvements, yielding unique and additive effects to the outcome (20). In line, larger depressive symptom improvement was related to a higher emphasis on the therapeutic relationship during CBASP (21). Mechanistically, Constantino et al. (22) showed that higher therapeutic alliance predicted decreases in hostile–submissive behavior, which, in turn, predicted less depressive symptoms in patients treated with CBASP. In line with this, decreases in patients' hostile–submissive behavior were significantly associated with a reduction of depressive symptoms and favorable treatment response (23).

However, in addition to these positive effects, it appears important to investigate negative effects of CBASP as well. Preliminary results of a self-constructed, non-validated questionnaire to assess side effects of a multimodal inpatient CBASP treatment program provided some interesting findings; however, the interpretation and generalizability of these results are hampered by methodological limitations of the questionnaire (24). Thus, research data with validated questionnaires (such as INEP) for specific negative effects during CBASP in CD and their relation to treatment response are lacking. In addition, it is of high clinical interest to further investigate negative effects in inpatient treatment, as inpatient treatment might trigger specific negative effects due to its short but intensive treatment (6).

Therefore, the objectives of the current study were to exploratively investigate (1) the rates of occurrence of negative effects of a multimodal inpatient CBASP treatment program and (2) the impact of specific negative effects on the clinician- and self-rated treatment response in order to determine their relevance.

MATERIALS AND METHODS

The study was conducted at the Affective Research Unit of the Department of Psychiatry and Psychotherapy, University of Freiburg Medical School, and approved by the Ethics Committee of the University of Freiburg. It has been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. All patients gave their written informed consent prior to their inclusion in the study. However, this pilot study has unfortunately not been pre-registered. The present study is part of a larger research project of which the feasibility and outcome data have already been published (14, 25).

Patients

Seventy consecutive patients who met the inclusion criteria of suffering from CD according to DSM-IV, aged 18–70 years, fluently speaking German, and being resistant to outpatient treatment were enrolled in the CBASP inpatient program. Treatment resistance was defined as fulfilling the criterion for either medication resistance (no response to two or more adequate trials of antidepressants) according to Thase and Rush (26) and/or psychotherapy resistance (no response to at least two health-insurance-reimbursed psychotherapies with at least 22 sessions each). Exclusion criteria were defined as a history of bipolar I disorder, comorbid substance dependency with <3 months of abstinence, antisocial personality disorder, severe forms of autism, and mental disorders due to organic factors according to the DSM-IV criteria. Of the 70 patients, 65 completed the study [dropout rate 7.1%; reasons for dropout: serious conflicts with other patients (three patients), severe psychosocial problems impossible to handle due to the distance to the patient's hometown (one patient), and diagnosis of mild cognitive impairment after 3 weeks of treatment (one patient)] [cf. (14)]. Completers ($n = 52$, 80% retention) filled out the INEP (3) between 6 and 12 months after discharge. No significant differences ($p > 0.05$) were found between completers who filled out the INEP and completers who did not ($n = 13$, 20%). The dropout patients refused to fill out follow-up questionnaires. The temporal variance of 6 to 12 months is due to the fact that this research question was developed after the study had already been designed (see **Limitations and Future Research**). In this manuscript, we analyze the data of the 52 patients who completed INEP.

Study Treatment: Multimodal Inpatient CBASP Treatment Program

The 12-week multimodal inpatient CBASP treatment program portrayed in this study is based on the CBASP treatment by McCullough (8) and was established in 2008. More specifically, this CBASP treatment program has been modified and manualized for inpatient use (27) and now includes the following CBASP-specific treatment elements [cf. (14)]: individual psychotherapy in CBASP sessions (two 50-min sessions per week; use of all CBASP strategies), CBASP group psychotherapy (two 90-min sessions per week, particularly focusing on the application of situational analyses including Kiesler Circle), CBASP body and movement therapy (one 60-min session per week, body-related exercises through various Kiesler Circle Training exercises), CBASP nursing staff sessions (one 30-min session per week; repetition of core treatment elements as well as exercises and role-plays to refresh the content of the CBASP individual sessions and group therapies), occupational group therapy (two 90-min sessions per week; art-related treatment of CBASP-relevant topics, e.g., significant others), and social counseling sessions (as needed, but at least one 30-min session per week; support in managing/resolving interpersonal and psychosocial problems such as divorce or job changes). As indicated, patients received two sessions per week over the course of 12 weeks leading to a total session number of 24 sessions on average exceeding the minimum of 18 sessions at least for CD (28). Of note, as a modification to the outpatient treatment, transference hypotheses are formulated not only for the individual therapist but also for the treatment ward team and for the patient group. In addition to this intensive inpatient treatment program, patients were able to participate in non-CBASP-specific sports and occupational therapies. Moreover, all patients received algorithm-based pharmacotherapy in accordance with current national and international guidelines for the treatment of depression (29, 30) and according to clinical experts supervision.

As discharge and the time thereafter generally play a major role in the success of the inpatient setting, the last 2 weeks of the multimodal inpatient CBASP treatment program focused on relapse prevention and follow-up by making arrangements for discharge from the hospital and continuation of treatment in the outpatient setting (in the form of a discharge plan). If patients continued to use the CBASP strategies they had learned and wanted a further treatment option in the multimodal inpatient CBASP treatment program, they could attend a 4-week inpatient CBASP refresher course at least 6 months after their first discharge. In addition, in at least some cities, CBASP support groups for patients were established to prevent relapse after discharge (27).

Among all patients, about 80% of the patients underwent outpatient psychotherapy after discharge. Of those, the percentual distribution of the therapy orientation is as follows: 46% cognitive behavioral therapy, 32% CBASP, 8% psychodynamic therapies, and 2% client-centered psychotherapy. In 18% of the patients, the continuation of a psychotherapy already started overlapping within the inpatient treatment; in 46% of the patients, the psychotherapy was still running at the time of the follow-up interview. Moreover, 42% of the patients visited the CBASP self-help groups established in Freiburg.

Measures

Inventory for the Assessment of Negative Effects of Psychotherapy

INEP is a self-report questionnaire assessing the negative effects of psychotherapy. Precisely, INEP records experiences and changes that patients have experienced in themselves and in their interaction with other people after the completion of their psychotherapy (3). The 21-item scale covers seven domains where negative effects may occur: "intrapersonal changes,"[1] "dependence," "family," "friends," "partnership," "stigmatization and financial concerns," and "malpractice." For example, the key items that measure dependence are formulated as follows: "During therapy and/or after its completion, it is harder for me to make important decisions on my own" and "During therapy and/or after its completion, I feel addicted to my therapist." The key items measuring intrapersonal changes are phrased like this: "Since the end of my therapy, I suffer less/more from the events of my past compared to the time before the therapy," "During

[1]The domain "intrapersonal changes" describes in the broadest sense negative effects on emotional experience and social functioning (3).

therapy and/or after its completion, I've had long periods of bad times," and "During therapy and/or after its completion, I had suicidal thoughts/intentions for the first time." Concerning malpractice, key items are as follows: "I felt hurt by the therapist's statements," "My therapist forced me to do things (exposure, role plays, etc.) that I didn't really want to do," or "During the therapy there were direct sexual assaults by my therapist." Patients were asked to indicate their agreement or disagreement with these statements on a four- or three-point Likert scale. In addition, patients must indicate for each item whether they attribute this change to psychotherapy or other life circumstances.

INEP in its final version has demonstrated good internal consistency ($\alpha = 0.86$), while the original subscale "malpractice" showed only satisfactory internal consistency ($\alpha = 0.73$). Initial results of factor analysis showed a seven-factor solution that supports its construct validity (3). In our sample, the total scale showed equally good internal consistency as indicated by Cronbach's alpha of $\alpha = 0.86$, while the subscale "negative effects" yielded a Cronbach's alpha of $\alpha = 0.84$, and, respectively, the subscale "malpractice," $\alpha = 0.78$ (excluding items 17, 18, and 19 due to no variance in our sample), both indicating good internal consistency. During follow-up data collection, INEP was assessed between 6 and 12 months after discharge.

24-Item Version of the Hamilton Rating Depression Scale

HRSD-24 is the 24-item version of the well-established clinician-rated Hamilton Rating Scale for Depression assessing the symptom severity of depression and served as primary outcome measure (31). Each item is rated from 0 to 2 or 0 to 4, total score is reported as a sum score and ranges from 0 to 76, while higher sum scores indicate more severe depressive symptoms. HRSD-24 was assessed at intake, discharge, and at 6 months follow-up by blinded and trained raters. *A priori*, treatment response was defined as a decrease in symptom severity of at least 50% in the HRSD-24. While the HRSD-24 showed only an acceptable internal consistency as indicated by Cronbach's alpha of $\alpha = 0.63$ in our sample, this instrument showed in general a good internal consistency indicated by a Cronbach's alpha of $\alpha = 0.79$ in other studies (32).

Beck Depression Inventory-II

BDI-II is an internationally widely used 21-item self-report questionnaire measuring somatic, cognitive, and affective symptoms of depression (33). It serves as a secondary outcome measure in the present study. Scores are ranging from 0 to 63, with higher values indicating more severe depressive symptoms. Like the HRSD-24, BDI-II was assessed at intake, discharge, and at 6-month follow-up. Treatment response was *a priori* defined in the same way as for HRSD-24, that is, a decrease in symptom severity of at least 50% of the BDI-II sum score. In line with internal consistency estimations reported in literature (34), the BDI-II yielded a Cronbach's alpha of $\alpha = 0.88$, indicating a very good internal consistency in our sample.

Other Baseline Measures

At the beginning of the study (baseline), sociodemographic questions were asked by a self-report questionnaire including age, gender, educational level, and marital status. Clinical characteristics were also assessed, including diagnosis of CD according to DSM-IV, early onset of depression, age at onset, inpatient treatment and psychotherapy in the past, medication and psychotherapy resistance, and suicide attempts in the past. Finally, axis I and axis II comorbidities were assessed with SCID I (35) and SCID II (36).

Statistics/Statistical Analyses

A data screening according to the suggestions of Tabachnick and Fidell (37) and a test of the assumptions of logistic regression were carried out (37). The data screening showed that between 6.2% and 36.9% of the variables used to measure treatment outcome were missing. In BDI-II, 6.2% of the data were missing at baseline. After completion of the treatment, 7.7% of the data were missing, and 6 months later, 35.4% of the data were missing. Regarding HRSD-24, all data were available for measurements at baseline and discharge. Six months after discharge, 6.2% of the HRSD-24 data were missing. The Little MCAR test (38) was performed to analyze missing values. The results were not significant, implicating that missing values appeared random. According to Tabachnick and Fidell (37), missing values were estimated using the expectation maximization (EM) procedure. Correlational analyses between demographic variables (i.e., gender, age, education, and relational status) and negative effects as indicated by the factors of the INEP were computed using Spearman-Rho correlations. To investigate the relationship between negative effects of psychotherapy and individual treatment response, a binary logistic regression was calculated using the backward stepwise method (the Backward:LR method). Two important assumptions for logistic regression (linearity in logistic regression and the absence of multicollinearity) were fulfilled. In order to evaluate the contribution of a single predictor to the model, the Wald test was calculated. The efficiency coefficient Exp(B), also called odds ratio (OR), and its confidence intervals were calculated to evaluate the effect of the predictor variables. All analyses were conducted using SPSS, version 21 (39). z-test *post-hoc* power analyses (two-tailed) were calculated using G*Power 3.1 (40, 41).

RESULTS

Patient Characteristics

The mean age at baseline of the 52 patients was 48.1 years (SD = 10.1 years); 61.5% were female. The mean patient sum score of the HRSD-24 at baseline was 31.3 (SD = 6.4), while the mean BDI-II sum score at baseline was 33.6 (SD = 10.5), both indicating severe depression. Moreover, the criteria for medication and psychotherapy resistance were each fulfilled by 88.5% of the sample. Further relevant sociodemographic and clinical characteristics are depicted in **Table 1**.

TABLE 1 | Sociodemographic characteristics of the sample ($N = 52$).

Characteristics	Patients ($N = 52$)
Age at entry, *M* (SD)	48.1 (10.1)
Sex, *n* (%)	
Male	20 (38.5)
Female	32 (61.5)
Educational level, *n* (%)	
No educational degree	4 (7.7)
Primary education	27 (51.9)
Secondary education	3 (5.8)
Higher education	18 (34.6)
Marital status, *n* (%)	
Single	11 (21.2)
Married/couples relationship	29 (55.8)
Divorced/in separation	12 (23.1)
Diagnosis of Chronic Depression (DSM-IV[a]), *n* (%)	
Double Depression	24 (46.2)
Recurrent Major Depression	17 (32.7)
Chronic Major Depression	11 (21.2)
Early onset of depression[b], *n* (%)	42 (80.8)
Age at onset *M* (SD)	15.0 (10.5)
Comorbid Axis I disorder[c], *n* (%)	43 (61.4)
Comorbid Axis II disorder[d], *n* (%)	47 (67.1)
Inpatient treatment in the past[e], *n* (%)	43 (82.7)
Psychotherapy in the past[f], *n* (%)	50 (96.2)
Medication resistance[g], *n* (%)	46 (88.5)
Psychotherapy resistance[h], *n* (%)	46 (88.5)
Suicide attempt in the past, *n* (%)	19 (36.5)
HRSD-24 score at baseline, *M* (SD)[i]	31.3 (6.4)
BDI-II score at baseline, *M* (SD)[j]	33.6 (10.5)

M, mean; SD, standard deviation; n, number.
[a] *DSM-IV, Diagnostic and Statistical Manual of Mental Disorders, 4th Edition.*
[b] *Before the age of 21.*
[c] *Assessed with Structured Clinical Interview (SCID) I (22).*
[d] *Assessed with Structured Clinical Interview (SCID) II (23).*
[e] *Inpatient treatment in a psychiatric or psychosomatic hospital.*
[f] *Treatments with minimum 22 sessions.*
[g] *No response to two or more adequate trials of antidepressants.*
[h] *No response to two or more health insurance-reimbursed psychotherapies with each minimum 22 sessions in Germany.*
[i] *HRSD-24, Hamilton Rating Depression Scale, 24 Items, scale 0–75 (20).*
[j] *BDI-II, Beck Depression Inventory-II, 21 Items, scale 0–63 (21).*

Rates of Occurrence of Reported Negative Effects

The 21-item scale covers seven domains of negative effects: "intrapersonal changes" ($M = -0.22$, SD =.59, Min = −1.33, Max = 1.33), "dependence" ($M = 0.21$, SD = 0.39, Min = 0, Max = 1.5), "family" ($M = -0.72$, SD = 1.11, Min = −3.0, Max = 1.0), "friends" ($M = -0.55$, SD = 1.00, Min = −3.0, Max = 1.0), "partnership" ($M = -0.10$, SD = 0.52, Min = −1.5, Max = 1.5), "stigmatization and financial concerns" ($M = 0.09$, SD = 0.34, Min = 0, Max = 2.33), and "malpractice" ($M = 0.08$, SD = 0.21, Min = 0, Max = 1.33). **Figure 1** presents the rates of occurrences of the seven INEP domains of negative effects caused by therapy. According to INEP, 92.3% reported having experienced at least one negative effect. Regarding the different domains, 45.2% reported having experienced dependence on their therapist. Experiences of stigmatization and financial concerns were reported by 35.9%, while intrapersonal changes in terms of symptom deterioration were experienced by 33.0% of patients. Furthermore, the lowest rates of negative effects were reported concerning family (13.5%), friends (13.5%), and partnership (17.2%). Some patients (6.1%) reported malpractice, with this comparatively high figure resulting from items stating that their therapist forced them to do things they did not want to do (such as role-playing) (two patients partly agreed, five patients agreed somewhat) and that patients felt hurt by therapists' statements (one patient totally agreed, one partly agreed, and eight agreed somewhat). No patient reported sexual abuse, physical assault, or other misconduct.

The Spearman-Rho correlation indicates that the factor "dependence" correlates non-significantly with sex ($\rho = -0.20$, $p > 0.05$), age ($\rho = -0.16$, $p > 0.05$), and educational status ($\rho = -0.14$, $p > 0.05$), and significantly with marital status ($\rho = -0.35$, $p < 0.05$), indicating a small to medium effect. Apart from these findings, only the factor "family" shows significant correlations with age ($\rho = -0.33$, $p < 0.05$) and educational status ($\rho = 0.34$, $p < 0.05$). The factors "intrapersonal changes," "friends," "partnership," "stigmatization and financial concerns," and "malpractice" did not show any significant correlational relationship with these demographics (all $p > 0.05$).

Prediction of Treatment Response Measured by HRSD-24

According to the HRSD-24 criterion for treatment response, 46 of the 52 patients (88.5%) responded to the 12-week multimodal inpatient CBASP treatment program. Six months after discharge, 32 patients (61.5%) still reached the response criterion. The results of the last step of the binary logistic regression using the backward stepwise method for treatment response regarding HRSD-24 are depicted in **Table 2**. The factor "intrapersonal changes" appears negatively related to treatment response at posttreatment [$b = -0.36$, Wald $\chi^2_{(1)} = 5.05$, $p = 0.03$]. The Exp(B) value indicates that when "intrapersonal changes" are increased by one unit, the odds ratio is.70 times as large and therefore patients are 30% less likely to respond to treatment. However, after 6-months of follow-up, the factor "dependence" is significantly associated with treatment response ($b = -1.02$, Wald $\chi^2_{(1)} = 5.08$, $p = 0.02$). The Exp(B) value indicates that when "dependence" is increased by one unit, the odds ratio is 0.36 times as large and therefore patients are 64% less likely to respond to treatment. Other factors were not significantly associated with treatment response ($p > 0.05$).

According to the HRSD-24 criterion for treatment response, z-test *post-hoc* power analyses revealed that only the following findings yielded acceptable power: the factor "family" on treatment response posttreatment (99%), yet not significant, and the factor "dependence" on treatment response after 6 months of follow-up (87%).

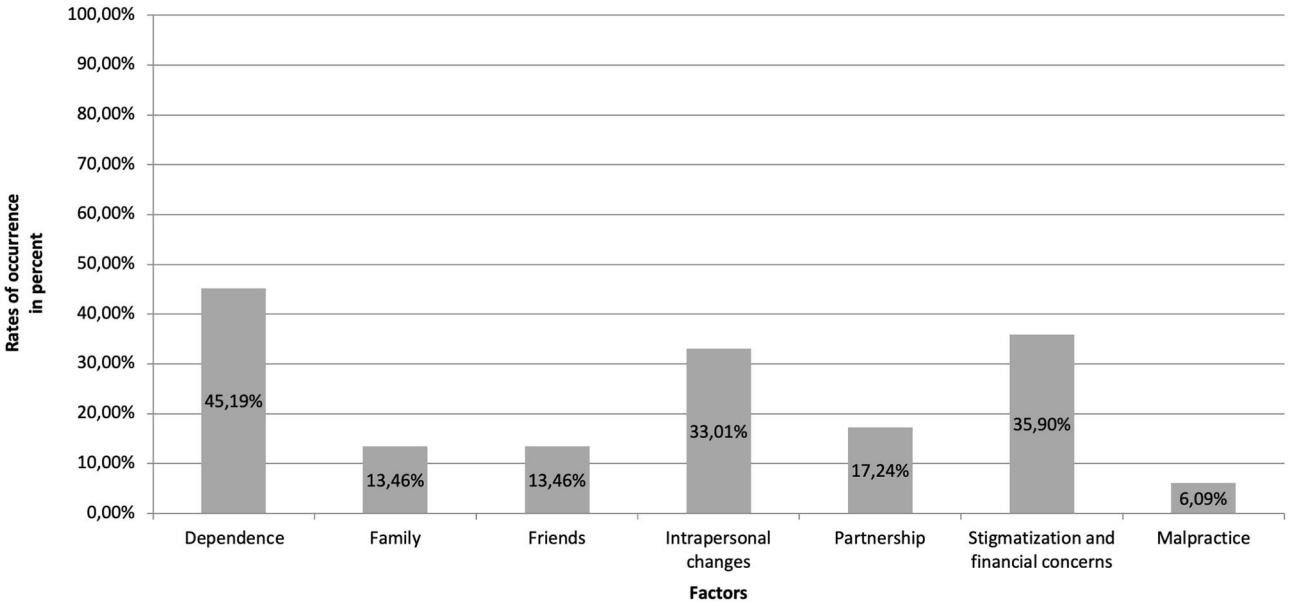

FIGURE 1 | Rates of occurrences of reported negative effects of psychotherapy according to the seven factors of the INEP (3).

TABLE 2 | Results of the logistic regression of negative effects on treatment response at discharge (T2) and follow-up 6 months after discharge (T3) measured by Hamilton Rating Depression Scale, 24-item version (HRSD-24).

Variables	*B*	Wald	*p*	Exp(*B*)	95.0% CI for Exp(*B*)	
					Lower	Upper
Criterion: Response on *HRSD-24* T2						
Family	−1.90	1.93	0.17	0.15	0.01	2.19
Intrapersonal changes	−0.36	5.05	0.03*	0.70	0.51	0.96
Criterion: Response on *HRSD-24* T3						
Dependence	−1.02	5.08	0.02*	0.36	0.15	0.88
Malpractice	0.56	1.61	0.20	1.75	0.74	4.17

T2, Assessment at discharge; T3, Follow up-assessment 6 months after discharge; HRSD-24, 24-item Version of the Hamilton Rating Depression Scale (20).
$^*p < 0.05$.

