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ORIGINAL PAPER

Negative symptoms, anxiety, and depression as mechanisms of change of a 12-month trial of assertive community treatment as part of integrated care in patients with first- and multi-episode schizophrenia spectrum disorders (ACCESS I trial)

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Abstract Assertive community treatment (ACT) has shown to be effective in improving both functional deficits and quality of life (QoL) in patients with severe mental illness. However, the mechanisms of this beneficial effect remained unclear. We examined mechanisms of change by testing potential mediators including two subdomains of negative symptoms, i.e. social amotivation as well as expressive negative symptoms, anxiety, and depression within a therapeutic ACT model (ACCESS I trial) in a sample of 120 first- and multi-episode patients with a schizophrenia spectrum disorder (DSM-IV). Path modelling served to test the postulated relationship between the respective treatment condition, i.e. 12-month ACT as part of integrated care versus standard care, and changes in functioning and QoL. The final path model resulted in 3 differential pathways that were all significant. Treatment-induced changes in social amotivation served as a starting point for all pathways, and had a direct beneficial effect on functioning and an additional indirect effect on it through changes in anxiety. Expressive negative symptoms were not related to functioning but served as a mediator between changes in social amotivation and depressive symptoms, which subsequently resulted in improvements in QoL. Our results suggest that social amotivation, expressive negative symptoms, depression, and anxiety functioned as mechanisms of change of ACCESS. An integrated and sequential treatment focusing on these mediators may optimise the generalisation effects on functioning as well as on QoL by targeting the most powerful mechanism of change that fits best to the individual patient.

Keywords Mediation · Amotivation · Quality of life · Functioning · Negative symptoms · Psychosis

Introduction

Patients with schizophrenia demonstrate severe deficits in psychosocial functioning (functioning), and report low quality of life (QoL) [1, 2]. These impairments can be present across all stages of the disorder [3, 4]. Studies demonstrated that functional recovery is predictive of a positive clinical course including remission of negative symptoms and disability [5, 6]. This underlines the importance of interventions that specifically target functional impairments early in the process.

Assertive community treatment (ACT) is a mental health service delivery model, in which long-term, high frequency contacts, shared and low caseload, and 24-h coverage are provided by multidisciplinary teams and mainly in the patient's natural environment [7]. Compared to standard care (SC), ACT has proven to be an effective intervention for patients with severe mental

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illness [8, 9]. An integrated care model including therapeutic ACT called ACCESS has been specifically designed for patients with schizophrenia spectrum disorders and evaluated in a controlled trial [10, 11]. This program produced significantly larger effects on functioning and QoL than SC. However, the mechanisms of change of this beneficial effect of ACCESS remained unclear. This requires moving beyond effectiveness analyses to the study of intervening variables (mediators) that account for the effect of a specific treatment, such as ACCESS, on the outcome of interest [12].

Generally, potential mediator variables need to be associated with both the predictor, i.e. the treatment condition (ACCESS vs. SC), and the outcome variable, i.e. functioning and QoL [13]. Anxiety, depression, and negative symptoms were identified as candidates for mediator variables for the following reasons. With regard to the predictor-mediator relationship, these variables are amenable to change by means of ACT compared to control conditions [8, 11]. With regard to the mediator-outcome relationship, studies provide evidence that high levels of depression and anxiety are associated with and predictive of low functioning and poor QoL [14–17]. Negative symptoms seem to be no single entity, but rather consist of two separate, interrelated subdomains of symptoms with different neurobiological underpinnings: expressive negative symptoms, reflecting a loss of initiative and spontaneity, and social amotivation, reflecting emotional and social withdrawal [18, 19]. However, most studies so far have only used composite scores and found that more severe negative symptoms are predictive of lower levels of functioning and QoL cross-sectionally and longitudinally [14, 16, 20, 21]. While studies reported that all variables mentioned above are correlated pairwise and are best understood as related but separate constructs [22–25], no study so far has tested the mediation effects of these variables on both functioning and QoL within one model. However, multiple mediators should be tested simultaneously to determine their relative effects [26].