Secondary Analysis: Prediction of Treatment Response Measured by BDI-II

According to the BDI-II criterion for treatment response, 27 out of the 52 patients (51.9%) met the response criterion at discharge. Six months after discharge, 18 (34.6%) patients still met the response criterion. **Table 3** displays the results of the last step of the binary logistic regression using the backward stepwise method for treatment response regarding BDI-II. The factor "dependence" [$b = -0.81$, Wald $\chi^2_{(1)} = 3.91$, $p < 0.05$] appears to be negatively associated with treatment response at posttreatment, while the Exp(B) value indicates that when "dependence" is increased by one unit, the odds ratio is 0.51 times as large and the patients are 49% less likely to respond to treatment. In the 6-month follow-up assessment, the factor "friends" appears negatively related to treatment response [$b = -0.69$, Wald $\chi^2_{(1)} = 4.87$, $p = 0.03$]. Other factors were not significantly associated with treatment response ($p > 0.05$).

According to the BDI-II criterion for treatment response, the power of these models for both posttreatment and after 6 months of follow-up was overall rather low with the factor "dependence" achieving the highest power (74%), yet slightly under the threshold of acceptable power (i.e., 80%).

DISCUSSION

To date, there are only a few published studies investigating specific negative effects and their impact on the outcome of different specific psychotherapies [exception, e.g., (7)]. A better understanding of the rates of occurrence and relevance of negative effects is also relevant to adequately inform the patient about possible risks of the treatment. This study therefore aimed at (1) assessing the negative effects of a multimodal inpatient CBASP treatment program, as measured by the established and validated instrument INEP (3), and (2) evaluating the

TABLE 3 | Results of the logistic regression of negative effects on treatment response at discharge (T2) and follow-up 6 months after discharge (T3) measured by Beck Depression Inventory (BDI-II).

Variables	*B*	Wald	*p*	Exp(*B*)	95.0% CI for Exp(*B*)	
					Lower	Upper
Criterion: Response on *BDI-II* T2						
Dependence	−0.81	3.91	0.05*	0.45	0.20	0.99
Criterion: Response on *BDI-II* T3						
Friends	−0.68	4.87	0.03*	0.51	0.28	0.93
Malpractice	0.62	2.28	0.13	1.86	0.83	4.15

T2, Assessment at discharge; T3, Follow-up-assessment 6 months after discharge; BDI-II, Beck Depression Inventory-II (21).
*$p < 0.05$.

impact on treatment response to assess the relevance of negative effects. To achieve the first objective, the reported rates of occurrence of negative effects of the multimodal inpatient CBASP treatment program were examined. Notably, over 90% of patients reported retrospectively to have experienced at least one negative effect during treatment. This finding is consistent with previous studies investigating negative effects in patient populations being treated in outpatient settings (3), but exceeds reported rates of occurrences in inpatient routine clinical care (5, 6). This percentage is also higher than in a recent study that also focused on depressive patients who, however, filled out a different questionnaire than INEP via the Internet and previously underwent outpatient psychotherapy (42). Our comparatively high percentage may be explained by the specific characteristics of patients with treatment-resistant CD, that is, severe symptoms, early onset (age < 21 years), suicidality, and high percentage of reported childhood maltreatment (10, 43, 44), as well as the high-dosage short-term inpatient CBASP program with a strong focus on negative relationship experiences during childhood and the therapist–patient relationship (45). Most frequently in this study, patients reported having developed a dependence on their therapist (almost half of the patients). Stigmatization, financial concerns, and intrapersonal changes due to transient symptom deterioration were reported by one-third of all patients (second most frequent). At first glance, the result that 6.1% of patients reported malpractice appears alarmingly high. A precise analysis of the items that form this scale, however, shows that this comparatively high percentage is due to two items stating that patients felt forced by the therapist to do things they did not want to do, and that patients felt hurt by therapists' statements. In the case of the first item, the patients probably thought mainly of the interpersonal role-plays, which are intended in the CBASP strategy situational analysis in group and individual therapies. Chronically depressed patients usually have difficulties performing the role plays at the beginning of treatment due to their pronounced interpersonal problems (46). In addition, some patients may initially find therapists' statements painful, which are being made in the context of disciplined personal involvement. Therapists address their patients' interpersonally difficult behavior and explain the possible interpersonal consequences, which may initially seem confrontational. The goal, however, is to facilitate long-term healing experiences in relationships. Accordingly, in the course of treatment, patients usually notice how helpful these interpersonal strategies are, which is supported by studies that show that after CBASP therapies, the interpersonal problems have actually decreased (47, 48). Since we could not find any negative correlation to the treatment outcome, such specific malpractice aspects appear to be benign. It should be stressed that 0% reported sexual abuse, physical assaults, or other misconduct. Of note, the subscale malpractice of the INEP showed questionable psychometric properties, for example, only satisfactory internal consistency (3). Concerning the second objective, the results of the regression analyses suggest that, in particular, dependence on the therapist, as the most frequent dimension of negative effects, seems to play a significant role for treatment response on a self- and clinician-rated instrument. While dependence on the therapist is negatively associated with self-rated treatment response defined by BDI-II at discharge, the same factor is negatively linked to clinician-rated treatment response by HRSD-24 also in the long run. Of note, the rate of occurrence of this negative effect dimension is in our study only slightly higher compared to a psychiatric inpatient sample with various mental disorders (5).

In general, adverse event methods seem to be heterogeneous and insufficiently reported in RCTs in CD (49). However, a recent study found that patients receiving supportive psychotherapy reported less severe adverse events in general and less severe adverse events related to personal life and to occupational life than patients receiving CBASP, while less adverse events related to suicidal thoughts were reported in CBASP compared with supportive psychotherapy (50). The authors discussed that the differences in the profile of adverse events may be explained by specific treatment elements, as adverse events related to personal and professional life, for example, may be considered a necessary and expected but temporary adverse treatment outcome of effective CBASP treatment. This is in line with our findings, which underline that most of the reported negative effects had no impact on the treatment outcome. However, given the limitations of this study (see below), our results cautiously suggest that the more a patient reports dependence on her/his therapist, the less likely she/he might benefit from treatment. Yet, there are many possible explanations for this preliminary finding:

- It appears plausible that the high number of personality disorders (61.4% overall, of which 5.7% were diagnosed with

a dependent personality disorder) and personality disorder traits (67.1% overall, of which 32.9% were diagnosed with dependent personality disorder traits) of our sample may explain the relatively high percentage of patients reporting dependence on their therapist. Since studies show that personality disorders *per se* are a negative predictor of the outcome of psychotherapy in depressed patients [e.g., (51)], they might function as the underlying factor being responsible for the finding that the reported dependence on the therapist is negatively related to treatment outcome.

- Notably, it could also be argued that the dependence factor is not a side effect, but simply a consequence of a poor therapeutic alliance during treatment. Since psychotherapy research has often confirmed that a positive therapeutic alliance is associated with a positive outcome [e.g., (15)], dependence as an indicator of a negative alliance could explain the worse response. However, it has recently been reported that patients' dependency on mental healthcare seems to be associated with a better therapeutic alliance (52). Indeed, a relationship between the therapeutic alliance and outcome in CBASP has been well-established in research (17, 18, 21), while in particular a positive early therapeutic alliance predicted beneficial outcomes in CBASP (19, 20). However, a history of drug abuse/dependence and lower past and lower current social adjustment predicted a significantly poorer therapeutic alliance in CBASP (53).
- In addition, the level of severity of the personality dimension "dependency" may have a differential influence on the treatment outcome. Interestingly, a recent study investigated the impact on treatment outcome of the personality dimension dependency according to Blatt (54) in treatment-resistant chronically depressed patients and found that patients with more maladaptive dependent features did not benefit from a long-term psychoanalytic psychotherapy (LTPP) or treatment as usual (TAU), while those with less maladaptive dependent features showed considerable gains from LTPP but not from TAU (55).
- The specific strategies of CBASP might trigger dependence on the therapist. Notably, many patients suffering from CD reported to have experienced both childhood maltreatment [e.g., (10, 44)] and current interpersonal problems such as submissive or hostile behavior (46, 47) or emotional and behavioral avoidance (56, 57). The association between childhood maltreatment and interpersonal problems has recently been reported (58). CBASP-specific techniques (in particular the disciplined personal involvement and the interpersonal discrimination exercise) may allow those patients to experience new healing and corrective relationships—sometimes for the first time in their lives, characterized by predictability, interpersonal closeness, and warmth. Conversely, this new experience could also initially promote dependence on their therapists, especially when isolated patients have no other positive significant others in their life. Of note, CBASP traditionally highlights the importance of using autonomy-promoting strategies such as to encourage patients to write out a complete sentence in the situational analysis and to stress the use of the patient's own wording in an intervention. While autonomy has been well-promoted within the therapeutic relationship, interpersonal change and avoidance behavior outside of treatment (e.g., in occupational and private life) were possibly not yet sufficiently addressed because of the limits of the specific inpatient treatment setting and a lack of transfer opportunities.
- The individual psychotherapy in this CBASP treatment program was delivered in a high intensity with two CBASP 50-min sessions per week that probably have fostered dependence. Additionally, the high intensity of social encounters between the entire team and the patients on the ward (e.g., group psychotherapy twice a week, nurse–patient encounters, and social worker contact) for a predominantly socially isolated patient group of chronic depressive patients with interpersonal dysfunctions might have contributed to an increased dependence, since the main phase of this CBASP treatment focused on the use of the Kiesler circle (e.g., enhancing the understanding of their stimulus character and impact on others) and on conducting situational analyses with subsequent role-playing events to modify inappropriate behavior using the potential of other patients in the group psychotherapy.
- Finally, the applied intensive multimodal inpatient CBASP treatment program was limited to 12 weeks. Patients who have experienced dependence on their therapist may not feel sufficiently prepared yet for the demands of daily life at the end of this comparatively short treatment period, which may lead to an unfavorable treatment outcome. However, the finding of an increased dependence might have been at least partially confounded by the individual aftercare plan as four-fifths of the participants received outpatient psychotherapy, yet one-third of those underwent CBASP, after discharge.

Moreover, our results showed that negative effects related to intrapersonal changes appear negatively related to treatment response defined by HRSD-24 at discharge. This result cautiously indicates that the more a patient has suffered from intrapersonal changes (like transient deterioration of symptoms) during therapy, the less likely he/she might benefit from the therapy in the short term, but not in the long term. Lastly, the result that negative effects on friends are negatively related to long-term treatment response defined by BDI-II after 6 months may indicate that the more a patient reports negative effects on friends caused by treatment, the less he/she may improve in terms of treatment response. This result may be interpreted against the background of theories and approaches that consider CD primarily as a relationship disorder (8).

Although taking into account that two-tailed analyses yield lower power in general, the results of the *post-hoc* power analyses however indicated that solely the finding of the factor dependence on treatment response seems to be relatively robust and should therefore be interpreted.

Limitations and Future Research

The interpretability of the results of this study is reduced by some limitations. First, the INEP data were collected exclusively

retrospectively during a follow-up period and the period between discharge and INEP survey varied between 6 and 12 months. Thus, recall effects such as memory bias and the primacy–recency effect, forgetfulness, retrieval errors, or important experiences occurring after treatment had been completed may have distorted the reported negative effects. Indeed, subjectively experienced negative effects of (group) psychotherapy seemed to decrease in the course of treatment (6). For example, a bias toward the course of the depression after the end of treatment is conceivable, whereby a positive symptom course after treatment could lead to a more positive assessment of the received treatment with fewer negative effects. On the other hand, negative effects of inpatient treatment programs could actually only occur after discharge, whereby these in particular could possibly be detrimental and therefore valuable to record. Future studies should distinguish between the assessment of negative effects during and after treatment to have a more nuanced profile of negative effects in the short and long run. Furthermore, the hindsight bias must be considered when interpreting the results of this study, that is, that patients who did not respond see their treatment in a less positive light and report more negative effects. This retrospective evaluation of negative effects also means that the short-term outcome was recorded before the evaluation of the negative effects. Therefore, the analyses should also be interpreted with caution, as the chronological sequence of the recording of statistical predictors before the variable to be predicted (here: outcome) could not be fulfilled in this way. It is essential that future studies should record negative effects regularly in the therapy process and at uniform measurement times. Future large-scale studies should integrate the assessment of negative effects of psychological interventions in the data collection and analysis design when planning the study as proposed by new guidelines (59). Secondly, INEP does not include any specific negative effects of an inpatient setting, such as group therapy sessions or conflicts with other patients or staff, nor does it consider the influence of pharmacotherapy, which should be directly addressed in future research. Moreover, INEP does not simultaneously capture positive effects as the Positive and negative Effects of Psychotherapy Scale (PANEPS) instrument does (7, 42), which is why this study could not examine the relationship between negative and positive effects (apart from the outcome). Future studies should therefore use a measurement that captures both positive and negative effects [e.g., by using the PANEPS; (40)] to further minimize priming and associated potential nocebo effects. However, one positive aspect of the INEP is the bipolar response format, which records not only deteriorations but also improvements or missing changes, thus partly preventing negative priming (3). Thirdly, although there are promising findings underlining the seven-factor structure of INEP (3), these seven factors still lack some psychometric evaluations. Fourthly, future studies should exclusively use the DSM-5 criteria and the term persistent depressive disorder. Yet, since this study was still conducted under the term of chronic depression, this term was used throughout our manuscript and in reference to the main outcome paper (14). For a diagnostic cross-walk, we refer to relevant literature [e.g., (60, 61)]. Finally, the lack of a control group, additional algorithm-based pharmacotherapy, and a relatively small sample size generally complicate the ability to interpret the results. Due to the lack of a control group, we could not rule out that negative effects could also be due to psychotherapy *per se*, and not specifically due to the inpatient CBASP treatment. As we investigated a multimodal inpatient CBASP program including multiple interventions and therapists, it is difficult to determine the percentage of variance attributable to individual CBASP sessions. However, since all members of the treatment team were trained in CBASP, the CBASP-specific techniques could also be used by all therapists in their respective therapies (e.g., disciplined personal involvement with interpersonal discrimination exercises). Compared to many inpatient psychotherapy programs, the intensity of CBASP can therefore be classified as very high, as patients also received 2 individual sessions per week over the course of 12 weeks leading to a total number of 24 sessions on average. However, this high CBASP intensity could have contributed to the findings.

CONCLUSIONS

In this study, a multimodal inpatient CBASP treatment program seems to be associated with negative effects, which may be explained by the specific characteristics of patients with treatment-resistant CD and the focus of CBASP techniques on the patient–therapist relationship. Interestingly, most reported negative effects do not appear to have an impact on treatment outcome. However, dependence on the therapist, as the most frequent dimension of negative effects, seems to be negatively linked to both observer- and self-rated treatment response. If large randomized controlled trials find that CBASP is more likely to trigger dependence on the therapist than other psychotherapy concepts and that this perceived dependence actually has a negative impact on outcomes, then clinical implications such as prolonging treatment and focusing more on self-help and autonomy of the patient should be considered.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

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

AUTHOR CONTRIBUTIONS

PH originally drafted and edited the manuscript. E-LB supervised, reviewed, and edited the manuscript. SH was

significantly involved in the computation of the statistical analyses and visualization of the results. CN was responsible for the acquisition of these data for the present work. All authors contributed to the article and approved the submitted version.

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REFERENCES

1. Jonsson U, Alaie I, Parling T, Arnberg FK. Reporting of harms in randomized controlled trials of psychological interventions for mental and behavioral disorders: a review of current practice. *Contemp Clin Trials.* (2014) 38:1–8. doi: 10.1016/j.cct.2014.02.005
2. Herzog P, Lauff S, Rief W, Brakemeier E. Assessing the unwanted: a systematic review of instruments used to assess negative effects of psychotherapy. *Brain Behav.* (2019) 9:e01447. doi: 10.1002/brb3.1447
3. Ladwig I, Rief W, Nestoriuc Y. Welche Risiken und Nebenwirkungen hat Psychotherapie?—Entwicklung des Inventars zur Erfassung Negativer Effekte von Psychotherapie (INEP). *Verhaltenstherapie.* (2014) 24:252–63. doi: 10.1159/000367928
4. Rozental A, Kottorp A, Forsström D, Månsson K, Boettcher J, Andersson G, et al. The negative effects questionnaire: psychometric properties of an instrument for assessing negative effects in psychological treatments. *Behav Cogn Psychother.* (2019) 47:1–14. doi: 10.1017/S1352465819000018
5. Rheker J, Beisel S, Kräling S, Rief W. Rate and predictors of negative effects of psychotherapy in psychiatric and psychosomatic inpatients. *Psychiatry Res.* (2017) 254:143–50. doi: 10.1016/j.psychres.2017.04.042
6. Schneibel R, Wilbertz G, Scholz C, Becker M, Brakemeier EL, Bschor T, et al. Adverse events of group psychotherapy in the in-patient setting—results of a naturalistic trial. *Acta Psychiatr Scand.* (2017) 136:1–12. doi: 10.1111/acps.12747
7. Moritz S, Fieker M, Hottenrott B, Seeralan T, Cludius B, Kolbeck K, et al. No pain, no gain? Adverse effects of psychotherapy in obsessive-compulsive disorder and its relationship to treatment gains. *J Obsessive Compuls Relat Disord.* (2015) 5:61–6. doi: 10.1016/j.jocrd.2015.02.002
8. McCullough JPJ. *Treatment for Chronic Depression: Cognitive Behavioral Analysis System of Psychotherapy (CBASP).* New York, NY: Guilford Press (2000).
9. McCullough JP, Schramm E, Penberthy JK. CBASP—*Cognitive Behavioral Analysis System of Psychotherapy: Chronische Depressionen effektiv behandeln*. Paderborn: Junfermann Verlag (2015).
10. Nelson J, Klumparendt A, Doebler P, Ehring T. Childhood maltreatment and characteristics of adult depression: meta-analysis. *Br J Psychiatry.* (2017) 210:96–104. doi: 10.1192/bjp.bp.115.180752
11. Köhler S, Guhn A, Betzler F, Stiglmayr C, Brakemeier E-L, Sterzer P. Therapeutic self-disclosure within DBT, schema therapy, and CBASP: opportunities and challenges. *Front Psychol.* (2017) 8:2073. doi: 10.3389/fpsyg.2017.02073
12. Negt P, Brakemeier E-L, Michalak J, Winter L, Bleich S, Kahl KG. The treatment of chronic depression with cognitive behavioral analysis system of psychotherapy: a systematic review and meta-analysis of randomized-controlled clinical trials. *Brain Behav.* (2016) 6:e00486. doi: 10.1002/brb3.486
13. Schramm E, Kriston L, Zobel I, Bailer J, Wambach K, Backenstrass M, et al. Effect of disorder-specific vs nonspecific psychotherapy for chronic depression. *JAMA Psychiatry.* (2017) 74:233. doi: 10.1001/jamapsychiatry.2016.3880
14. Brakemeier E-L, Radtke M, Engel V, Zimmermann J, Tuschen-Caffier B, Hautzinger M, et al. Overcoming treatment resistance in chronic depression: a pilot study on outcome and feasibility of the cognitive behavioral analysis system of psychotherapy as an inpatient treatment program. *Psychother Psychosom.* (2015) 84:51–6. doi: 10.1159/000369586
15. Flückiger C, Del AC, Wampold BE, Horvath AO. The alliance in adult psychotherapy: a meta-analytic synthesis. *Psychotherapy.* (2018) 55:316–40. doi: 10.1037/pst0000172
16. Horvath AO, Del Re AC, Flückiger C, Symonds D. Alliance in individual psychotherapy. *Psychotherapy.* (2011) 48:9–16. doi: 10.1037/a0022186
17. Arnow BA, Manber R, Blasey C, Blalock JA, Rothbaum BO, Thase ME, et al. Therapeutic reactance as a predictor of outcome in the treatment of chronic depression. *J Consult Clin Psychol.* (2003) 71:1025–35. doi: 10.1037/0022-006X.71.6.1025
18. Klein DN, Schwartz JE, Santiago NJ, Vivian D, Vocisano C, Arnow B, et al. Therapeutic alliance in depression treatment: controlling for prior change and patient characteristics. *J Consult Clin Psychol.* (2003) 71:997–1006. doi: 10.1037/0022-006X.71.6.997
19. Arnow BA, Steidtmann D, Blasey C, Manber R, Constantino MJ, Klein DN, et al. The relationship between the therapeutic alliance and treatment outcome in two distinct psychotherapies for chronic depression. *J Consult Clin Psychol.* (2013) 81:627–38. doi: 10.1037/a0031530
20. Santiago NJ, Klein DN, Vivian D, Arnow BA, Blalock JA, Kocsis JH, et al. The therapeutic alliance and CBASP-specific skill acquisition in the treatment of chronic depression. *Cognit Ther Res.* (2005) 29:803–17. doi: 10.1007/s10608-005-9638-5
21. Vocisano C, Arnow B, Blalock JA, Vivian D, Manber R, Rush AJ, et al. Therapist variables that predict symptom change in psychotherapy with chronically depressed outpatients. *Psychotherapy.* (2004) 41:255–65. doi: 10.1037/0033-3204.41.3.255
22. Constantino MJ, Laws HB, Coyne AE, Greenberg RP, Klein DN, Manber R, et al. Change in patients' interpersonal impacts as a mediator of the alliance-outcome association in treatment for chronic depression. *J Consult Clin Psychol.* (2016) 84:1135–44. doi: 10.1037/ccp0000149
23. Constantino MJ, Laws HB, Arnow BA, Klein DN, Rothbaum BO, Manber R. The relation between changes in patients' interpersonal impact messages and outcome in treatment for chronic depression. *J Consult Clin Psychol.* (2012) 80:354–64. doi: 10.1037/a0028351
24. Brakemeier E-L, Herzog P, Radtke M, Schneibel R, Breger V, Becker M, et al. CBASP als stationäres Behandlungskonzept der therapieresistenten chronischen Depression: Eine Pilotstudie zum Zusammenhang von Nebenwirkungen und Therapieerfolg. PPmP—Psychother Psychosom *Medizinische Psychol.* (2018) 68:399–407. doi: 10.1055/a-0629-7802
25. Brakemeier E-L, Engel V, Schramm E, Zobel I, Schmidt T, Hautzinger M, et al. Feasibility and outcome of cognitive behavioral analysis system of psychotherapy (CBASP) for chronically depressed inpatients: a pilot study. *Psychother Psychosom.* (2011) 80:191–4. doi: 10.1159/000320779
26. Thase ME, Rush AJ. When at first you don't succeed: sequential strategies for antidepressant nonresponders. *J Clin Psychiatry.* (1997) 23–9.
27. Brakemeier EL, Normann C. *Praxisbuch CBASP. Behandlung chronischer Depression*. Weinheim, Basel: Beltz (2012).
28. Cuijpers P, van Straten A, Schuurmans J, van Oppen P, Hollon SD, Andersson G. Psychotherapy for chronic major depression and dysthymia: a meta-analysis. *Clin Psychol Rev.* (2010) 30:51–62. doi: 10.1016/j.cpr.2009.09.003
29. Middleton H, Shaw I, Hull S, Feder G. NICE guidelines for the management of depression. *BMJ.* (2005) 330. doi: 10.1136/bmj.330.7486.267
30. DGPPN, BÄK, KBV, AWMF. *S3-Leitlinien/Nationale VersorgungsLeitlinie: Unipolare Depression*. 2. Auflage. Heidelberg: Springer (2017).
31. Hamilton M. A rating scale for depression. *J Neurol Neurosurg Psychiatry.* (1960) 23:56–62. doi: 10.1136/jnnp.23.1.56
32. López-Pina J, Sánchez-Meca J, Rosa-Alcázar AI. The hamilton rating scale for depression: a meta-analytic reliability generalization study. *Int J Clin Heal Psychol.* (2009) 9:143–59.
33. Beck AT, Steer RA, Brown GK. *Beck Depression Inventory-II*. San Antonio, TX: Harcourt Assessment Inc. (1996).
34. Hautzinger M, Keller F, Kühner C. *Das Beck Depressionsinventar II. Deutsche Bearbeitung und Handbuch zum BDI-II*. Frankfurt/Main: Pearson. (2006).

35. First MB, Spitzer RL, Gibbon M, Williams JBW. *Structured Clinical Interview for DSM-IV Axis I Disorders SCID-I : Clinician Version*. Washington, DC: American Psychiatric Publishing (1997).
36. First MB, Gibbon M, Spitzer RL, Benjamin LS. *User's Guide for the Structured Clinical Interview for DSM-IV Axis II Personality Disorders: SCID-II*. Washington, DC: American Psychiatric Press (1997).
37. Tabachnick BG, Fidell LS. *Using Multivariate Statistics*. Boston: Pearson Education (2013). p. 983.
38. Little RJA. A test of missing completely at random for multivariate data with missing values. *J Am Stat Assoc.* (1988) 83:1198. doi: 10.1080/01621459.1988.10478722
39. IBM Corp. Released 2012. *IBM SPSS Statistics for Windows, Version 21.0*. Armonk, NY: IBM Corp.
40. Faul F, Erdfelder E, Lang AG, Buchner A. G*Power 3: a flexible statistical power analysis program for the social, behavioral, and biomedical sciences. *Behav Res Methods.* (2007) 39:175–91. doi: 10.3758/BF03193146
41. Erdfelder E, Faul F, Buchner A, Lang AG. Statistical power analyses using G*Power 3.1: Tests for correlation and regression analyses. *Behav Res Methods.* (2009) 41:1149–60. doi: 10.3758/BRM.41.4.1149
42. Moritz S, Nestoriuc Y, Rief W, Klein JP, Jelinek L, Peth J. It can't hurt, right? Adverse effects of psychotherapy in patients with depression. *Eur Arch Psychiatry Clin Neurosci.* (2018) 269:577–86. doi: 10.1007/s00406-018-0931-1
43. Sabaß L, Padberg F, Normann C, Engel V, Konrad C, Helmle K, et al. Cognitive behavioral analysis system of psychotherapy as group psychotherapy for chronically depressed inpatients: a naturalistic multicenter feasibility trial. *Eur Arch Psychiatry Clin Neurosci.* (2018) 268:783–96. doi: 10.1007/s00406-017-0843-5
44. Wiersma JE, Hovens JGFM, van Oppen P, Giltay EJ, van Schaik DJF, Beekman ATF, et al. The Importance of childhood trauma and childhood life events for chronicity of depression in adults. *J Clin Psychiatry.* (2009) 70:983–9. doi: 10.4088/JCP.08m04521
45. Köhler S, Sterzer P, Normann C, Berger M, Brakemeier E. Überwindung der Therapieresistenz bei chronischer Depression. *Nervenarzt.* (2016) 87:701–7. doi: 10.1007/s00115-015-0034-4
46. Bird T, Tarsia M, Schwannauer M. Interpersonal styles in major and chronic depression: a systematic review and meta-analysis. *J Affect Disord.* (2018) 239:93–101. doi: 10.1016/j.jad.2018.05.057
47. Constantino MJ, Manber R, DeGeorge J, McBride C, Ravitz P, Zuroff DC, et al. Interpersonal styles of chronically depressed outpatients: profiles and therapeutic change. *Psychother Theory, Res Pract Train.* (2008) 45:491–506. doi: 10.1037/a0014335
48. Constantino MJ, Adams ML, Pazzaglia AM, Bernecker SL, Ravitz P, McBride C. Baseline patient characteristics as predictors of remission in interpersonal psychotherapy for depression. *Psychother Res.* (2013) 23:190–200. doi: 10.1080/10503307.2013.765997
49. Meister R, von Wolff A, Mohr H, Nestoriuc Y, Härter M, Hölzel L, et al. Adverse event methods were heterogeneous and insufficiently reported in randomized trials on persistent depressive disorder. *J Clin Epidemiol.* (2016) 71:97–108. doi: 10.1016/j.jclinepi.2015.10.007
50. Meister R, Lanio J, Fangmeier T, Härter M, Schramm E, Zobel I, et al. Adverse events during a disorder-specific psychotherapy compared to a nonspecific psychotherapy in patients with chronic depression. *J Clin Psychol.* (2019) 76:7–19. doi: 10.1002/jclp.22869
51. Markowitz JC, Skodol AE, Petkova E, Cheng J, Sanislow CA, Grilo CM, et al. Longitudinal effects of personality disorders on psychosocial functioning of patients with major depressive disorder. *J Clin Psychiatry.* (2007) 68:186–93. doi: 10.4088/JCP.v68n0202
52. Geurtzen N, Keijsers GPJ, Karremans JC, Hutschemaekers GJM. Patients' care dependency in mental health care: development of a self-report questionnaire and preliminary correlates. *J Clin Psychol.* (2018) 74:1189–206. doi: 10.1002/jclp.22574
53. Santiago NJ, Klein DN, McCullough JP, Riso LPL. Pretreatment correlates of the therapeutic alliance in the chronically depressed. *J Contemp Psychother.* (2002) 32:281–90. doi: 10.1023/A:1020524910971
54. Blatt SJ. *Experiences of Depression: Theoretical, Clinical, And Research Perspectives. Experiences of depression: Theoretical, Clinical, and Research Perspectives*. Washington, DC: American Psychological Association (2005). doi: 10.1037/10749-000
55. Rost F, Luyten P, Fearon P, Fonagy P. Personality and outcome in individuals with treatment-resistant depression-exploring differential treatment effects in the tavistock adult depression study (TADS). *J Consult Clin Psychol.* (2019) 87:433–45. doi: 10.1037/ccp0000391
56. Brockmeyer T, Kulessa D, Hautzinger M, Bents H, Backenstrass M. Differentiating early-onset chronic depression from episodic depression in terms of cognitive-behavioral and emotional avoidance. *J Affect Disord.* (2015) 175:418–23. doi: 10.1016/j.jad.2015.01.045
57. Ley P, Helbig-Lang S, Czilwik S, Lang T, Worlitz A, Brücher K, et al. Phenomenological differences between acute and chronic forms of major depression in inpatients. *Nord J Psychiatry.* (2011) 65:330–7. doi: 10.3109/08039488.2011.552121
58. Klein JP, Stahl J, Hüppe M, McCullough JP, Schramm E, Ortel D, et al. Do interpersonal fears mediate the association between childhood maltreatment and interpersonal skills deficits? A matched cross-sectional analysis. *Psychother Res.* (2018) 30:1–12. doi: 10.1080/10503307.2018.1532125
59. Guidi J, Brakemeier EL, Bockting CLH, Cosci F, Cuijpers P, Jarrett RB, et al. Methodological Recommendations for Trials of Psychological Interventions. *Psychother Psychosom.* (2018) 87:276–84. doi: 10.1159/000490574
60. Klein JP, Willenborg B, Schweiger U. Diagnostik affektiver Störungen im DSM-5: Neuerungen und Kontroversen. *Fortschritte der Neurol Psychiatr.* (2015) 82:655–64. doi: 10.1055/s-0034-1385377
61. Association American Psychiatric. Diagnostisches und Statistisches Manual Psychischer Störungen DSM-5®. In: Falkai P, Wittchen H-U, editors. *Diagnostisches und Statistisches Manual Psychischer Störungen DSM-5®*. Göttingen: Hogrefe (2015). p. 369–382.

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Change in Interpersonal and Metacognitive Skills During Treatment With Cognitive Behavioral Analysis System of Psychotherapy and Metacognitive Therapy: Results From an Observational Study

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Sürig S, Ohm K, Grave U, Glanert S, Herzog P, Fassbinder E, Borgwardt S and Klein JP (2021) Change in Interpersonal and Metacognitive Skills During Treatment With Cognitive Behavioral Analysis System of Psychotherapy and Metacognitive Therapy: Results From an Observational Study. Front. Psychiatry 12:619674. doi: 10.3389/fpsyt.2021.619674

Background: Interpersonal skills deficits and dysfunctional metacognitive beliefs have been implicated in the etiology and maintenance of depression. This study aimed to investigate the association between changes in these skills deficits and change in depressive symptoms over the course of treatment with Cognitive Behavioral Analysis System of Psychotherapy (CBASP) and Metacognitive Therapy (MCT).

Methods: In this prospective, parallel group observational study, data was collected at baseline and after 8 weeks of an intensive day clinic psychotherapy program. Based on a shared decision between patients and clinicians, patients received either CBASP or MCT. Ninety patients were included in the analyses (CBASP: age $M = 38.7$, 40.5% female, MCT: age $M = 44.7$, 43.3% female). Interpersonal deficits were assessed with the short-form of the Luebeck Questionnaire for Recording Preoperational Thinking (LQPT-SF) and the Impact Message Inventory (IMI-R). Metacognitive beliefs were assessed with the Metacognition Questionnaire-30 (MCQ-30). The Quick Inventory of Depressive Symptomatology (QIDS-SR16) was utilized to assess depressive symptoms. A regression analysis was conducted to assess variables associated with outcome. ANCOVAs were utilized to investigate whether improvement in skills deficits is dependent on type of treatment received.

Results: Improvements in preoperational thinking and increases in friendly-dominant behavior were associated with change in depressive symptoms. There was no association between reductions in dysfunctional metacognitive beliefs and a decrease in depressive symptoms. While both treatment groups showed significant improvements in

interpersonal and metacognitive skills, there was no significant between-group difference in the change scores for either of these skills.

Conclusion: Our findings suggest that changes in interpersonal skills seem to be of particular relevance in the treatment of depression. These results have to be replicated in a randomized-controlled design before firm conclusions can be drawn.

Keywords: depression, interpersonal skills, social cognition, metacognitive beliefs, metacognitive therapy, cognitive behavioral analysis system of psychotherapy

INTRODUCTION

Depression is one of the most common psychiatric disorders (1) and associated with a great burden of disease (2). Its course is often recurrent (3), treatment-resistant (4) and about one third of patients with depression experience a chronic course (5). According to DSM-5, persistent depressive disorder (PDD) can be diagnosed when symptoms are present for at least 2 years and symptom-free intervals have never lasted more than 8 weeks at a time (6).

Numerous factors that contribute to the etiology and maintenance of depression have been suggested (7), e.g., dysfunctional expectations (8, 9). Moreover, these factors include skills deficits targeted by "third wave" behavioral therapies that are associated with depression but not captured by the existing diagnostic criteria. Skills deficits that are targeted in these modern psychotherapies include deficits in interpersonal skills (theoretically intended to be primarily targeted in Cognitive Behavioral Analysis System of Psychotherapy (CBASP; 10)) and metacognitive skills (theoretically intended to be primarily targeted in Metacognitive Therapy (MCT; 11)). A better understanding of the associations of changes in these skills deficits with outcome might contribute to improving existing psychotherapies for depression (10).

CBASP was specifically developed as a treatment for PDD (11, 12) and is recommended as a first line treatment by the European Psychiatric Association (13). Numerous studies demonstrate the effectiveness of CBASP in the treatment of PDD (14, 15). With an emphasis on utilizing the relationship between patient and therapist as a therapeutic tool, CBASP addresses the interpersonal deficits of chronically depressed individuals (11, 12). Patients with depression have been found to exhibit hostile and submissive interpersonal behavior and these behavior patterns are even more pronounced in individuals suffering from PDD (16). This hostile-submissive behavior might be associated with experiences of early emotional abuse (17) and this association might be mediated by a specific deficit in social cognition termed preoperational thinking (17). The term preoperational thinking was originally coined by Piaget's theory of cognitive-affective development (18). McCullough proposes that chronically depressed individuals exhibit a perceptual and behavioral disconnection from their environment as they are unable to perceive the consequences of their interpersonal behavior and adapt it accordingly. Being entrapped in the present moment and unable to disengage from an egocentric worldview makes it impossible to effectively connect with others (11). This global and prelogical way of thinking has been summarized in the words of one chronically depressed patient: "Whatever I do, nothing will ever change" (19). Utilizing the Luebeck Questionnaire for Recording Preoperational Thinking (LQPT) as a measure specifically developed to assess preoperational thinking (20), studies found higher levels of preoperational thinking in chronically depressed patients compared to episodically depressed patients and healthy controls (17, 19–22). Further, preoperational thinking is associated with early emotional abuse and this association might be mediated by interpersonal fears (19).

MCT is a transdiagnostic treatment approach based on the assumption that perseverative thinking styles underlie psychopathology (23). According to the metacognitive model of depression, depressive symptomatology is maintained by inflexible and maladaptive thinking styles, called the cognitive attentional syndrome (CAS). The CAS comprises rumination and worry, threat monitoring and dysfunctional coping behaviors and is maintained by positive (i.e., concerning the usefulness of engaging in the CAS) and negative (i.e., concerning the uncontrollability and danger of thoughts) metacognitive beliefs (23, 24). Studies could show that negative metacognitive beliefs contribute to certain symptoms of depression (i.e., rumination) (25, 26). Depressive rumination however maintains and exacerbates depressed mood (27, 28). Also, negative metacognitive beliefs have been found to prospectively predict depression (29). MCT aims to identify and modify negative repetitive thinking as well as dysfunctional metacognitive beliefs (30). Meta-analyses have found MCT to be effective in the treatment of depression (31, 32).

In summary, there is convincing evidence for the contribution of interpersonal and metacognitive skills deficits to depression and for the efficacy of CBASP and MCT in treating depression. Fewer studies evaluated these skills deficits as underlying treatment mechanisms. Patients treated with CBASP have been found to exhibit more friendly-dominant behaviors after treatment (33, 34). Studies investigating MCT as a treatment for depression could show that negative metacognitive beliefs decreased over the course of treatment (35, 36). There are few studies that investigated the association between changes in skills deficits and changes in depressive symptomatology. Decreases in hostile-submissive behaviors have been found to be associated with depression reduction (37, 38). Constantino et al. (39) tested a mediation model and could show that higher therapeutic alliance predicted decreases in hostile-submissiveness which in turn related to less depressive symptomatology in patients

treated with CBASP. Examining the efficacy of MCT and implicated change mechanisms, Hjemdal et al. (40) could show that change in dysfunctional metacognitive beliefs predicted change in depression from pre-treatment to 1-year follow-up. To our knowledge, thus far no study examined whether change in preoperational thinking predicts reduction in depressive symptoms. Furthermore, there are no studies comparing the relative contribution of changes in interpersonal skills and changes in metacognitive skills to outcome.

Therefore, this present study aims to investigate the associations between interpersonal skills deficits as well as dysfunctional metacognitive beliefs and depressive symptomatology. We hypothesize that improvement in interpersonal as well as metacognitive skills is associated with a decrease in depressive symptoms. Further, we aim to investigate whether changes in interpersonal and metacognitive skills are specific to the respective type of treatment. We hypothesize that patients treated with CBASP show a greater improvement in interpersonal skills compared to patients treated with MCT while patients treated with MCT show a greater improvement in metacognitive skills. Another aim of this study was to develop and validate a short-form of the LQPT to assess preoperational thinking that allows for more time-efficient administration and facilitates administration for depressed individuals that may struggle with diminished abilities to concentrate.

MATERIALS AND METHODS

Patient Sample

This prospective, parallel group observational study uses data from the ICARE study (Investigating Care Dependency And its Relation to OutcomE) that aims to investigate the German version of the Care Dependency Questionnaire (41). The ICARE study was conducted in accordance with the Declaration of Helsinki and approved by the ethics committee of the University of Lübeck (reference number 17-049). Patients were recruited from the day treatment program for depression at the Department of Psychiatry and Psychotherapy, University of Lübeck, Germany. The treatment program focuses on treating depressive disorders with CBASP or MCT and lasts for 8 weeks. Patients did not receive financial compensation.

Inclusion criteria were the presence of a depressive disorder diagnosis as well as a minimum age of 18 and adequate understanding of the German language. Exclusion criteria were acute suicidality at admission, a known diagnosis of an organic mental disorder, schizophrenia, schizotypal disorder or delusional disorder, bipolar disorder, primary diagnosis of substance abuse or substance dependence of alcohol, cannabinoids, sedatives, cocaine, or hallucinogens, or a physical illness requiring immediate treatment. As we aimed to only include patients who were not yet familiar with the treatment program, patients were excluded if they had been admitted to the day clinic in the previous 12 months. Informed written consent was obtained from all patients. The diagnosis of depressive disorders was done by utilizing a diagnostic interview that was based on DSM-5 (42).

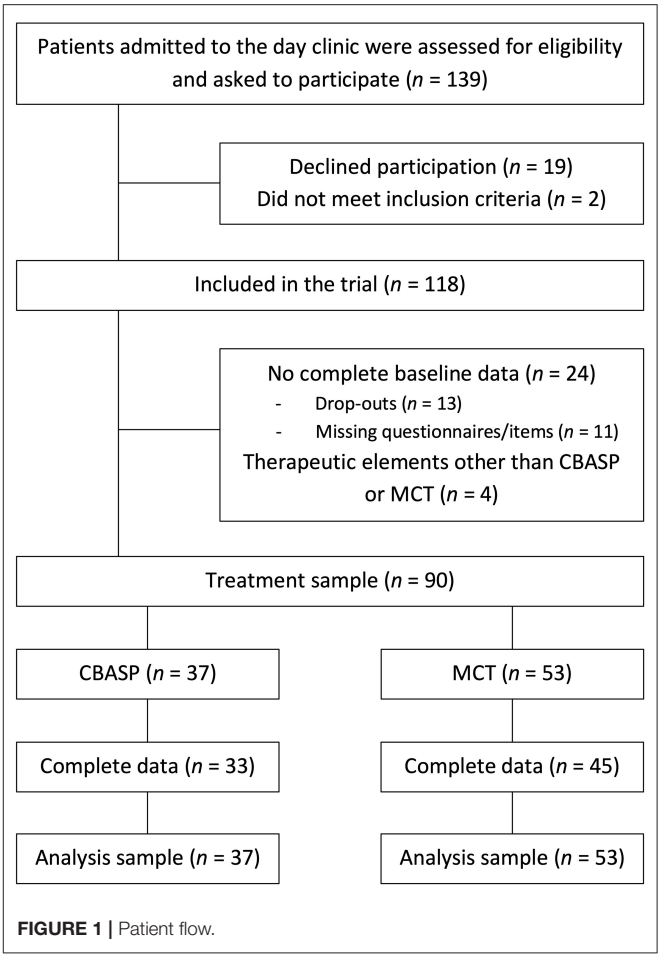

FIGURE 1 | Patient flow.

Recruitment began in January 2019 and ended in January 2020. A full patient flow can be found in **Figure 1**. Briefly, 139 patients were assessed for eligibility and asked to participate and 90 patients were included in the analyses.

Intervention

Patients received 8 weeks of intensive treatment with either CBASP or MCT. The decision between CBASP and MCT was made in a shared decision-making process between the clinician and the patient after the intake interview, based on the following algorithm: diagnosis of the patient (e.g., patients with a PDD were recommended to choose CBASP while patients with comorbid diagnosis of anxiety or obsessive-compulsive disorder were recommended to choose MCT), presenting complaint (e.g., patients with primary interpersonal difficulties received a recommendation for CBASP while patients with primary worry and rumination received a recommendation for MCT) and the patient's preference. Patients received specific therapeutic elements unique to the treatment modality (CBASP or MCT) including one session of individual therapy with a psychologist or medical doctor, one session of group therapy with a psychologist or medical doctor and one session with a nurse specialist per week. Therapy is delivered under weekly team supervision and

a weekly visit by a senior physician. In addition, all patients received further multimodal interventions, including physical therapy, occupational therapy as well as a nurse specialist group focusing on mindfulness training. They also received guideline-adherent pharmacotherapy (43).

Cognitive Behavioral Analysis System of Psychotherapy (CBASP)

CBASP aims to teach patients to reduce preoperational thinking and engage in more adaptive interpersonal behaviors (11). Situation analyses constitute a central therapeutic element alongside with disciplined personal involvement of the therapist. In an operationalized procedure patient and therapist revisit interpersonal situations with the aim of challenging preoperational thinking and developing new behavioral alternatives. Interpersonal discrimination exercises are aimed at increasing safety in the therapeutic relationship by demonstrating the differences between the therapist's responses to certain patient behaviors and the responses of maltreating significant others. A prototypical treatment with CBASP comprised the following therapeutic elements: list of significant others, transference hypothesis, situation analyses and disciplined personal involvement of the therapist.

Metacognitive Therapy (MCT)

MCT is a transdiagnostic treatment approach based on the assumption that perseverative thinking styles constitute a maintaining factor for several psychiatric disorders. A disorder specific case formulation and treatment procedure for depression was developed (30). MCT focuses on identifying and modifying negative repetitive thinking styles such as worry and rumination. For the case formulation, trigger thoughts, worry and rumination, threat monitoring strategies and maladaptive coping behaviors are explored alongside with their maintaining positive and negative metacognitive beliefs. Attentional Training Technique (ATT) as well as Detached Mindfulness (DM) constitute central elements of MCT that aim at modifying the control of attention and heightening metacognitive awareness of inner experiences and the detachment from maladaptive thoughts and beliefs. A prototypical treatment with MCT comprised the following therapeutic elements: metacognitive case formulation, DM, ATT and worry/rumination postponement.

Instruments

Luebeck Questionnaire for Recording Preoperational Thinking Short-Form (LQPT-SF)

The LQPT is a self-assessment instrument developed to record preoperational thinking as a specific cognitive psychopathology of individuals suffering from PDD. In its original version, it consists of 20 items each in the form of written scenarios depicting difficult interpersonal situations. Participants are required to choose between two response options reflecting either a high or a low level of preoperational thinking (e.g., "Nobody likes me. I am always disappointed by others. I cannot rely on others." indicating a preoperational response to a friend canceling a dinner invitation as opposed to "Too bad my friend cannot come. I hope he is well. I will call him tomorrow and ask what is going on." or "I knew he never liked me, this only proves it." as a preoperational response to not being invited to a birthday party as opposed to "I will call my neighbor. I would like to go to this party."). Items are scored 0 and 1 with a low total score indicating a high level of preoperational thinking. In several studies, the LQPT has been shown to be a reliable and valid instrument (Cronbach's $\alpha = 0.90$) (20, 21, 44). The LQPT is publically available online (https://bit.ly/3q3zqGd).

As completing the LQPT can be time-consuming as well as demanding for participants due to its length, we aimed to devise a short-form of the LQPT (LQPT-SF). A principal component analysis for categorical variables (CAT-PCA) performed on the LQPT scores of sample data gathered by Klein et al. (19) resulted in the retention of one component with an eigenvalue of 7.86 that was able to explain 39.30 % of variance. Eleven items with very good or better loadings on this component were summarized in the LQPT-SF, namely item 2, 5, 6, 7, 9, 11, 12, 14, 16, 18, and 21 (45). The LQPT-SF demonstrated excellent internal consistency (Cronbach's $\alpha = 0.91$) as well as acceptable convergent construct validity as indicated by significant correlations with relevant IMI subscales of chronically depressed patients (submissive subscale, $r = -0.44$, hostile subscale, $r = -0.37$, friendly-dominant subscale, $r = 0.50$). Further, the LQPT-SF showed excellent discriminant abilities as evidenced by significant results for all comparisons: PDD ($M = 4.91$, $SD = 3.34$) vs. ED ($M = 8.00$, $SD = 3.02$), $t = -4.03$, $p < 0.001$, PDD vs. HC ($M = 10.60$, $SD = 0.72$), $t = -11.04$, $p < 0.001$, and ED vs. HC, $t = -4.51$, $p < 0.001$, with effect sizes of 0.95, 2.12 and 1.18, respectively. For the effect sizes, Hedge's g was calculated for the pairwise comparisons due to differences in sample sizes (46). In this present study, the LQPT-SF was completed at baseline and end of treatment.

Metacognition Questionnaire-30 (MCQ-30)

The MCQ-30 is a self-report questionnaire that assesses metacognitive beliefs, judgements and monitoring tendencies (47). It consists of 30 items that are rated on a four-point Likert scale ranging from 1 (do not agree) to 4 (agree very much), e.g., "My worrying is dangerous for me." There are five subscales (cognitive confidence, positive beliefs about worry, cognitive self-consciousness, negative beliefs concerning uncontrollability and danger, need to control thoughts). The MCQ-30 demonstrates good internal consistency (Cronbach's $\alpha = 0.91$) as well as good validity (47). Patients completed the MCQ-30 at baseline and end of treatment.

Impact Message Inventory (IMI-R)

The IMI-R is a transactional instrument used to assess interpersonal impact messages according to the dimensions of the interpersonal circumplex model (48). Following the assumption of interpersonal complementarity, treating clinicians completed the IMI to assess the participants' interpersonal behavior patterns at baseline and end of treatment. The IMI-R has 56 items that are rated on a four-point Likert scale ranging from 1 (not at all) to 4 (very much so). Items begin with the phrase "When I am with this person, he/she makes me feel…," followed by e.g., "…distant from him/her" as a sample hostile

item or "…in charge" as a sample submissive item (49). The IMI-R demonstrates good psychometric properties as Cronbach's α coefficients for the octants range from 0.68 to 0.86 (50). Following previous research, we focus on the hostile-submissive and friendly-dominant subscale of the IMI-R (37, 39).

Quick Inventory of Depressive Symptomatology (QIDS-SR16)

The QIDS-SR16 is a self-assessment instrument that contains 16 items assessing depressive symptomatology of the last seven days. Items are scored from 0 to 3 with higher scores reflecting greater impairment. For three domains (sleep, appetite/weight and restlessness/agitation) only the highest scored item is included in the total score. Total QIDS-SR16 scores range from 0 to 27 with total scores indicating the following: scores of 5 or lower no depression, 6 to 10 mild depression, 11 to 15 moderate depression, 16 to 20 severe depression and scores greater 21 very severe depression (51). The German version of the QIDS-SR16 demonstrates adequate internal consistency (Cronbach's $\alpha = 0.77$) (52). Patients completed the QIDS-SR16 on a weekly basis.

Childhood Trauma Questionnaire Short-Form (CTQ-SF)

The CTQ-SF is a self-report instrument that assesses childhood maltreatment before the age of 18 (53). It contains 28 items that can be summarized in five subscales of emotional abuse, physical abuse, sexual abuse, emotional neglect and physical neglect. Items are rated on a 5-point Likert scale ranging from never true to very often true (e.g., "When I was growing up people in my family said hurtful or insulting things to me"). The German version of the CTQ-SF demonstrated good internal consistency as evidenced by Cronbach's $\alpha = 0.94$ (54). The CTQ-SF was completed at baseline.

Statistical Analyses

Statistical analyses were conducted using SPSS 24.0 (55). If not otherwise specified, statistical tests were evaluated as two-sided tests with significance levels set at $p < 0.05$. A modified intention-to-treat analysis was employed using all participants with complete baseline data. Individual missing values were replaced with the individual participant mean for the respective scale if the number of missing items was <20% (56). Missing sum scores were replaced using the mean of the posterior distribution from the fully conditional specification method obtained by iterative Markov Chain Monte Carlo estimation (57) using 20 imputations per missing value. Prior to conducting the analyses, relevant assumptions were tested.

Paired sample *t*-tests were conducted to investigate pre-post treatment differences in depressive symptomatology (assessed by the QIDS), interpersonal skills (assessed by the LQPT-SF and the IMI-R) and metacognitive skills (assessed by the MCQ-30).

We conducted a hierarchical multiple regression analysis in order to investigate variables significantly associated with change in depressive symptomatology as assessed by change in QIDS scores over the course of therapy. In a first step, baseline scores of the QIDS and of all variables assessing skills deficits were entered in order to control for their influence. In a second step, change scores of the LQPT-SF, hostile-submissive and friendly-dominant IMI as well as MCQ-30 were entered in the model. We tested the assumptions of the regression analysis by examining independence of residuals, linearity, homoscedasticity, multicollinearity and normal distribution.

In order to assess whether improvement in interpersonal skills (assessed by the LQPT-SF and the IMI-R) and metacognitive skills (assessed by the MCQ-30) is dependent on type of treatment intervention (CBASP vs. MCT), several ANCOVAs were conducted with the relevant outcome measure (LQPT-SF, IMI-R and MCQ-30) as dependent variable and therapeutic concept (CBASP vs. MCT) as predictor while controlling for the respective baseline scores. We tested the assumptions of the ANCOVAs by examining linearity, homogeneity of regression slopes and variances, normal distribution and homoscedasticity. *Post-hoc* power analyses were conducted with G*Power 3.1 by calculating f^2 and setting alpha at 0.05 (58).

We conducted sensitivity analyses for the hierarchical regression model as well as for the ANCOVAs to correct for potential confounding variables. All variables where we found baseline imbalances were included as covariates (age, onset of depression, comorbid disorder, exposure to childhood adversity). To correct for baseline differences regarding the presence of comorbid disorders, the presence of anxiety (ICD-10 F40 or F41 diagnosis) or obsessive-compulsive disorder (ICD-10 F42 diagnosis) was combined in one variable (comorbid diagnosis).

Effect size estimates for repeated measures were calculated by taking the correlation between pre- and post-scores into account. For the regression analysis, f^2 was calculated to estimate the effect size of adding individual variables to the model by dividing the squared partial correlation of an individual variable by its reciprocal. Cohen's f^2 will be interpreted as $f^2 = 0.02$ indicating a small effect, $f^2 = 0.15$ indicating a medium effect and $f^2 = 0.35$ indicating a large effect (59).

RESULTS

Sample Characteristics

Detailed clinical characteristics of the sample can be found in **Table 1**. Thirty-seven patients were treated with CBASP compared to 53 patients being treated with MCT. Seventy-three percent of all patients were diagnosed with PDD. Patients treated with CBASP more often suffered from early onset depression (<21 years) and were younger compared to patients treated with MCT. Also, they reported higher rates of emotional abuse as assessed by the CTQ-SF. Treatment groups did not differ significantly in gender, marital status, language, school education or employment status (**Table 1**).

Statistical Analyses

Pre-post Differences

At the end of treatment, patients exhibited significantly less depressive symptomatology as assessed by the QIDS compared to their admission, $t_{(52)} = 6.51$, $p < 0.01$, $d = -0.69$ (95% CI [−0.99 to −0.38]). They also exhibited less preoperational thinking, $t_{(52)} = -6.53$, $p < 0.001$, $d = 0.69$ (95% CI [0.38–0.98]), increases

TABLE 1 | Demographic and clinical characteristics.

	All		CBASP		MCT		
Variables	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Test statistic U**
Age in years	42.21	12.70	38.65	12.70	44.70	12.22	1246.50*
Number of previous episodes	6.94	8.04	7.17	6.51	6.78	9.02	649.00
CTQ-SF							
Total	46.89	16.24	50.20	17.00	44.80	15.56	520.50
Emotional abuse	11.70	5.80	13.77	6.21	10.46	5.22	467.50*
Physical abuse	7.23	3.61	7.81	3.82	6.83	3.44	527.50^{+}
Sexual abuse	5.64	1.74	5.60	1.67	5.66	1.80	628.00
Emotional neglect	14.19	5.53	15.31	4.73	13.41	5.94	550.50
Physical neglect	8.80	3.54	9.47	4.20	8.33	2.95	625.00
	N	**%**	**N**	**%**	**N**	**%**	**Test statistic χ^{2a}**
Female gender	38	42.2	15	40.5	23	43.4	1.48
Unemployed	41	45.6	19	51.4	22	41.5	0.85
Chronic depression	66	73.3	30	81.1	36	67.9	1.93
Early onset of depression	50	55.6	29	78.4	21	39.6	13.25*
Marital status							6.29
Married	32	35.6	8	21.6	24	45.3	
Single	45	5.0	21	56.8	24	45.3	
Divorced	13	14.4	8	21.5	5	9.4	
School education							1.57
Lower	24	26.7	9	24.3	15	28.3	
Middle	32	35.5	13	35.1	19	35.9	
Higher	15	16.7	7	18.9	8	15.1	
Highest	18	20.0	8	21.6	10	18.9	
Number of comorbid disorders							
No comorbid disorder	16	18.2	6	16.2	11	21.2	2.15
1	44	50.5	19	41.4	25	48.1	
2	17	19.3	9	24.3	8	15.4	
3	11	12.5	3	8.1	8	15.4	
Comorbid disorders							
Substance use	8	8.9	3	8.1	5	9.4	0.05
Psychotic disorders	2	2.2	2	5.4	0	–	2.93
Anxiety disorders	23	25.6	5	13.5	18	34.0	4.79*
OCD	7	7.8	0	–	7	13.2	5.30*^{a}
Trauma	10	11.1	2	5.4	8	15.1	2.07
Somatoform disorders	2	2.2	1	2.7	1	1.9	0.07
Eating disorders	1	1.1	1	2.7	0	–	1.45
Personality disorders	11	12.2	7	18.9	4	7.5	2.63

CBASP, cognitive behavioral analysis of psychotherapy; MCT, metacognitive therapy; OCD, obsessive compulsive disorder; CTQ-SF, childhood trauma questionnaire short-form. Test statistics were computed to compare CBASP with MCT. $^{+}p < 0.10$, $^{*}p < 0.05$. ^{a}Fisher's exact p-value was investigated if cell counts were <5.

in friendly-dominant behaviors, $t_{(52)} = -4.38$, $p < 0.001$, $d = 0.46$ (95% CI [0.15–0.74]), and lower levels of dysfunctional metacognitive beliefs, $t_{(52)} = 7.56$, $p < 0.001$, $d = -0.80$ (95% CI [−1.06 to −0.45]). There was no significant change in hostile-submissive behaviors, $t_{(52)} = 1.00$, $p = 0.32$, $d = -0.10$ (95% CI [−0.39 to −0.19]). Effect size measures indicate a large pre-post effect of change in depressive symptoms for CBASP patients, $t_{(52)} = 5.33$, $p < 0.001$, $d = -0.88$ (95% CI [−1.27 to −0.65]), and a medium effect for patients treated with MCT, $t_{(52)} = 4.13$, $p < 0.001$, $d = -0.57$ (95% CI [−0.84 to −0.24]). On a descriptive level, patients treated with CBASP seem to show a larger decrease in preoperational thinking compared to MCT patients while patients treated with MCT exhibited a larger decrease in dysfunctional metacognitive beliefs (**Table 2**). Concerning the subscales of the MCQ-30, both patient groups demonstrate the largest improvement in the negative metacognitive beliefs subscale (MCT: M = 4.19, SD = 3.68, CBASP: M = 1.99, SD = 3.49) followed by improvements in the need to control

TABLE 2 | Outcome variables.

	All				CBASP				MCT			
Variables	**Mean**	**SD**	***t***	***d***	**Mean**	**SD**	***t***	***d***	**Mean**	**SD**	***t***	***d***
QIDS												
Week 0	14.52	5.54			14.62	5.23			14.45	5.80		
Week 8	10.78	5.59			10.12	6.13			11.24	5.20		
Difference	3.74	5.45	6.51*	−0.69	4.50	5.13	5.33*	−0.88	3.21	5.66	4.13*	−0.57
LQPT-SF												
Week 0	6.28	2.99			6.10	2.87			6.40	3.10		
Week 8	7.98	2.91			8.27	2.92			7.78	2.91		
Difference	1.70	2.47	−6.53*	0.69	2.17	2.56	−5.15*	0.85	1.39	2.39	−4.21*	0.58
MCQ-30												
Week 0	73.06	14.56			69.55	12.64			75.52	15.41		
Week 8	63.72	12.68			62.85	12.44			64.33	12.93		
Difference	9.34	11.71	7.56*	−0.80	6.69	8.83	4.61*	−0.76	11.19	13.13	6.21*	−0.86
IMI Hos-Sub												
Week 0	2.58	0.45			2.59	0.48			2.58	0.44		
Week 8	2.54	0.49			2.57	0.58			2.52	0.43		
Difference	−0.04	0.41	1.00	−0.10	−0.03	0.43	0.35	−0.05	−0.06	0.41	1.02	−0.15
IMI Fri-Dom												
Week 0	2.35	0.51			2.31	0.48			2.37	0.54		
Week 8	2.57	0.49			2.57	0.53			2.58	0.46		
Difference	0.22	0.48	−4.38*	0.46	0.25	0.46	−3.35*	0.57	0.20	0.50	−2.92*	0.42

*CBASP, cognitive behavioral analysis of psychotherapy; MCT, metacognitive therapy; QIDS, quick inventory of depressive symptomatology; LQPT-SF, luebeck questionnaire for recording preoperational thinking short-form; MCQ-30, metacognition questionnaire 30; IMI, impact message inventory completed by therapists; Hos-Sub, hostile submissive subscale; Fri-Dom, friendly dominant subscale. Effect sizes d were calculated for pre-post differences. *$p < 0.001$.*

thoughts subscale (MCT: M = 2.78, SD = 3.87, CBASP: 1.82, SD = 3.12).

Variables Associated With Outcome

Main Analysis

The full model of the multiple regression analysis was statistically significant, $R^2 = 0.51$, $F_{(9, 80)} = 9.24$, $p < 0.001$, adjusted $R^2 = 0.46$. Adding the change variables to the model led to a statistically significant increase in $R^2 = 0.23$, $F_{(4, 80)} = 9.29$, $p < 0.001$. The LQPT-SF change scores, B =0.73, SE = 0.22, $p = 0.001$, as well as friendly-dominant IMI change scores, B = 4.06, SE = 1.29, $p = 0.002$, were significantly associated with QIDS change. For each change of one unit in LQPT-SF change scores, the average mean in the change of QIDS change is about 0.73 with all other variables held constant. For each change of one unit in friendly-dominant change scores, the average mean in the change of QIDS change is about 4.06 with all other variables held constant. Baseline QIDS scores, B = 0.55, SE = 0.10, $p < 0.001$, and baseline friendly-dominant IMI scores, B = 3.28, SE = 1.35, $p = 0.02$, were significant contributors to the model. Improvement in metacognitive skills as assessed by the MCQ-30 was not significantly associated with QIDS change, $p = 0.26$. Rerunning the analysis with MCQ-30 negative metacognitive beliefs about the uncontrollability of rumination subscale instead of MCQ-30 total score yielded essentially the same results (B = 1.74, SE = 0.18, $p = 0.33$). For the main analysis, we also calculated f^2 as a measure of effect size for the individual independent variables. LQPT-SF change scores and friendly-dominant change scores yielded effect sizes of $f^2 = 0.14$ and $f^2 = 0.12$, respectively, indicating a medium effect (**Table 3**).

Sensitivity Analysis Investigating the Impact of Baseline Imbalances

When repeating the regression analysis and including variables with baseline imbalances to correct for potential confounding effects, neither age, B = = 0.03, SE = 0.04, 95% CI [−0.12, 0.05], $p = 0.45$, nor onset of depression, B = −1.26, SE = 1.17, 95% CI [−3.60, 1.08], $p = 0.29$, presence of comorbid diagnosis, B = −0.16, SE = 1.11, 95% CI [−2.37, 2.05], $p = 0.88$, nor emotional abuse, B = 0.01, SE = 0.10, 95% CI [−0.18, 0.21], $p = 0.88$, were significant predictors of QIDS change. Results for the remaining variables remained essentially the same (LQPT-SF change scores: B = 0.69, SE = 0.24, 95% CI [0.22–1.16], $p = 0.004$, friendly-dominant IMI change scores: B = 3.70, SE = 1.46, 95% CI [0.79–6.60], $p = 0.01$).

Sensitivity Analysis With Follow-Up Data

Using follow-up data, a sensitivity analysis was conducted by repeating the main analysis but utilizing the change in depressive symptoms from baseline to follow-up as the dependent variable. Thirty-six patients completed a 10-month follow-up (CBASP: $n = 15$, MCT: $n = 21$). The unstandardized effect size of friendly-dominant IMI change scores was similar to the one obtained in

TABLE 3 | Regression analysis.

	Model 1				Model 2				
Variables	***B***	***SE***	**95 % CI**	***t***	***B***	***SE***	**95 % CI**	***t***	***f²***
QIDS W0	0.55	0.11	[0.33, 0.76]	4.97**	0.55	0.10	[0.35, 0.74]	5.50**	0.38
LQPT-SF W0	−0.03	0.20	[−0.42, 0.36]	−0.15	0.26	0.20	[−0.14, 0.66]	1.30	0.02
MCQ-30 W0	−0.05	0.04	[−0.13 to 0.04]	−1.04	−0.04	0.05	[−0.14, 0.05]	−0.91	0.01
IMI Hos-Sub W0	−0.67	1.43	[−3.51, 2.17]	−0.47	0.22	1.43	[−2.63, 3.06]	0.15	<0.001
IMI Fri-Dom W0	1.78	1.24	[−0.68, 4.25]	1.44	3.28	1.35	[0.59, 5.97]	2.43*	0.07
Δ LQPT-SF	–	–	–	–	0.73	0.22	[0.29, 1.16]	3.31*	0.14
Δ MCQ-30	–	–	–	–	0.06	0.05	[-0.04, 0.16]	1.14	0.02
Δ IMI Hos-Sub	–	–	–	–	−0.19	1.36	[−2.90, 2.53]	−0.14	<0.001
Δ IMI Fri-Dom	–	–	–	–	4.06	1.29	[1.50, 6.63]	3.15*	0.12
R^2 *(adjusted)*	0.28 *(0.24)*				0.51 *(0.46)*				
ΔR^2	0.28				0.23				
ΔF	6.60				9.29				

*QIDS, quick inventory of depressive symptomatology; LQPT-SF, luebeck questionnaire for recording preoperational thinking short-form; MCQ-30, metacognition questionnaire 30; IMI, impact message inventory completed by therapists; Hos-Sub, hostile submissive subscale; Fri-Dom, friendly dominant subscale. **p < 0.001, *p < 0.05.*

the main analysis, B = 3.66, SE = 1.34, 95% CI [−3.24, 10.56] but the variable did not reach significance ($p = 0.29$). LQPT-SF change scores were not significantly associated with QIDS change at follow-up, B = −0.05, SE = 0.60, CI [−1.28, 1.18], $p = 0.94$. Baseline QIDS scores remained a significant predictor of the model, B = 0.53, SE = 0.26, 95% CI [0, 1.05], $p = 0.05$.

CBASP vs. MCT

Contrary to expectations, treatment group did not significantly predict change in preoperational thinking, $F_{(1, 87)} = 2.05$, $p = 0.16$, $\eta_p^2 = 0.02$, hostile-submissive, $F_{(1, 87)} = 0.19$, $p = 0.67$, $\eta_p^2 = 0.002$, as well as friendly-dominant behaviors, $F_{(1, 87)} = 0.06$, $p = 0.81$, $\eta_p^2 = 0.001$, and was not a significant predictor of change in metacognitive skills, $F_{(1, 87)} = 0.08$, $p = 0.37$, $\eta_p^2 = 0.009$, when controlling for the respective baseline scores. Effect size measures as indicated by η_p^2 revealed a small effect of treatment group for LQPT-SF change scores, $\eta_p^2 = 0.02$. *Post-hoc* power analyses revealed low power to detect effects of 1 - β ranging from 0.06 to 0.30. Baseline scores of LQPT-SF, $F_{(1, 87)} = 21.65$, $p < 0.001$, $\eta_p^2 = 0.20$, hostile-submissive, $F_{(1, 87)} = 13.42$, $p < 0.001$, $\eta_p^2 = 0.13$, as well as friendly-dominant IMI scores, $F_{(1, 87)} = 33.01$, $p < 0.001$, $\eta_p^2 = 0.28$, and baseline MCQ-30 scores, $F_{(1, 87)} = 34.80$, $p < 0.001$, $\eta_p^2 = 0.29$, were each significant predictors of the respective change score. Following the intention-to-treat approach, all patients with baseline data were included in the analyses. Upon closer inspection of the data, there was one patient presenting with unusual values for the LQPT-SF change scores. Rerunning the ANCOVA and excluding this patient did not lead to a significant change in results but to an increase in $F_{(1, 86)} = 3.00$, $p = 0.09$, $\eta_p^2 = 0.03$.

Sensitivity Analysis Investigating the Impact of Baseline Imbalances

Treatment group was not a significant predictor of change in preoperational thinking, $F_{(1, 74)} = 1.31$, $p = 0.26$, $\eta_p^2 = 0.02$, hostile-submissive, $F_{(1, 74)} = 0.04$, $p = 0.62$, $\eta_p^2 = 0.003$, or friendly-dominant behavior, $F_{(1, 74)} = 1.78$, $p = 0.19$, $\eta_p^2 = 0.02$, and also did not significantly predict change in metacognitive skills, $F_{(1, 74)} = 0.83$, $p = 0.37$, $\eta_p^2 = 0.01$, when correcting for baseline imbalances.

DISCUSSION

Summary of Results

In this study, we examined the association between change in interpersonal as well as metacognitive skills and depressive symptomatology during treatment with CBASP and MCT. Improvements in preoperational thinking as well as increases in friendly-dominant behaviors were associated with change in depressive symptoms. There was no association between change in dysfunctional metacognitive beliefs or hostile-submissive behavior and a reduction in depressive symptoms. Contrary to our expectations, treatment groups did not differ in the magnitude of change in interpersonal and metacognitive skills. The LQPT-SF appears to be a reliable and valid instrument as demonstrated by high internal consistency, convergent validity with relevant IMI subscales and excellent discriminant abilities.

Comparison to Existing Studies

We were the first to demonstrate that improvements in preoperational thinking are associated with outcome as postulated by the CBASP model (11). Our present results extend the findings of Sondermann et al. (22), who also suggest the implication of preoperational thinking in depressive symptom severity as they found a high degree of preoperational thinking to be associated with a higher severity of depressive symptoms over an observation period of 2 years.

In line with previous research (33, 34, 39), patients treated with CBASP exhibited more friendly-dominant behaviors at the end of treatment. However, contrary to Constantino et al. (37,

39), increases in friendly-dominant and not decreases in hostile-submissive behaviors were associated with change in depressive symptoms. While several studies report decreases of hostile-submissive behaviors over the course of treatment with CBASP (33, 34, 39), patients in our sample did not exhibit significant changes in the hostile-submissive subscale. Possibly, differences in treatment duration may account for these conflicting results. The treatment program offered in this study entailed 8 weeks of treatment with a weekly individual and group session according to the therapeutic concept. However, CBASP as adapted for inpatient treatment usually involves 12 weeks of treatment with biweekly sessions (60) and other studies have followed this procedure (33, 34, 61). Increases in friendly-dominant behaviors that may be expressed in increased abilities to express one's own needs may be more readily detectable by others while decreases in hostile-submissive behaviors may need more time to manifest themselves. Thus, possibly we would have also detected change in hostile-submissive behaviors, if patients had been treated for a longer period of time in higher frequency, as this would have allowed more time for treatment effects to take place. This reasoning may also explain why Brakemeier et al. (34) could show stronger increases in friendly-dominant behaviors and greater reductions in depression severity over the course of treatment with CBASP. Nevertheless, improvements in interpersonal skills may contribute to changes in social relationships that have been found associated with reduced probability of relapse in patients treated with CBASP (62).

Patients did improve in dysfunctional metacognitive beliefs, but these decreases were not associated with decreases in depressive symptoms. Hjemdal et al. (40) and Faissner et al. (63) found that reductions in metacognitive beliefs predicted change in depression. However, Faissner et al. (63) also reported that changes in the Dysfunctional Attitudes Scale (DAS) were a better predictor of changes in depressive symptoms than changes in the MCQ-30 subscales. Considering that items of the DAS touch into interpersonal areas that are relevant in CBASP (e.g., "People will probably think less of me if I make a mistake") these results may support our notion that especially changes in interpersonal skills seem to be of relevance for a reduction in depressive symptoms. The DAS has been found to exhibit significant high correlations with the LQPT (64).

Contrary to expectations, changes in skills deficits were not specific to the type of treatment received. This result can be interpreted against the background of the contextual model of psychotherapy (65). This model argues against the notion that certain specific ingredients are necessary for the success of a therapy. Rather, the contextual model argues that the the ingredients of therapy will be succesfull as long as the patient accepts their rationale and believes in their effectiveness. A competing explanation for our findings is that specific ingredients are indeed necessary for the success of therapy but treatment duration in our study was too short for these specific ingredients to achieve their full effect. On a different note, the group context of the clinical setting may offer experiences of interpersonal effective behavior irrespective of the treatment group. Not only does group psychotherapy foster interpersonal learning (66), but common spaces of the day clinic also promote engagement with others. Positive interpersonal interactions thus may contribute to improvement in interpersonal skills for patients treated with MCT. Also, improvements in dysfunctional metacognitive beliefs may influence changes in interpersonal behaviors and vice versa. According to the metacognitive model of depression, depressive rumination is associated with heightened perseverative self-focused attention (30). Thus, disengaging from ruminative thoughts and challenging dysfunctional metacognitive beliefs may open up attentional resources previously occupied with self-focused attention and enable active engagement with the social environment. ATT as utilized in the present treatment has been found effective in reducing self-focused attention (67). Patients treated with CBASP also exhibited significant improvements in dysfunctional metacognitive skills. As depressed patients are described to suffer from stressful interpersonal experiences which they at least in part generate themselves (68), improvements in interpersonal skills may lead to more positive interpersonal experiences. Assuming that there are less stressful interpersonal situations to ruminate about, dysfunctional metacognitive beliefs concerned with the uncontrollability of rumination may be likely to decrease. Also, a diffusion of skills taught in group and individual therapy may contribute to our results (e.g., CBASP patients might have learned about MCT skills from their fellow patients).

Strengths and Limitations

The present study yields several strengths: First, the longitudinal design enabled us to investigate both pre-post treatment differences as well as the association between changes in interpersonal skills and metacognitive beliefs and depressive symptom severity. To our knowledge, this is the first study that investigated change in preoperational thinking and its association with symptom change in depression and that focused on change in both interpersonal as well as metacognitive skills over the course of treatment in depressed patients. Second, the observational design of our study increases the ecological validity of our findings (69). Thus, this increases the generalizability of our findings to real world clinical settings. Of note, sociodemographic data of this present naturalistic study are comparable to general population data (70).

There are also limitations that warrant discussion. First and foremost, we cannot establish temporal precedence of change in skills deficits before change in depressive symptoms. Due to the rather short treatment duration of 8 weeks, data regarding skills deficits was collected at baseline and end of treatment only in order to allow for treatment effects to take place. However, temporal precedence of the proposed mediating variable is often regarded a prerequisite when investigating mechanisms of change and establishing causal effects (71, 72). Nevertheless, the use of cross-sectional designs to test mediation is prevalent (72). The correlational evidence of this present study may be seen as an important starting point for future research (71, 73). Future studies should further investigate the proposed mechanisms of change by including additional data measurement points in order to allow for the investigation of mediation models by establishing

temporal precedence. Due to the observational study design, patients were not randomly assigned to treatment with CBASP or MCT. Rather, choice of treatment was based on diagnosis, presenting complaints and patients' preferences. While we aimed to statistically control for observed baseline imbalances, we cannot account for unobserved confounding variables influencing our results. Future studies conducted as randomized controlled trials would minimize the influence of potential confounding effects (74). Due to the non-randomization, the treatment groups (CBASP vs. MCT) also differed in sample size. As unbalanced groups contribute to reduced power, future studies should pay attention to equally balanced groups in order to maximize power. Also due to the observational study design, sample size was determined by admission rate and capacities of the day clinic. With this present sample size, our study was only powered to detect large effects between treatments. This needs to be kept in mind when interpreting results (esp. concerning differential treatment effects) and future studies should focus on analyzing larger samples. As self-report questionnares were used, reporting biases may have influenced results. Also, as there was no separation of patient groups in common spaces of the day clinic, we could not control for eventual diffusion effects as patients may exchange information and experiences about their treatments. Also, as the majority of patients in this study suffered from PDD, generalizability to episodically depressive samples may be limited. Addressing this limitation, future studies could investigate whether diagnosis of depression may constitute a moderating factor to the association between improvement in interpersonal or metacognitive skills deficits and change in depressive symptoms. Finally, due to the small sample size at follow-up and thus low power to detect effects, long-term data should be further investigated as results may point toward friendly-dominant behavior change being associated with change in depressive symptomatology also at 10 months follow-up.

CONCLUSION

We found that changes in interpersonal skills might be of relevance in reducing depressive symptomatology. Increases in friendly-dominant behaviors and a less preoperational style of thinking were associated with alleviation of depressive symptoms, thereby supporting McCullough's interpersonal model of depression. These findings also have implications for treatment as they emphasize the importance of addressing interpersonal challenges in the treatment of depression. Future research is needed to investigate potential moderators (e.g., chronicity of depression) and mediators of the association between change in interpersonal and metacognitive skills and change in depressive symptomatology.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethics Committee. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

JK with support from SG: conception and design. KO and SS: acquisition of data. SS and KO with support from JK: analysis of data. SS and JK: interpretation of data. SS: drafting of manuscript. All authors made substantial contribution to the manuscript and gave approval to the final version before submission.

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REFERENCES

1. Kessler RC, Berglund P, Demler O, Jin R, Merikangas KR, Walters EE. Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the national comorbidity survey replication. *Arch Gen Psychiatry.* (2005) 62:593–602. doi: 10.1001/archpsyc.62.6.593
2. Whiteford HA, Degenhardt L, Rehm J, Baxter AJ, Ferrari AJ, Erskine HE, et al. Global burden of disease attributable to mental and substance use disorders: findings from the global burden of disease study 2010. *Lancet.* (2013) 382:1575–86. doi: 10.1016/S0140-6736(13)61611-6
3. Solomon DA. Multiple recurrences of major depressive disorder. *Am J Psychiatry.* (2000) 157:229–33. doi: 10.1176/appi.ajp.157.2.229
4. Murphy JA, Sarris J, Byrne GJ. A review of the conceptualisation and risk factors associated with treatment-resistant depression. *Depress Res Treat.* (2017) 2017:1–10. doi: 10.1155/2017/4176825
5. Murphy JA, Byrne GJ. Prevalence and correlates of the proposed DSM-5 diagnosis of chronic depressive disorder. *J Affect Disord.* (2012) 139:172–80. doi: 10.1016/j.jad.2012.01.033
6. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders: DSM-5.* 5th ed. Arlington, VA: American Psychiatric Association (2013).
7. Malhi GS, Mann JJ. Depression. *Lancet.* (2018) 392:2299–312. doi: 10.1016/S0140-6736(18)31948-2
8. Kube T, Siebers VHA, Herzog P, Glombiewski JA, Doering BK, Rief W. Integrating situation-specific dysfunctional expectations and dispositional optimism into the cognitive model of depression – a path-analytic approach. *J Affect Disord.* (2018) 229:199–205. doi: 10.1016/j.jad.2017.12.082
9. Kube T, Herzog P, Michalak CM, Glombiewski JA, Doering BK, Rief W. Further specifying the cognitive model of depression: situational expectations and global cognitions as predictors of depressive symptoms. *Clin Psychol Eur.* (2019) 1, 1–21. doi: 10.32872/cpe.v1i4.33548

10. Schweiger JI, Kahl KG, Klein JP, Sipos V, Schweiger U. Innovation in psychotherapy, challenges, and opportunities: an opinion paper. *Front Psychol.* (2019) 10:495. doi: 10.3389/fpsyg.2019.00495
11. McCullough JP. *Treatment for chronic depression: Cognitive Behavioral Analysis System of Psychotherapy (CBASP) (1999-04419-000)*. New York, NY: Guilford Press (2000).
12. McCullough JP. *Treating chronic depression with disciplined personal involvement: cognitive behavioral analysis system of psychotherapy (CBASP)*. New York, NY: Springer. (2006). doi: 10.1007/978-0-387-31066-4
13. Jobst A, Brakemeier E-L, Buchheim A, Caspar F, Cuijpers P, et al. European psychiatric association guidance on psychotherapy in chronic depression across Europe. *Eur Psychiatry.* (2016) 33:18–36. doi: 10.1016/j.eurpsy.2015.12.003
14. Furukawa TA, Efthimiou O, Weitz ES, Cipriani A, Keller MB, Kocsis JH, et al. Cognitive-behavioral analysis system of psychotherapy, drug, or their combination for persistent depressive disorder: personalizing the treatment choice using individual participant data network metaregression. *Psychother Psychosom.* (2018) 87:140–53. doi: 10.1159/000489227
15. Negt P, Brakemeier, E.-L., Michalak J, Winter L, Bleich S, et al. The treatment of chronic depression with cognitive behavioral analysis system of psychotherapy: a systematic review and meta-analysis of randomized-controlled clinical trials. *Brain Behav.* (2016) 6:e00486. doi: 10.1002/brb3.486
16. Bird T, Tarsia M, Schwannauer M. Interpersonal styles in major and chronic depression: a systematic review and meta-analysis. *J Affect Disord.* (2018) 239:93–101. doi: 10.1016/j.jad.2018.05.057
17. Klein JP, Grasshoff L, Hermanns R, Haeger S, Sondermann S, Kühnen T, et al. Präoperatorisches denken bei verschiedenen psychischen störungen: zwei querschnittsstudien zum besseren verständnis des CBASP. *Zeitschrift Psychiatr Psychol Psychother*. (2020) 68:191–9. doi: 10.1024/1661-4747/a000418
18. Inhelder B, Piaget J, Parsons A, Milgram S. *The Growth of Logical Thinking: From Childhood to Adolescence (2004-16276-000)*. New York, NY: Basic Books (1958).
19. Klein JP, Stahl J, Hüppe M, McCullough JP, Schramm E, Ortel D, et al. Do interpersonal fears mediate the association between childhood maltreatment and interpersonal skills deficits? A matched cross-sectional analysis. *Psychother Res.* (2018) 0:1–12. doi: 10.1080/10503307.2018.1532125
20. Kühnen T, Knappke F, Otto T, Friedrich S, Klein JP, Kahl KG, et al. Chronic depression: development and evaluation of the luebeck questionnaire for recording preoperational thinking (LQPT). *BMC Psychiatry.* (2011) 11:199. doi: 10.1186/1471-244X-11-199
21. Klein JP, Kensche M, Becker-Hingst N, Stahl J, Späth C, Mentler T, et al. Development and psychometric evaluation of the interactive test of interpersonal behavior (ITIB): a pilot study examining interpersonal deficits in chronic depression. *Scand J Psychol.* (2016) 57:83–91. doi: 10.1111/sjop.12222
22. Sondermann S, Stahl J, Grave U, Outzen J, Moritz S, Klein JP. Preoperational thinking as a measure of social cognition is associated with long-term course of depressive symptoms. A longitudinal study involving patients with depression and healthy controls. *Front Psychiatry.* (2020) 11:652. doi: 10.3389/fpsyt.2020.00652
23. Wells A, Matthews G. Modelling cognition in emotional disorder: the S-REF model. *Behav Res Ther.* (1996) 34:881–8. doi: 10.1016/S0005-7967(96)00050-2
24. Sun X, Zhu C, So SHW. Dysfunctional metacognition across psychopathologies: a meta-analytic review. *Eur Psychiatry.* (2017) 45:139–53. doi: 10.1016/j.eurpsy.2017.05.029
25. Papageorgiou C, Wells A. Metacognitive beliefs about rumination in recurrent major depression. *Cogn Behav Pract.* (2001) 8:160–4. doi: 10.1016/S1077-7229(01)80021-3
26. Papageorgiou C, Wells A. An empirical test of a clinical metacognitive model of rumination and depression. *Cognit Ther Res.* (2003) 27:261–73. doi: 10.1023/A:1023962332399
27. Nolen-Hoeksema S. The role of rumination in depressive disorders and mixed anxiety/depressive symptoms. *J Abnorm Psychol.* (2000) 109:504–11. doi: 10.1037/0021-843X.109.3.504
28. Nolen-Hoeksema S, Morrow J. Effects of rumination and distraction on naturally occurring depressed mood. *Cogn Emot.* (1993) 7:561–70. doi: 10.1080/02699939308409206
29. Papageorgiou C, Wells A. A prospective test of the clinical metacognitive model of rumination and depression. *Int J Cogn Ther.* (2009) 2:123–31. doi: 10.1521/ijct.2009.2.2.123
30. Wells A. *Metacognitive Therapy For Anxiety and Depression*. New York, NY: Guilford Press (2009).
31. Normann N, van Emmerik AA, Morina N. The efficacy of metacognitive therapy for anxiety and depression: a meta-analytic review. *Depress Anxiety.* (2014) 31:402–11. doi: 10.1002/da.22273
32. Normann N, Morina N. The efficacy of metacognitive therapy: a systematic review and meta-analysis. *Front Psychol.* (2018) 9:2211. doi: 10.3389/fpsyg.2018.02211
33. Brakemeier, E.-L., Engel V, Schramm E, Zobel I, Schmidt T, et al. Feasibility and outcome of cognitive behavioral analysis system of psychotherapy (CBASP) for chronically depressed inpatients: a pilot study. *Psychother Psychosom.* (2011) 80:191–4. doi: 10.1159/000320779
34. Brakemeier, E.-L., Radtke M, Engel V, Zimmermann J, Tuschen-Caffier B, et al. Overcoming treatment resistance in chronic depression: a pilot study on outcome and feasibility of the cognitive behavioral analysis system of psychotherapy as an inpatient treatment program. *Psychother Psychosom.* (2015) 84:51–6. doi: 10.1159/000369586
35. Papageorgiou C, Wells A. Group metacognitive therapy for severe antidepressant and CBT resistant depression: a baseline-controlled trial. *Cognit Ther Res.* (2015) 39:14–22. doi: 10.1007/s10608-014-9632-x
36. Wells A, Fisher P, Myers S, Wheatley J, Patel T, Brewin CR. Metacognitive therapy in treatment-resistant depression: a platform trial. *Behav Res Ther.* (2012) 50:367–73. doi: 10.1016/j.brat.2012.02.004
37. Constantino MJ, Laws HB, Arnow BA, Klein DN, Rothbaum BO, Manber R. The relation between changes in patients' interpersonal impact messages and outcome in treatment for chronic depression. *J Consult Clin Psychol.* (2012) 80:354–64. doi: 10.1037/a0028351
38. Klein JP, Probst T, Kriston L, Assmann N, Bailer J, Eich H, et al. Changes in therapeutic alliance and in social inhibition as mediators of the effect of the cognitive behavioral analysis system of psychotherapy: a secondary analysis from a randomized clinical trial. *Psychother Psycho.* (2020) 89:261–2. doi: 10.1159/000506082
39. Constantino MJ, Laws HB, Coyne AE, Greenberg RP, Klein DN, Manber R, et al. Change in patients' interpersonal impacts as a mediator of the alliance-outcome association in treatment for chronic depression. *J Consult Clin Psychol.* (2016) 84:1135–44. doi: 10.1037/ccp,0000149
40. Hjemdal O, Solem S, Hagen R, Kennair LEO, Nordahl HM, Wells A. A randomized controlled trial of metacognitive therapy for depression: analysis of 1-year follow-up. *Front Psychol.* (2019) 10:1842. doi: 10.3389/fpsyg.2019.01842
41. Geurtzen N, Keijsers GPJ, Karremans JC, Hutschemaekers GJM. Patients' care dependency in mental health care: development of a self-report questionnaire and preliminary correlates. *J Clin Psychol.* (2018) 74:1189–206. doi: 10.1002/jclp.22574
42. Fassbinder E, Klein JP, Sipos V, Schweiger U. *Therapie-Tools Depression*. Weinheim: Beltz (2015).
43. DGPPN, BÄK, KBV, AWMF. *S3-Leitlinie/Nationale VersorgungsLeitlinie: Unipolare Depression (2. Auflage)*. Berlin: Springer (2017).
44. Sargin AE, Uca O, Kose S, Türkçapar H. Reliability, validity, and factorial structure of the turkish version of the luebeck questionnaire for recording preoperational thinking (Turkish LQPT). *Psychiatry Clin Psychopharmacol.* (2018) 28:191–8. doi: 10.1080/24750573.2017.1411575
45. Tabachnick BG, Fidell LS. *Using Multivariate Statistics*. Upper Saddle River, NJ: Pearson Education (2013).
46. Rosnow RL, Rosenthal R. Computing contrasts, effect sizes, and counternulls on other people's published data: general procedures for research consumers. *Psychol Meth.* (1996) 1:331–40. doi: 10.1037/1082-989X.1.4.331
47. Wells A, Cartwright-Hatton S. A short form of the metacognitions questionnaire: properties of the MCQ-30. *Behav Res Ther.* (2004) 42:385–96. doi: 10.1016/S0005-7967(03)00147-5
48. Kiesler DJ, Schmidt JA, Wagner CC. A circumplex inventory of impact messages: an operational bridge between emotion interpersonal behavior. In Plutchik R, Conte RH. editors. *Circumplex Models of Personality and*

Emotions. Washington, DC: American Psychological Association (1997). p. 221–44.
49. Kiesler DJ, Schmidt JA. *The Impact Message Inventory: Form IIA Octant Scale Version*. Richmond: Virginia Commonwealth University (1993).
50. Caspar F, Berger T, Fingerle H, Werner M. Das deutsche IMI. *Psychother Dialog.* (2016) 17:e1–10. doi: 10.1055/s-0042-105981
51. Reilly TJ, MacGillivray SA, Reid IC, Cameron IM. Psychometric properties of the 16-item quick inventory of depressive symptomatology: a systematic review and meta-analysis. *J Psychiatr Res.* (2015) 60:132–40. doi: 10.1016/j.jpsychires.2014.09.008
52. Roniger A, Späth C, Schweiger U, Klein J. A psychometric evaluation of the german version of the quick inventory of depressive symptomatology (QIDS-SR16) in outpatients with depression. *Fortschr Neurol Psychiatr.* (2015) 83:e17–22. doi: 10.1055/s-0041-110203
53. Bernstein DP, Stein JA, Newcomb MD, Walker E, Pogge D, Ahluvalia T, et al. (2003). Development and validation of a brief screening version of the Childhood Trauma Questionnaire. *Child Abuse & Neglect*, 27, 169–190. doi: 10.1016/S0145-2134(02)00541-0
54. Wingenfeld K, Spitzer C, Mensebach C, Grabe H, Hill A, Gast U, et al. Die deutsche version des childhood trauma questionnaire (CTQ): erste befunde zu den psychometrischen kennwerten. *Psychother Psycho Med Psychol.* (2010) 60:442–50. doi: 10.1055/s-0030-1247564
55. IBM Corp. *IBM SPSS Statistics for Mac, Version (24.0)*. (2016). Armonk, NY: IBM Corp.
56. Downey RG, King CV. Missing data in likert ratings: a comparison of replacement methods. *J Gen Psychol.* (1998) 125:175–91. doi: 10.1080/00221309809595542
57. van Buuren S. Multiple imputation of discrete and continuous data by fully conditional specification. *Stat Meth Med Res.* (2007) 16:219–42. doi: 10.1177/0962280206074463
58. Faul F, Erdfelder E, Buchner A, Lang, A-G. Statistical power analyses using G*Power 3.1: tests for correlation and regression analyses. *Behav Res Meth.* (2009) 41:1149–60. doi: 10.3758/BRM.41.4.1149
59. Cohen J. *Statistical Power Analysis For the Behavioral Sciences*. Hillsdale, NJ: Lawrence Erlbaum Associates (1988).
60. Brakemeier E-L, Normann C. *Praxisbuch CBASP: Behandlung Chronischer Depression*. Weinheim: Beltz (2012).
61. Keller MB, McCullough JP, Klein DN, Arnow B, Dunner DL, Gelenberg AJ, et al. A comparison of nefazodone, the cognitive behavioral-analysis system of psychotherapy, and their combination for the treatment of chronic depression. *N Eng J Med.* (2000) 342:1462–70. doi: 10.1056/NEJM200005183422001
62. Brakemeier E-L, Herzog P, Radtke M, Schneibel R, Breger V, et al. CBASP als stationäres behandlungskonzept der therapieresistenten chronischen depression: eine pilotstudie zum zusammenhang von nebenwirkungen und therapieerfolg. *Psychother Psycho Med Psychol.* (2018) 68:399–407. doi: 10.1055/a-0629-7802
63. Faissner M, Kriston L, Moritz S, Jelinek L. Course and stability of cognitive and metacognitive beliefs in depression. *Depress Anxiety.* (2018) 35:1239–46. doi: 10.1002/da.22834
64. Stahl J. *Evaluation Eines Interaktiven Testsystems Zur Erfassung Interpersonellen Veerhaltens "Interactive Test of Interpersonal Behavior" ITIB*. [thesis]. Universität zu Lübeck (2018). p. 155.
65. Wampold BE. How important are the common factors in psychotherapy? An update. *World Psychiatry.* (2015) 14:270–7. doi: 10.1002/wps.20238
66. Yalom ID, Leszcz M. *The Theory and Practice of Group Psychotherapy*. 5th ed. New York, NY: Basic Books (2005).
67. Papageorgiou C, Wells A. Treatment of recurrent major depression with attention training. *Cogn Behav Pract.* (2000) 7:407–13. doi: 10.1016/S1077-7229(00)80051-6
68. Hammen C. Stress and depression. *Annu Rev Clin Psychol.* (2005) 1:293–319. doi: 10.1146/annurev.clinpsy.1.102803.143938
69. Leichsenring F. Randomized controlled versus naturalistic studies: a new research agenda. *Bull Menninger Clin.* (2004) 68:137–51. doi: 10.1521/bumc.68.2.137.35952
70. Späth C, Hapke U, Maske U, Schröder J, Moritz S, Berger T, et al. Characteristics of participants in a randomized trial of an internet intervention for depression (EVIDENT) in comparison to a national sample (DEGS1). *Int Interv.* (2017) 9:46–50. doi: 10.1016/j.invent.2017.05.003
71. Kazdin AE. Mediators and mechanisms of change in psychotherapy research. *Annu Rev Clin Psychol.* (2007) 3:1–27. doi: 10.1146/annurev.clinpsy.3.022806.091432
72. Lemmens LH, Müller VN, Arntz A, Huibers MJ. Mechanisms of change in psychotherapy for depression: an empirical update and evaluation of research aimed at identifying psychological mediators. *Clin Psychol Rev.* (2016) 50:95–107. doi: 10.1016/j.cpr.2016.09.004
73. Hayes AF, Rockwood NJ. Regression-based statistical mediation and moderation analysis in clinical research: observations, recommendations, and implementation. *Behav Res Ther.* (2017) 98:39–57. doi: 10.1016/j.brat.2016.11.001
74. Sterne JAC, Hernán MA, McAleenan A, Reeves BC, Higgins JPT. Assessing risk of bias in a non-randomized study. In Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA, editors. *Cochrane Handbook for Systematic Reviews of Interventions*. 2nd ed. Chichester: John Wiley & Sons (2019). p. 621–41.

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Investigating Care Dependency and Its Relation to Outcome (ICARE): Results From a Naturalistic Study of an Intensive Day Treatment Program for Depression

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Background: This study explores the association of experienced dependency in psychotherapy as measured with the CDQ (Care Dependency Questionnaire) and treatment outcome in depression. Furthermore, the course of care dependency and differences in the CDQ scores depending on the received type of treatment, MCT (metacognitive therapy), or CBASP (cognitive behavioral analysis system of psychotherapy), were investigated.

Methods: The study follows a prospective, parallel group observational design. Patients suffering from depression received an 8-week intensive day clinic program, which was either CBASP or MCT. The treatment decision was made by clinicians based on the presented symptomatology and with regard to the patients' preferences. The patients reported depressive symptoms with the QIDS-SR16 (Quick Inventory of Depressive Symptomatology) and levels of experienced care dependency with the German version of the CDQ on a weekly basis. Mixed-model analyses were run to account for the repeated-measures design.

Results: One hundred patients were included in the analyses. Results indicate that higher levels of care dependency might predict a less favorable outcome of depressive symptomatology. Levels of care dependency as well as depressive symptoms decreased significantly over the course of treatment. There was no significant between-group difference in care dependency between the two treatment groups.

Conclusion: The results suggest that care dependency might be associated with a worse treatment outcome in depressed patients. In general, care dependency seems to be a dynamic construct, as it is changing over time, while the levels of care dependency seem to be independent from the received type of treatment. Future research should continue investigating the mechanisms of care dependency in a randomized controlled design.

Clinical Trial Registration: https://www.drks.de/drks_web/, identifier: DRKS00023779.

Keywords: care dependency, cognitive behavioral analysis system of psychotherapy (CBASP), metacognitive therapy (MCT), depression, adverse effects, side effects

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INTRODUCTION

Dependency from another is a natural phenomenon that can be found in many species, especially in humans. As we are able to develop stable relationships, we learn that "from a secure personal base [. . .], an adult goes out to explore and [. . .] returns from time to time," when feeling insecure, fragile, or threatened [(1), p. 46]. Bowlby (1) further states that the deeply grounded feeling of a stable attachment figure is necessary for a confident, autonomous functioning over the whole life span, regardless of age. Thus, as described above, a certain degree of dependency seems to be indispensable in living an autonomous life that is accompanied by spontaneous actions of the individual.

On the other hand, just the word dependency itself is often associated with a negative trait, that—if it becomes too intense—may harm relationships and even cause psychiatric disorders, such as a dependent personality disorder that is characterized by a persistent, excessive craving of being supported in different areas of live, including relationships and resulting in submissiveness (2). The therapeutic relationship between patient and therapist has been described as essential for a desirable outcome (3, 4). Considering that therapist and patient spend a considerable amount of time together with the patient opening up about sensitive topics, the question arises whether dependency may evolve in psychotherapy as well and how it may affect the outcome of treatment.

This question has only rarely been addressed. Dependency has been regarded as one facet of adverse effects of psychotherapy (5), but several reviews showed that adverse events were rarely reported at all. Jonsson et al. (6) stated that only one-fifth of 132 trials reported that they monitored adverse events and even fewer actually reported adverse events. More recently, in a systematic review of 60 studies that were reported in 126 publications, it was also found that adverse events were insufficiently reported in randomized trials on persistent depressive disorder (7). These findings are in line with observations from other researchers (8–11). Additionally, the terminology of adverse events and the way how they are measured if noted at all is differing as well (6, 12, 13).

Looking at dependency as one specific aspect of adverse effects in psychotherapy, literature review is very limited. Bornstein and Bowen (14) noted earlier that there are a number of studies that assumed a correlation between dependency and depression (15), as well as other conditions such as eating disorders, anxiety disorders, alcoholism, and psychosomatic disorders (16–18). More recently, dependency was identified as a possible risk factor in psychotherapy (19, 20). Furthermore, dependency has been associated with characteristics of the patients such as passive and helpless stance (21). However, there are certain studies that gave indications for a positive effect of dependency (13, 22). Lately, Geurtzen et al. (21) addressed this problem more systematically by developing an instrument, the Care Dependency Questionnaire (CDQ) that reliably allows the measurement of the experienced dependency (23). In their first two studies utilizing the CDQ, different observations have been made. They found a positive correlation between the severity of symptoms and care dependency in a sample with 742 patients suffering from various psychiatric disorders (21), while this was not appearing in their second study with a group of students in clinical training (23). In the second study, the authors found no significant correlation between care dependency and the treatment outcome. Instead, they found a positive association between care dependency and the therapeutic alliance. A better therapeutic alliance in turn has been identified as a variable that supports a better treatment outcome (24). These findings suggest that dependency might even play a positive role for treatment success.

Besides the question *if* dependency is affecting treatment outcome, little effort has been made to understand *how* it develops over time. With regard to the development of care dependency, the aforementioned authors found that certain aspects of dependency decreased over the therapy sessions (23). On a broader view, Schneibel et al. (25) investigated the development of adverse events in group psychotherapy and found a general decrease of unwanted events and adverse treatment reactions, as measured by the questionnaire Unwanted Events and Adverse Treatment Reactions (UE-G), which examines negative implications of group therapy regarding content, size, repercussions, other patients, and the therapist (26). The authors found a general decrease of unwanted effects, which supports the idea that adverse effects may reduce over time.

Furthermore, in the recent past the question was arising, whether adverse effects in psychotherapy depend on the type of treatment. Meister et al. (27) found that patients in supportive psychotherapy reported less severe adverse events than patients who have been treated with the Cognitive Behavioral Analysis System of Psychotherapy (CBASP) by McCullough (28). In a study from (29), the authors observed that 36% of the patients treated with CBASP experienced symptom deterioration and 52% reported conflicts with the treatment team. The hypothesis arises that the intense therapeutic techniques and the intimate relationship between the therapist and the patient as a characteristic of CBASP treatment might influence the experience of negative effects during treatment. In contrast to CBASP, other existing therapeutic approaches in the treatment of depression mainly focus on reducing the typical depressive symptoms such as rumination, inhibition of drive, or loss of interests, while the specific emotional dynamics between the therapist and the patient gain less attention. One of these approaches is the metacognitive therapy (MCT) by Wells (30). To our knowledge, with regard to this type of treatment, there has been no such discussion as the one mentioned above. In sum, looking at the distinct nature of the two types of treatment, there are several differences at hand. First of all, a difference between the two treatments can be found in the nature of the individual case formulation: while in CBASP the biography of the patient builds up the basis for the following treatment, MCT is solely focusing on the current symptomatology and its related metacognitive beliefs. CBASP is further working with the intense relationship between the therapist and the patient. The therapist is disclosing his/her emotions in a disciplined way on a regular basis to help the patient experience the effect of his/her behavior. In contrast, MCT is working with a more distant relationship that is mainly focusing on the systematic reduction of depressive symptoms in a very clear and straightforward attempt while

emotional situations within the sessions are not worked on in a standardized manner as in the case of CBASP. In sum, CBASP and MCT, which both represent effective treatments for depression, function in very different ways with regard to the consideration of the therapeutic relationships.

In sum, the role of care dependency remains still unclear. It is an open question whether dependency might even contribute to a successful therapy or is rather an adverse effect that impairs effective treatment. From what has been shown so far, we hypothesize that (i) a higher degree of dependency as indicated by the CDQ is associated with a less favorable outcome in depression at the end of treatment. Also, the investigation of the development of care dependency over time is of particular interest as it may offer answers to the question if CD is a construct that can be influenced and worked on in psychotherapy. Therefore, the study investigates the experienced levels of care dependency over the course of treatment (ii). Furthermore, the possibility that care dependency is dependent on the treatment type remains an unresolved issue. Thus, besides the question whether care dependency is affecting the treatment outcome, the study aims to assess whether the CDQ scores differ depending on the type of treatment received, MCT or CBASP (iii).

MATERIALS AND METHODS

The current study follows a pragmatic, prospective, parallel group observational study design. We recruited patients at the day treatment program for depression at the Department of Psychiatry and Psychotherapy, University of Lübeck, Germany, who followed an 8-week treatment of individualized and group therapy (consisting of CBASP or MCT mainly) between January 2019 and March 2020. The present study was conducted in accordance with the Declaration of Helsinki. Approval was received by the ethics committee of the University of Lübeck (ref. 17-049) and registered by German Clinical Trials Register (ref. DRKS00023779).

Participants

All patients admitted to the day clinic program for depression were asked to participate in the study. Almost all patients were suffering from a current depressive episode as defined by diagnostic criteria in DSM-V. Inclusion criteria were a minimum age of 18 years as well as an adequate understanding of the German language. To avoid carryover effects from previous admissions, we included only patients who have not been admitted to the treatment program within the last 12 months. Exclusion criteria for the day treatment program included acute suicidality, a history of substance use disorder, schizophrenia, delusional disorder, or bipolar disorder as well as an acute somatic illness that requires urgent treatment. Patients could only be admitted to the day clinic program if their therapist confirmed that they did not meet any of these exclusion criteria. Following the pragmatic nature of our study, we did not exclude patients from this study if they were found to meet exclusion criteria upon admission to the treatment program as long as it was clinically justifiable to treat the patient in the day clinic program. Patients did not receive any financial compensation, and all participants signed written informed consent. For an overview of the recruitment and the dropout rate, please refer to the study flowchart (**Figure 1**). Patients were labeled as "dropout" if they prematurely ended treatment, withdrew consent to participate in the study, or had more than 20% of missing data on the questionnaires even after repeated prompting/support to complete them.

Intervention

All patients in the day clinic program receive intensive psychotherapy, mainly CBASP or MCT. This includes one weekly session of individual therapy by psychotherapists and three weekly sessions of group therapy by a multidisciplinary team including nurses, occupational therapists, and psychotherapists. Psychotherapists in both modalities (CBASP and MCT) were physicians in training for psychiatrist and psychotherapist, psychologists in psychotherapy training, and psychological psychotherapists. All therapists received training in both methods (CBASP and MCT) through training certified training sites. Team trainings, biweekly team supervision, and weekly supervision for therapists were mandatory. In addition, most patients received psychopharmacological treatment according to the German guidelines for depression (31); took part in occupational therapy, physical therapy, and group mindfulness exercises; and received weekly sessions with nurse specialists.

The selection of the treatment modality followed a shared-decision model and rested on three factors: diagnosis (persistent vs. episodic depression), presenting complaint (interactional problems vs. worry and rumination), and patient preference. In general, patients with persistent depressive disorder and/or primary interpersonal problems were offered CBASP while patients with major depressive disorder, anxiety disorder, or obsessive-compulsive disorder and/or primary problems of worry and rumination were offered MCT.

CBASP usually consisted of the following elements: significant other history, transference hypothesis, situational analyses during group therapy, individual therapy, and therapy administered by nurse specialists. Individual therapy included contingent personal responsivity and interpersonal discrimination exercises during individual therapy. In CBASP, therapy aims to help the patient improve his/her interpersonal skills as chronically depressed patients often have difficulties recognizing the effect their behavior has on others. Typical statements of CBASP patients in the beginning of a therapy include: "People always reject me" or "No matter what I do, I cannot change anything" (28). Improvement mainly is gained with the help of "situational analysis," a specific tool that helps the patient to differentiate between the actual and a desired outcome in an interpersonal situation. In addition, CBASP is using techniques of disciplined personal involvement (DPI) that address occurring interpersonal situations between the therapist and the patient and include the disclosure of the therapists' positive and negative emotions triggered by the patient. These techniques help the patient to understand and experience the effect of his/her behaviors.

MCT usually consisted of case formulation, MCT group therapy, and the following techniques that were introduced

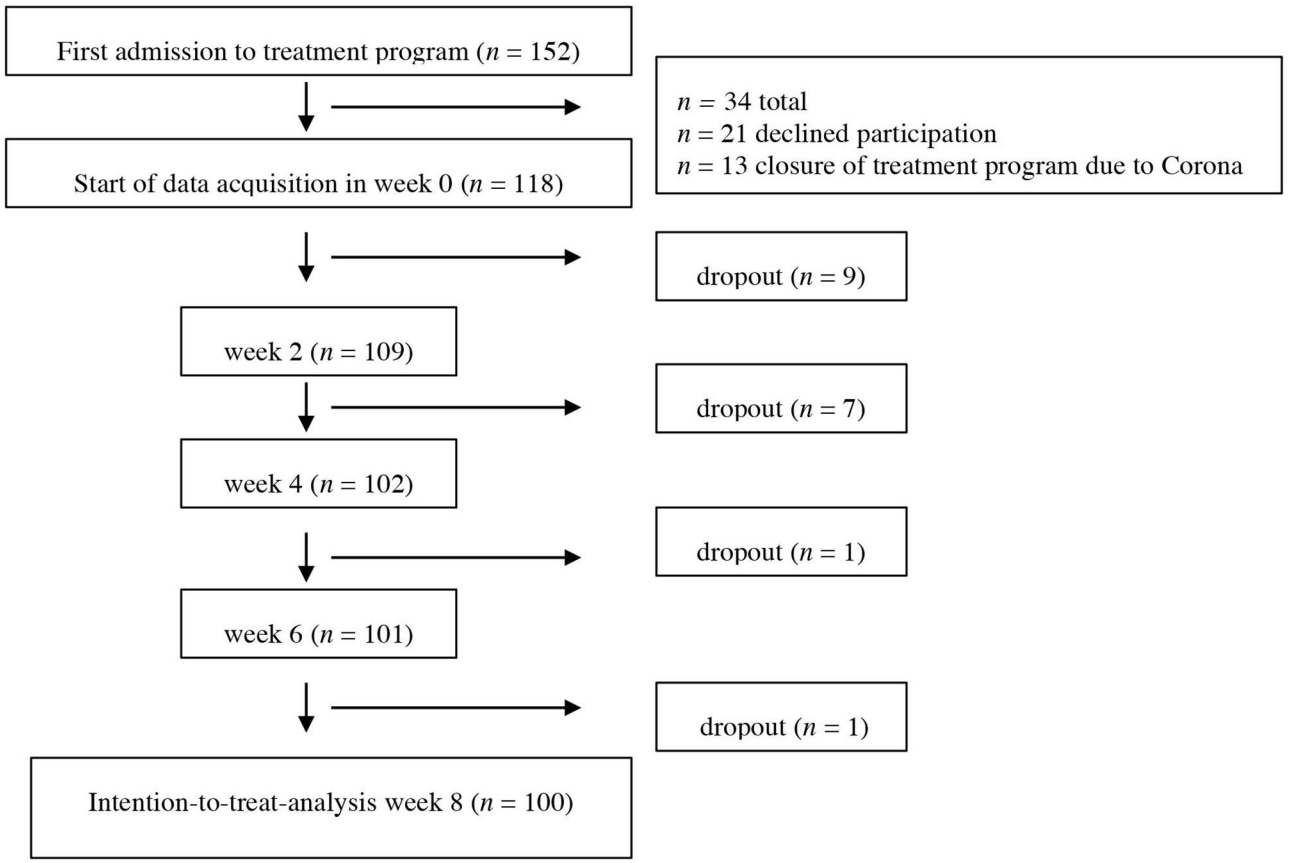


FIGURE 1 | Flowchart of participants. Dropout is referring to cases that were missing data (more than 20% or missing all data points needed for analyses).

in individual therapy and reinforced in therapy administered by nurse specialists: attention training technique, detached mindfulness, and worry/rumination postponement. The focus of MCT is on the development of metacognitive skills that help to prevent reoccurring worry and rumination. Typical statements of MCT patients before treatment include: "Worrying helps me to be prepared for future events." or "I cannot control/stop the process of rumination" (30). Techniques applied include worry/rumination postponement, modifying negative and positive metacognitive beliefs, and attention training techniques.

Assessments

During the course of treatment, patients completed various measures including the Quick Inventory of Depressive Symptomatology—Self Report (32) and the CDQ in the form of paper-pencil. The CDQ was collected in weeks 2, 4, 6, and 8. The QIDS-SR was filled out on a weekly basis from week 0 to week 8.

CDQ

To measure the level of care dependency, we used the revised 18-items questionnaire of Geurtzen et al. (21). The CDQ is a self-assessment questionnaire that asks the patient about his experienced degree of reliance on the therapist. In the present study, experiences as measured in the CDQ were always referring to the therapist of the individual therapy sessions even though patients had experiences with other therapists, for example in group therapies, as well. It consists of three unidimensional subscales, namely, "lack of perceived alternatives," "submissive dependency," and "need for contact." All have been shown to have moderate internal consistency as indicated by Cronbach's alpha, 0.77 on average over the different time points measured. Scores of the subscales can be combined in a total scale (0.87 on average) for an encompassing assessment of perceived dependency. The total scale represents the mean of the three subscales. Items are rated on a seven-point Likert scale ranging from 1 (completely disagree) to 7 (fully agree). The instrument was translated to the German language by three experienced clinicians, following the forward–backward method (33) which is most commonly used (34). The reliability analysis based on the current dataset showed good to very good internal consistency for all subscales. Using the scores for week 2, Cronbach's alpha for "lack of perceived alternatives" was 0.76, "submissive dependency" was 0.70, and "need for contact" was 0.85. Also, for week 4, week 6, and week 8, Cronbach's alpha showed good to very good values, ranging from 0.76 to 0.82 for "lack of perceived alternatives," 0.86 to 0.89 for "need for contact," and 0.74 to 0.82 for "submissive dependency."

Quick Inventory of Depressive Symptomatology—Self Report (QIDS-SR16)

To measure the severity of depressive symptoms over the course of treatment, we used the German version of the QIDS-SR which has shown acceptable internal consistency (Cronbach's alpha = 0.77) and a high correlation with the Beck Depressive Inventory II (BDI-II), $r = 0.81$ (35). It comprises 16 questions assessing depressive symptoms experienced during the last 7 days. Patients' score can vary between 0 and 27, with a higher score indicating a higher degree of symptom severity.

Statistical Analyses

Statistical analyses were conducted using SPSS (IBM SPSS Statistics for Mac, version 21.0). All statistical tests were two-tailed tests with significance levels set at $p \leq 0.05$. Pre–post effect size estimates were calculated by dividing the difference between the groups to compare by the pooled standard deviation of the two groups. Effect size measures will be interpreted as $d = 0.2$ indicating a small effect, $d = 0.5$ indicating a medium effect, and $d = 0.8$ indicating a large effect (36). Analyses were conducted using the intention-to-treat sample (ITT), which included all participants with complete baseline data irrespective of protocol deviations (e.g., meeting exclusion criteria such as current substance use disorder or history of bipolar disorder). For this analysis, individual missing values in the CDQ were replaced using the individual participant mean for the respective subscale if the number of missing items did not exceed 20% (37). Missing sum scores of the QIDS-SR and CDQ (ranging from 3 to 19%) were replaced using the mean of the posterior distribution from the fully conditional specification method obtained by iterative Markov Chain Monte Carlo estimation (38) using 10 imputations per missing value. Single cases that were missing more than 20% of data or missing complete CDQ and QIDS data were declared as dropouts and not considered in ITT (see first part of flowchart, **Figure 1**). Analyses to investigate differences in experienced care dependency between the two treatments included 41 patients in the CBASP group and 55 patients in the MCT group (four patients were excluded for this analysis as they received individualized Cognitive Behavioral Therapy). In order to control for the effect of repeated measures data, linear mixed models (LMM) were used. Subject ID was included as a random factor in all analyses.

Main Analyses: Associations of Depression and Care Dependency

For the first hypothesis (higher CDQ is associated with less favorable outcome), we ran a first model with the QIDS as dependent variable. The four different time points of the CDQ (week 2, week 4, week 6, and week 8) were used as a time-variant covariate while the received concept (CBASP vs. MCT) was used as a time-invariant covariate. Thus, the CDQ served as level 1 unit (within-subject) and the type of treatment as level 2 unit (between-subject). Additionally, we controlled for the baseline score of the QIDS.

Secondary Analyses: Development of Care Dependency and Its Relation to Type of Treatment

For the second (change of CDQ score during treatment) and third hypotheses (influence of the treatment concept on CDQ change), a second model was run with the CDQ scores as dependent variable. We used four different time points of the QIDS score as time-variant covariate while the therapeutic concept again was used as time-invariant covariate. In this model, the QIDS score served as level 1 unit (within-subject) and the treatment type as level 2 unit (between-subject). Here, we controlled for the baseline score of the CDQ. Each of the two models was run four times: one with the CDQ total score and one each for all of the three CDQ subscales.

Sensitivity Analyses

We also calculated the following sensitivity analyses. For the per protocol analysis, we included only participants who met all the inclusion and exclusion criteria. Thus, we excluded 12 participants due to a known history of substance use disorder, bipolar disorder, or delusional disorder. For a separate analysis that was aimed at increasing statistical power, we used a combined dataset which consists of the current dataset and an older dataset in the same treatment program ($n = 75$, 55% female, mean age 41.54 (SD = 14.22), ranging from 19 to 64 years. This older data set was recruited between May 2017 and March 2018 using the same in- and exclusion procedures, following the same diagnostic procedure, the same interventions, and the same assessments with two exceptions: the treatment duration was only 6 weeks, and the CDQ was collected in weeks 2 and 6 only. Accordingly, this analysis encompassed two instead of four measured observation times with regard to the CDQ (week 2 and week 6). The final dataset encompassed data of 175 individuals (48% female), mean age 41.43 (SD = 13.53), ranging from 18 to 68 years.

RESULTS

Main Sample Characteristics

Analysis is based on the data of 100 individuals. Patients were between 18 and 68 years old ($M = 41.3$, $SD = 13$). About 43% were female, 54% were employed, and about 25% were living together in a relationship. Ninety-six percent of the patients were suffering from a current depressive episode, while half of them suffered from a persistent depressive disorder (longer than 2 years with at least some of depressive symptoms). Almost 60% described an early onset (<21 years). A total of 81% received psychotropic medication; of these, more than one-third was treated with selective serotonin reuptake inhibitors (SSRIs). For a detailed description of demographical and clinical characteristics (see **Table 1**). The development of depressive symptomatology during treatment is found in **Figure 2**. With regard to the efficacy of treatments, an ANCOVA was calculated to reveal possible differences between the two types of treatments. The results showed no significant differences in the efficacy of treatments when controlling for the QIDS baseline score, $F_{(1,94)} = 2.78$, $p = 0.10$, $\eta_p^2 = 0.03$. The symptomatic change as indicated by

TABLE 1 | Clinical characteristics and demographics.

	All		CBASP		MCT		
	n = 100		*n* = 41		*n* = 55		
Clinical characteristics	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Test statistic U**
Age	41.34	13.05	38.12	12.91	43.39	12.97	861.00
Severity of QIDS-SR 16 week 0	14.41	5.30	15.15	4.86	13.92	5.22	1108.00
Number of depressive episodes	3.36	1.49	7.34	6.75	8.49	15.21	914.00
	***N*/%**		***N***	**%**	***N***	**%**	**Test statistic χ^2**
Diagnoses							
PDD							
Persistent depressive episode with intermittent depressive episodes, with current episode	45		23	56.1	21	38.2	4.73
Recurrent depressive episode with current depressive episode	46		13	31.7	32	58.2	8.37*
First depressive episode	4		3	1.6	0	0	14.57*
Other	5		2	4.9	2	3.6	8.84*
Early onset of depression (before age of 21)	57		31	75.6	22	40	13.61*
Medication	81		33	81	44	80	0.98
SSRI	36		16	39	18	32.7	
Combination of AD	12		3	7.3	8	14.5	
Lithium or antipsychotic augmentation	13		4	9.8	9	16.3	
Demographics	***N*/%**		***N***	**%**	***N***	**%**	**Test statistic χ^2**
Female gender	43		18	43.9	23	41.8	0.26
Marital status							10.52
Married	33		9	22	24	43.6	
Single	52		23	56.1	26	47.3	
Divorced	15		9	22	5	9.1	
Language							9.04
German	93		36	87.8	53	96.4	
Other	7		5	12.2	2	3.6	
School education							5.53
Lower	30		11	26.8	15	27.3	
Middle	32		15	36.5	18	32.7	
Higher	16		7	17.1	8	14.5	
Highest	21		8	19.5	13	23.6	
No diploma	1		0	0	1	1.8	
Employment status							7.03
Full-time	28		11	26.8	15	27.3	
Part-time	18		5	12.2	12	21.8	
Marginally	8		5	12.2	3	5.5	
Not employed	46		20	48.8	25	45.5	

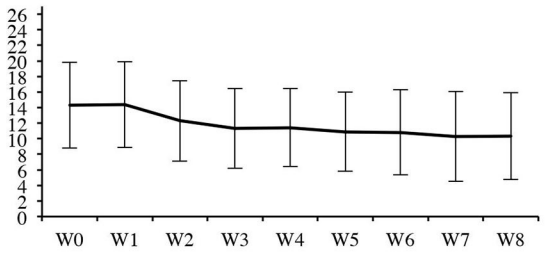
CBASP, cognitive behavioral analysis of psychotherapy; MCT, metacognitive therapy. Test statistics were computed to compare CBASP with MCT. $^*p < 0.05$.

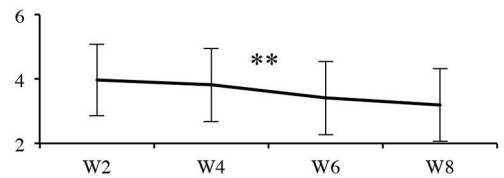
the QIDS change score was $M = 4.99$ ($SD = 5.69$) for CBASP and $M = 3.07$ ($SD = 5.29$) for MCT.

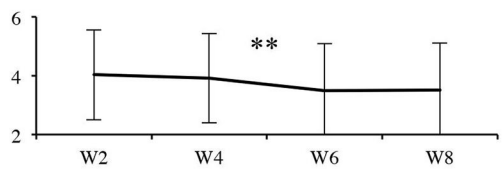
Main Analyses: Associations of Depression and Care Dependency

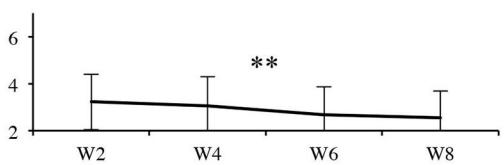
For the ITT, only one of the four examined subscales of the CDQ ("lack of perceived alternatives") was significantly associated with the development of depressive symptomatology over the course of treatment, $B = 0.44$, $SE = 0.21$, $p = 0.036$. Running the same analysis for the per protocol dataset, several subscales could be identified as significant predictors for depressive symptoms: "lack of perceived alternatives" with $B = 0.58$, $SE = 0.23$, $p = 0.010$, "need for contact" with $B = 0.38$, $SE = 0.16$, $p = 0.021$, and the total score with $B = 0.49$, $SE = 22$, $p = 0.031$. Only the subscale "submissive dependency" did not reach a statistical significant level, $p > 0.05$. Running the mixed-model analysis for the combined dataset, we identified two of the three subscales as well as the total scale as potential predictors for depressive symptomatology at the end of treatment with "lack of perceived alternatives," $B = 0.61$, $SE = 0.19$, $p = 0.002$, "need for contact,"

Variables	Mean	SD	*t*	*d*
QIDS-SR				
Week 0	14.30	5.38		
Week 1	14.36	5.01		
Week 2	12.29	5.14		
Week 3	11.31	5.12		
Week 4	11.43	5.02		
Week 5	10.90	5.03		
Week 6	10.80	5.29		
Week 7	10.28	5.47		
Week 8	10.36	5.60		
Difference	3.94	5.33	7.39**	.72
CDQ				
Lack of perceived alternatives				
Week 2	3.97	1.11		
Week 4	3.82	1.12		
Week 6	3.41	1.14		
Week 8	3.19	1.12		
Difference	.78	1.07	7.63**	.70
Need for contact				
Week 2	4.03	1.53		
Week 4	3.91	1.52		
Week 6	3.49	1.61		
Week 8	3.52	1.60		
Difference	.51	1.36	3.72**	.33
Submissive Dependency				
Week 2	3.22	1.18		
Week 4	3.05	1.24		
Week 6	2.67	1.19		
Week 8	2.54	1.11		
Difference	.68	1.17	5.94**	.59
Total score				
Week 2	3.74	1.11		
Week 4	3.59	1.14		
Week 6	3.19	1.12		
Week 8	3.08	1.09		
Difference	.66	.99	6.96**	.60









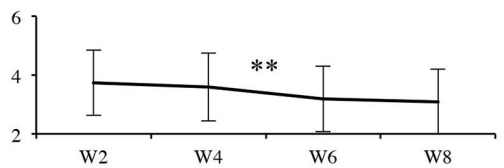


FIGURE 2 | Results of secondary analyses. Development of depressive symptoms and care dependency. QIDS-SR, quick inventory of depressive symptomatology, short form; CDQ, care dependency questionnaire, effect sizes *d* were calculated for pre-post differences. *$p < 0.05$, **$p < 0.001$.

$B = 0.45$, $SE = 0.14$, $p = 0.001$, "submissive dependency," $B = 0.34$, $SE = 0.17$, $p = 0.043$, and the total score, $B = 0.62$, $SE = 0.19$, $p = 0.001$. For a detailed overview of all results of the different analyses for all subscales (please see **Table 2**).

Secondary Analyses: Development of Care Dependency and Its Relation to Type of Treatment

The LMM revealed a significant time effect for all CDQ subscales as well as the CDQ total scale, all $p < 0.001$. More precisely, *post-hoc* t-tests showed a decrease in the following subscales: lack of perceived alternatives, $t_{(99)} = 7.63$, $p = 0.000$, $d = 0.70$ (95% CI: 0.57–0.99), need for contact $t_{(99)} = 3.72$, $p = 0.000$, $d = 0.33$ (95% CI: 0.33–0.79) and submissive dependency $t_{(99)} = 5.94$, $p = 0.000$, $d = 0.59$ (95% CI: 0.44–0.91) as well as the total scale $t_{(99)} = 6.96$, $p = 0.000$, $d = 0.60$, (95% CI: 0.46–0.88). A detailed overview of the results is found in **Figure 2**. This effect was also found for the per protocol analysis and the combined dataset. The LMM

TABLE 2 | Results of multilevel-model main analysis.

Dataset	Value	SE	*t*	*p*
ITT (*n* = 100)				
Lack of perceived alternatives	0.44	0.21	2.11	0.036*
Need for contact	0.27	0.15	1.81	0.071
Submissive dependence	0.16	0.18	0.89	0.376
Total score	0.38	0.21	1.84	0.066
PP (*n* = 88)				
Lack of perceived alternatives	0.57	0.22	2.58	0.010*
Need for contact	0.38	0.16	2.31	0.021*
Submissive dependence	0.14	0.19	0.76	0.446
Total score	0.48	0.22	2.17	0.031*
Combined dataset (*n* = 175)				
Lack of perceived alternatives	0.61	0.19	3.15	0.002**
Need for contact	0.45	0.14	3.23	0.001**
Submissive dependence	0.34	0.17	2.03	0.043*
Total score	0.62	0.29	3.25	0.001**

*CDQ scores as predictors for depressive symptomatology at the end of treatment. ITT, intention-to-treat analysis; PP, per protocol; SE, standard deviation. *$p < 0.05$, **$p \leq 0.001$.*

did not show any significant differences in care dependency between the two types of treatments for the different subscales, $p > 0.05$. These results were found for all datasets (ITT, PP, combined dataset).

DISCUSSION

Summary of Results

The present study gives a first insight on different aspects of the specific construct of care dependency in a group of depressed patients with regard to its possible positive or negative impact on symptom severity, the development of care dependency over the course of treatment, and whether the degree of experienced care dependency differs between two quite distinct therapeutic concepts in the treatment of depression, namely, CBASP and MCT. The results suggest that a higher degree of care dependency at the beginning of treatment might be associated with a less favorable treatment outcome. The degree of experienced care dependency decreased over the course of time while there were no differences in care dependency with regard to the two different therapeutic concepts.

In the main analysis, we found indicators of an association between care dependency and outcome when following the ITT and per protocol analysis approach. More precisely, for the ITT, the subscale "lack of perceived alternatives" appeared to be a possible predictor for the development of depressive symptoms. When excluding patients with a known history of substance use disorder, bipolar disorder, or delusional disorder in the per protocol analysis, additionally the subscales "need for contact" as well as the total scale of the CDQ reached statistical significance, possibly owing to the more homogenous sample. Due to the relatively small datasets, we combined the current dataset of this study with the dataset of an earlier iteration of the study. In this analysis, we found all the subscales to be associated with the development of depressive symptoms. Since these results only emerged on the sensitivity analyses, this needs to be confirmed in future studies.

Investigating the course of care dependency showed a clear picture for all subscales across all datasets, indicating that care dependency seems to be dynamic construct that is reducing over time. The degree of experienced care dependency seems to be independent from the received type of therapeutic treatment.

Comparison to Existing Studies

In general, studies investigating adverse effects of psychotherapy are rare (6, 7, 9). Furthermore, as mentioned before, the incoherent picture of definitions that are used (e.g., side effects, negative effects, adverse events), and the numerous ways how they are reported, is impeding the comparison to earlier studies. As far as we know, we were the first to investigate the specific construct of care dependency over time in a clinical sample of moderately depressed patients as indicated by the Quick Inventory of Depressive Symptoms.

Care Dependency as a Predictor for Symptomatic Development in Depressed Patients

Taking the results of the main analysis into consideration, we found hints that aspects of care dependency might serve as potential predictors with regard to the development of depressive symptoms. These results were detected partly in the ITT and the PP and across all subscales and the total scale in the combined data analysis. For all analyses across all datasets, we found a positive direction of effects, which allows the assumption that a higher degree of experienced care dependency is associated with a higher degree of depressive symptomatology at the end of treatment. These findings are in line with results from the first study operating the CDQ by Geurtzen et al. (21) who found a higher degree of care dependency to be associated

with a higher degree of symptom severity in a large cross-sectional sample of 742 outpatients with different psychiatric disorders. The negative potential of experienced dependency was also discussed and taken into consideration before (19, 20, 39, 40). However, another study from Geurtzen et al. (23) could not find the negative association with symptom development in a sample of students receiving clinical training. As the same authors mentioned, the different findings may be due to the different characteristics of the samples, patients vs. students. In sum, the question whether dependency as measured by the CDQ is beneficial for treatment outcome or not should be subject to future studies that further investigate this question in larger samples to give a better understanding of the complex construct of care dependency.

Development of Care Dependency

At the beginning of treatment, patients' medium answer to the CDQ items was in between "slightly disagree" (3) and "neutral" (4). This observation is close to what has been shown by the Dutch colleagues in their first CDQ study with a mixed patient sample (21), but stronger than what has been found by the same colleagues when running the study with students in clinical training for CBT (23), who scored around 2, "strongly disagree." The differences might reflect the extent of symptom severity as well as the increased despair and the need for psychological treatment in the clinical samples. With regard to the development over time, we found a continuous decrease of care dependency over the treatment from week 2 to week 8 in all the subscales as well as the total scale. Again, studies to compare the development of adverse effects or even care dependency are scarcely available. However, the results support the view that care dependency differs from a personality trait, which is assumed to be a rather stable construct (2). Precisely, care dependency could be "elicited or reinforced by creating a specific therapeutic context" [(23), p. 10]. The researchers found no relation between dependency as a trait and care dependency.

What remains unclear is the question what actually influences the reduction of experienced feelings of care dependency. Thinking about possible factors that may influence feelings of dependency, the construct of self-efficacy inevitable comes up. Self-efficacy is defined as "people's beliefs about their capabilities to produce designated levels of performance that exercise influence over events that affect their lives" [(41), p. 71]. It can be assumed that a stronger belief of self-efficacy could reduce the feelings of dependency. The important role of self-efficacy for treatment outcome in depression has already been discussed in the late 90s (42). The authors assumed the self-efficacy theory of depression to be an additional model next to the prominent hopelessness model and Beck's cognitive model at these times in the explanation and understanding of depression. Various studies were able to show the influence of self-efficacy for a variety of somatic and psychological diseases, such as substance use disorders (43, 44), chronic low back pain (45), human immunodeficiency virus (46), posttraumatic stress disorder (47), and depression (47–51). In these studies, researchers found that self-efficacy is strongly associated or influencing the development of depressive symptoms.

When it comes to the distinct relationship between dependency and self-efficacy, the number of available studies is limited. However, Iancu et al. (52) investigated a small sample of patients suffering from social anxiety disorder and found that the social anxiety sore correlated negatively with self-efficacy and positively with dependency. This study indicates lower rates of self-efficacy and higher rates of dependency to be associated with a higher symptom severity. These results support the view that there might be a relationship between self-efficacy and dependency as well. Certainly, future studies are needed to investigate the relationship between care dependency and self-efficacy. However, it becomes clear that *if* care dependency is affecting the treatment outcome in a negative way, it should be examined which factors might influence feelings of dependency so that these can be worked on or in case of self-efficacy reinforced.

However, besides changes in self-efficacy as an internal variable that might influence feelings of dependency, one should further take external factors into consideration, too. For example, it is without doubt that psychopharmacological treatment can induce emotional and behavioral effects in patients (53, 54). These effects can be various and include feeling emotionally numb and caring less about others (55). In the recent study, about four-fifths (81%) were treated with antidepressant medication. Due to the small number of those without medication, we did not compare the two groups. However, future studies should investigate whether medication might exert an influence on care dependency. Additionally, other external variables should be taken into consideration in future studies. For example, the patients in this study received individual as well as group therapy. Even though the patient is completing the CDQ with regard to the main therapist, the question of influences of interactions with accompanying group therapists arises. So far, it is unclear if these affected the levels of care dependency toward the main therapist. It would be desirable to study care dependency in outpatient settings in particular as the possible influence of other confounding factors might be reduced and thus the specific aspects of care dependency may become more visible.

Secondary Analyses: Care Dependency and Its Relation to Type of Treatment

To our knowledge, there are no other studies that investigated whether care dependency differs with regard to the received treatment. Our results show that there is no difference between the two treatment groups. This could be due to a lack of statistical power and should be reinvestigated in a larger sample. Results from Klein et al. (56) indicate that CBASP is associated with a stronger therapeutic alliance compared to supportive psychotherapy. Adding the results from the Dutch colleagues (21, 23), who found a stronger therapeutic alliance to be associated with higher levels of dependency, a higher degree of experienced dependency might be reflected in CBASP compared to Supportive Psychotherapy. However, we have no

information on MCT in this regard and the comparability is very limited at this point. Also, the fact that patients shared a notable amount of therapies besides the individual therapy and that these experiences possibly exerted an influence on the therapeutic experience, might have reduced differences between CBASP and MCT. Future studies that investigate outpatient settings, which are less sensitive to confounding variables such as other shared therapies or relationship building with other patients, could shed more light on this matter. Additionally, when interpreting our results with regard to the chosen treatment type, the question arises whether there might have been differences between the patients that we did not take into consideration, such as distinct personality traits. Future studies should investigate possible differences between treatment groups before and control for these in their statistical analyses. Furthermore, there appeared some significant differences with regard to the characteristics of the depressive symptomatology. More precisely, patients with an early beginning of depression were found more often in the CBASP group than in the MCT arm. It is questionable whether this difference plays a crucial role with regard to the development of care dependency. However, the fact that care dependency levels seem to be unaffected from the type of treatment could also suggest the idea that care dependency is a construct that is independent from the therapists' behavior. This should be investigated in future studies.

Strengths and Limitations

Regarding the strengths of the study, to our knowledge, we were the first to investigate care dependency in a longitudinal study design in a clinical setting over four points in time, to explore its relation to depressive symptoms, and to explore differences in experienced care dependency in two main treatments for depression, CBASP and MCT. According to Leichsenring (57), important aspects in order to increase the ecological validity are an observational design, a dropout analysis, and pretreatment assessment. These criteria have been met. Furthermore, the study represents the reality of psychotherapeutic treatments. Another strength that should be mentioned is the high representativity of sociodemographic data in this naturalistic study, as we find an almost equal division of male and female participants, a wide range of school education, and a high number of employed people in full or part time (46%) which results in a good comparability with general population data. These characteristics support the generalizability of the findings in this study to real-world clinical settings and are comparable to general population data (58).

Still there are some limitations that require attention when interpreting our results. First of all, sample size calculation was based on estimates and issues with regard to the naturalistic design of the study, including the given fact that possible admissions to the study depend on external factors such as the available treatment capacities. However, the study is lacking an adequate sample size calculation. For our main analysis, we were imputing up to 19% of missing data. Even though we followed the recommendation of Downey and King (37), this is a strong interference in our dataset that may lead to a loss of statistical power. This interference might have been reflected in the different outcomes of our analyses. We tried to reduce this possible bias with the help of sensitivity analyses. In sum, generalizability of our findings is limited at this point in time and needs further investigation.

When investigating the development of care dependency, we did not take any other variables, such as self-efficacy, into consideration. This would have been helpful to understand the mechanism of the development and course of care dependency better. With respect to the comparison between MCT and CBASP, it has to be mentioned that the presented groups were rather small, which is a limiting factor when comparing groups. Additionally, patients were assigned to one group or the other depending on their diagnosis, the presented complains and patients' preferences. This may enhance the risk of confounding variables affecting our results (59). Even though we could not identify any problematic consequences of the chosen group allocation, future studies should focus on randomized controlled trials to reduce the potential of confounding effects. Allocating patients in a randomized way also could help to control for unobserved differences, e.g., differences with regard to the personality of the patients. In the current study, we did not control for personality variables that in turn might affect care dependency as well.

In sum, we investigated the complex construct of care dependency. We consciously took possible different aspects of care dependency into consideration as the systematic investigation of this specific construct is relatively new and the available literature appears to be very limited. Our data suggest that care dependency might play a crucial role as a predictor for symptomatic change, declines over the course of treatment but does not seem to be affected by two distinct therapeutic strategies, CBASP vs. MCT. Future research should focus on investigating care dependency as a possible predictor in randomized controlled studies.

CONCLUSION

The results suggest that care dependency might negatively affect outcome in patients with depression. In general, care dependency seems to be a dynamic construct, as it is changing over time, while the levels of care dependency seem to be independent from the received type of treatment. Future research should continue investigating the mechanisms of care dependency in a randomized design to understand its potential benefits and harms for treatment outcome, to identify possible variables that influence the degree of reported care dependency and finally, to increase generalizability of the results.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

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

AUTHOR CONTRIBUTIONS

Conception and design: JK with support from SG. Analysis of data: SG with support from SS and JK. Interpretation of data: SG and JK with support from EF. Drafting of manuscript: SG. All authors made substantial contribution to the manuscript and gave approval to the final version before submission.

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REFERENCES

1. Bowlby J. *A Secure Base*. New York, NY: Basic Books (1988).
2. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders (DSM-5®)*. American Psychiatric Publishing (2013). doi: 10.1176/appi.books.9780890425596
3. Horvath AO, Del Re AC, Flückiger C, Symonds D. Alliance in individual psychotherapy. *Psychotherapy*. (2011) 48:9–16. doi: 10.1037/a0022186
4. Lambert MJ, Barley DE. Research summary on the therapeutic relationship and psychotherapy outcome. *Psychotherapy*. (2001) 38:357–61. doi: 10.1037/0033-3204.38.4.357
5. Rozental A, Boettcher J, Andersson G, Schmidt B, Carlbring P. Negative effects of internet interventions: a qualitative content analysis of patients' experiences with treatments delivered online. *Cogn Behav Ther*. (2015) 44:223–36. doi: 10.1080/16506073.2015.1008033
6. Jonsson U, Alaie I, Parling T, Arnberg FK. Reporting of harms in randomized controlled trials of psychological interventions for mental and behavioral disorders: a review of current practice. *Contemp Clin Trials*. (2014) 38:1–8. doi: 10.1016/j.cct.2014.02.005
7. Meister R, von Wolff A, Mohr H, Nestoriuc Y, Härter M, Hölzel L, et al. Adverse event methods were heterogeneous and insufficiently reported in randomized trials on persistent depressive disorder. *J Clin Epidemiol*. (2016) 71:97–108. doi: 10.1016/j.jclinepi.2015.10.007
8. Bystedt S, Rozental A, Andersson G, Boettcher J, Carlbring P. Clinicians' perspectives on negative effects of psychological treatments. *Cogn Behav Ther*. (2014) 43:319–31. doi: 10.1080/16506073.2014.939593
9. Cuijpers P, Reijnders M, Karyotaki E, de Wit L, Ebert DD. Negative effects of psychotherapies for adult depression: a meta-analysis of deterioration rates. *J Affect Disord*. (2018) 239:138–45. doi: 10.1016/j.jad.2018.05.050
10. Hoffmann SO, Rudolf G, Strauß B. Unerwünschte und schädliche Wirkungen von Psychotherapie. *Psychotherapeut*. (2008) 53:4–16. doi: 10.1007/s00278-007-0578-2
11. Märtens M. Misserfolge und misserfolgsforschung in der psychotherapie. *Psychother Dialog*. (2005) 6:145–9. doi: 10.1055/s-2004-834767
12. Herzog P, Lauff S, Rief W, Brakemeier EL. Assessing the unwanted: a systematic review of instruments used to assess negative effects of psychotherapy. *Brain Behav*. (2019) 9:1–13. doi: 10.1002/brb3.1447
13. Linden M. How to define, find and classify side effects in psychotherapy: from unwanted events to adverse treatment reactions. *Clin Psychol Psychother*. (2013) 20:286–96. doi: 10.1002/cpp.1765
14. Bornstein RF, Bowen RF. Dependency in psychotherapy: toward an integrated treatment approach. *Psychotherapy*. (1995) 32:520–34. doi: 10.1037/0033-3204.32.4.520
15. O'Neill RM, Bornstein RF. Orality and depression in psychiatric inpatients. *J Pers Disord*. (1991) 5:1–7. doi: 10.1521/pedi.1991.5.1.1
16. Bornstein RF, Greenberg RP. Dependency and eating disorders in female psychiatric inpatients. *J Nerv Ment Dis*. (1991) 179:148–52. doi: 10.1097/00005053-199103000-00006
17. Hayward C, King R. Somatization and personality disorder traits in nonclinical volunteers. *J Pers Disord*. (1990) 4:402–6. doi: 10.1521/pedi.1990.4.4.402
18. Reich J, Noyes R, Troughton E. Dependent personality disorder associated with phobic avoidance in patients with panic disorder. *Am J Psychiatry*. (1987) 144:323–6. doi: 10.1176/ajp.144.3.323
19. Leitner A, Märtens M, Koschier A, Gerlich K, Liegl G, Hinterwallner H, et al. Patients' perceptions of risky developments during psychotherapy. *Psychother Psychosom*. (2013) 43:95–105. doi: 10.1007/s10879-012-9215-7
20. Parker G, Fletcher K, Berk M, Paterson A. Development of a measure quantifying adverse psychotherapeutic ingredients: the experiences of therapy questionnaire (ETQ). *Psychiatry Res*. (2013) 206:293–301. doi: 10.1016/j.psychres.2012.11.026
21. Geurtzen N, Keijsers GPJ, Karremans JC, Hutschemaekers GJM. Patients' care dependency in mental health care: development of a self-report questionnaire and preliminary correlates. *J Clin Psychol*. (2018) 74:1189–206. doi: 10.1002/jclp.22574
22. Clemens NA. Dependency on the psychotherapist. *J Psychiatr Pract*. (2010) 16:50–3. doi: 10.1097/01.pra.0000367778.34130.4a
23. Geurtzen N, Keijsers GPJ, Karremans JC, Hutschemaekers GJM. Care dependency may help and hurt psychological treatment: a treatment-analogue study with students in clinical training. *J Psychother Integr*. (2019) 29:374–88. doi: 10.1037/int0000150
24. Flückiger C, Del AC, Wampold BE, Horvath AO. The alliance in adult psychotherapy: a meta-analytic synthesis. *Psychotherapy*. (2018) 55:316–40. doi: 10.1037/pst0000172
25. Schneibel R, Wilbertz G, Scholz C, Becker M, Brakemeier EL, Bschor T, et al. Adverse events of group psychotherapy in the in-patient setting - results of a naturalistic trial. *Acta Psychiatr Scand*. (2017) 136:247–58. doi: 10.1111/acps.12747
26. Linden M, Walter M, Fitz K, Muschalla B. Unerwünschte therapiewirkungen bei verhaltenstherapeutischer gruppentherapie: häufigkeit und spektrum. *Nervenarzt*. (2015) 86:1371–82. doi: 10.1007/s00115-015-4297-6
27. Meister R, Lanio J, Fangmeier T, Härter M, Schramm E, Zobel I, et al. Adverse events during a disorder-specific psychotherapy compared to a nonspecific psychotherapy in patients with chronic depression. *J Clin Psychol*. (2020) 76:7–19. doi: 10.1002/jclp.22869
28. McCullough JP. Treatment for chronic depression using Cognitive Behavioral Analysis System of Psychotherapy (CBASP). *J Clin Psychol*. (2003) 59:833–46. doi: 10.1002/jclp.10176
29. Herzog P, Häusler S, Normann C, Brakemeier E-L. Negative effects of a multimodal inpatient CBASP program: rate of occurrence and their impact on treatment outcome in chronic and treatment-resistant depression. *Front Psychiatry*. (2021) 12:575837. doi: 10.3389/fpsyt.2021.575837

30. Wells A. *Metacognitive Therapy for Anxiety and Depression*. New York, NY: Guilford Press (2011).
31. Schneider F, Härter M, Schorr S. *S3-Leitlinie/Nationale VersorgungsLeitlinie Unipolare Depression*. Berlin: Springer-Verlag (2017).
32. Reilly TJ, MacGillivray SA, Reid IC, Cameron IM. Psychometric properties of the 16-item quick inventory of depressive symptomatology: a systematic review and meta-analysis. *J Psychiatr Res.* (2015) 60:132–40. doi: 10.1016/j.jpsychires.2014.09.008
33. Beaton DE, Bombardier C, Guillemin F, Ferraz MB. Guidelines for the process of cross-cultural adaptation of self-report measures. *Spine.* (2000) 25:3186–91. doi: 10.1097/00007632-200012150-00014
34. Acquadro C, Conway K, Hareendran A, Aaronson N. Literature review of methods to translate health-related quality of life questionnaires for use in multinational clinical trials. *Value Health.* (2008) 11:509–21. doi: 10.1111/j.1524-4733.2007.00292.x
35. Roniger A, Späth C, Schweiger U, Klein JP. A psychometric evaluation of the German version of the quick inventory of depressive symptomatology (QIDS-SR16) in outpatients with depression. *Fortschr Neurol Psychiatr.* (2015) 83:e17–22. doi: 10.1055/s-0041-110203
36. Cohen J. *Statistical Power Analysis for the Behavioral Sciences*. New York, NY: American Press (1988).
37. Downey RG, King CV. Missing data in likert ratings: A comparison of replacement methods. *J Gen Psychol.* (1998) 125:175–91. doi: 10.1080/00221309809595542
38. Van Buuren S. Multiple imputation of discrete and continuous data by fully conditional specification. *Stat Methods Med Res.* (2007) 16:219–42. doi: 10.1177/0962280206074463
39. Gunderson JG. The borderline patient's intolerance of aloneness: insecure attachments and therapist availability. *Am J Psychiatry.* (1996) 153:752–8. doi: 10.1176/ajp.153.6.752
40. Modestin J. Counter-transference reactions contributing to completed suicide. *Br J Med Psychol.* (1987) 60:379–85. doi: 10.1111/j.2044-8341.1987.tb02757.x
41. Bandura A. Self-efficacy. *Encyclop Hum Behav.* (1994) 4:77–81.
42. Maddux JE, Meier LJ. Self-efficacy and depression. In: *Self-Efficacy, Adaptation, and Adjustment*. Boston, MA: Springer US (1995). p. 143–69. doi: 10.1007/978-1-4419-6868-5_5
43. DiClemente CC, Prochaska JO, Gibertini M. Self-efficacy and the stages of self-change of smoking. *Cognit Ther Res.* (1985) 9:181–200. doi: 10.1007/BF01204849
44. Kadden RM, Litt MD. The role of self-efficacy in the treatment of substance use disorders. *Addict Behav.* (2011) 36:1120–6. doi: 10.1016/j.addbeh.2011.07.032
45. Altmaier EM, Russell DW, Kao CF, Lehmann TR, Weinstein, James N. Role of self-efficacy in rehabilitation outcome among chronic low back pain patients. *J Couns Psychol.* (1993) 40:335–9.
46. Johnson MO, Neilands TB, Dilworth SE, Morin SF, Remien RH, Chesney MA. The role of self-efficacy in HIV treatment adherence: validation of the HIV Treatment Adherence Self-Efficacy Scale (HIV-ASES). *J Behav Med.* (2007) 30:359–70. doi: 10.1007/s10865-007-9118-3
47. Blackburn L, Owens GP. The effect of self efficacy and meaning in life on posttraumatic stress disorder and depression severity among veterans. *J Clin Psychol.* (2015) 71:219–28. doi: 10.1002/jclp.22133
48. Ehrenberg MF, Cox DN, Koopman RF. The relationship between self-efficacy and depression in adolescents. *Adolescence.* (1991) 26:361.
49. Klasen F, Otto C, Kriston L, Patalay P, Schlack R, Ravens-Sieberer U. Risk and protective factors for the development of depressive symptoms in children and adolescents: results of the longitudinal BELLA study. *Eur Child Adolesc Psychiatry.* (2015) 24:695–703. doi: 10.1007/s00787-014-0637-5
50. Muris P. Relationships between self-efficacy and symptoms of anxiety disorders and depression in a normal adolescent sample. *Pers Individ Dif.* (2002) 32:337–48. doi: 10.1016/S0191-8869(01)00027-7
51. Tahmassian K, Moghadam NJ. Relationship between self-efficacy and symptoms of anxiety, depression, worry and social avoidance in a normal sample of students. *Iran J Psychiatry Behav Sci.* (2011) 5:91–8.
52. Iancu I, Bodner E, Ben-Zion IZ. Self esteem, dependency, self-efficacy and self-criticism in social anxiety disorder. *Compr Psychiatry.* (2015) 58:165–71. doi: 10.1016/j.comppsych.2014.11.018
53. Goldsmith L, Moncrieff J. The psychoactive effects of antidepressants and their association with suicidality. *Curr Drug Saf.* (2012) 6:115–21. doi: 10.2174/157488611795684622
54. Hughes S, Lacasse J, Fuller RR, Spaulding-Givens J. Adverse effects and treatment satisfaction among online users of four antidepressants. *Psychiatry Res.* (2017) 255:78–86. doi: 10.1016/j.psychres.2017.05.021
55. Read J, Cartwright C, Gibson K. Adverse emotional and interpersonal effects reported by 1829 New Zealanders while taking antidepressants. *Psychiatry Res.* (2014) 216:67–73. doi: 10.1016/j.psychres.2014.01.042
56. Klein JP, Probst T, Kriston L, Assmann N, Bailer J, Eich H, et al. Changes in therapeutic alliance and in social inhibition as mediators of the effect of the cognitive behavioral analysis system of psychotherapy: a secondary analysis from a randomized clinical trial. *Psychother Psychosom.* (2020) 89:261–2. doi: 10.1159/000506082
57. Leichsenring F. Randomized controlled versus naturalistic studies: a new research agenda. *Bull Menninger Clin.* (2004) 68:137–51. doi: 10.1521/bumc.68.2.137.35952
58. Späth C, Hapke U, Maske U, Schröder J, Moritz S, Berger T, et al. Characteristics of participants in a randomized trial of an Internet intervention for depression (EVIDENT) in comparison to a national sample (DEGS1). *Intern Intervent.* (2017) 9:46–50. doi: 10.1016/j.invent.2017.05.003
59. Sterne JA, Hernán MA, McAleenan A, Reeves BC, Higgins JP. Assessing risk of bias in a non-randomized study. In: Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA, editors. *Cochrane Handbook for Systematic Reviews of Interventions.* 1st Edn. Chichester: Wiley (2019). p. 621–41. doi: 10.1002/9781119536604.ch25

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