Against this background, the aim of this study was to identify mechanisms of change of the ACCESS program in functioning and QoL. For this purpose, we tested the hypothesis that the beneficial effect of ACCESS on changes in QoL and functioning is mediated by changes in negative symptoms (expressive negative symptoms and social amotivation), anxiety, and depressive symptoms. Finally, we included potential covariates (age, gender, education, living/vocational status, duration of untreated psychosis, number of treatment contacts) in the mediation model to control for their influence on functioning and QoL.

Method

Sample

Patients were included in the study if they (1) were between 18 and 65 years of age; (2) were currently treated with quetiapine immediate release (IR) or if such a treatment had been initiated; and (3) met the diagnostic criteria for a first- or multi-episode schizophrenia spectrum disorder as assessed by the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I) [27]. Exclusion criteria were other psychotic disorders and an IQ score below 70. Additionally, first-episode patients were not allowed to be included if their previous adherent treatment lasted longer than 6 months. Multi-episode patients had to have at least one relapse with psychotic symptoms and subsequent hospitalisation due to medication non-adherence within the last 24 months to be included [28].

Procedures

Data were collected between April 2005 and December 2008 within the context of the ACCESS I trial that evaluated the effectiveness of a 12-month therapeutic ACT as part of integrated care (ACCESS) in patients with schizophrenia treated with quetiapine (IR) compared to standard care (SC) using a catchment area comparison design [10, 11]. Both catchment areas are located in Hamburg (Germany), i.e. University Medical Center Hamburg-Eppendorf (UKE) and Asklepios Westhospital Rissen (AWR). ACCESS was offered to participants within the UKE catchment area ($n = 64$, 53.3%); SC to participants within the AWR catchment area ($n = 56$, 46.7%). The study was approved by the local institutional review board (IRB Hamburg, Germany 2515), informed consent was obtained, and the study was registered at ClinicalTrials.gov (NCT01081418).

Interventions

Assertive community treatment and integrated care

The ACCESS team consisted of a consultant psychiatrist, one psychiatrist, two psychologists, and one nurse, who were well trained in cognitive-behavioural, dynamic, and/or family therapy, and who administered 60–80% of all therapy sessions in the patient's natural environment. The maximum caseload was 15 patients per ACCESS therapist compared to 30–50 patients in the standard care condition. Each patient was discussed in weekly team meetings, or more often if required, and could make use of the extended availability of the ACT service and the 24-h crisis service.

ACT was implemented as part of a specialised psychosis integrated care treatment program, which included a specialised psychosis inpatient and outpatient unit, two day-units, an occupational rehabilitation centre, and eight psychiatrists in private practice.

Standard care

This control condition provided similar structural conditions as in ACCESS including a treatment network with open and closed inpatient wards, day clinics, an outpatient centre, and eight private psychiatrists. Most of them had completed an intensive training in psychotherapy and a 5-year hospital-based training. In contrast to ACT, therapy sessions took place in the psychiatrist's office and were limited to the official working hours.

Antipsychotic and psychotropic medication

All patients were initially treated with one antipsychotic, i.e. quetiapine IR in this study, to reduce effects of different antipsychotic agents on the treatment-effects of ACCESS and SC. We therefore applied for and successfully received funding for this study from Astra Zeneca, who produces quetiapine IR. Patients were allowed to take concomitant psychotropic medication and to switch from quetiapine IR to another antipsychotic or antipsychotic augmentation therapy without study exclusion at any time based on the decision of the treating psychiatrist.

Measures

The Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q-18) [29] is a self-report instrument developed for patients with schizophrenia to assess their satisfaction with several life domains. Each of its 18 items is rated on a 5-point Likert scale ranging from 'not at all or never' to 'frequently or all the time' depending on how often a person reports aspects of QoL. Higher values indicate better QoL. The Q-LES-Q-18 allows for the calculation of an average score of four domains, i.e. physical health, subjective feelings, leisure time activities, and social relationships, as a global QoL index.

The Positive And Negative Syndrome Scale (PANSS) [30] was administered to assess the severity of positive, negative, and general symptoms over the past week. This interview-based rating scale contains 30 items anchored by 1 (absent) to 7 (extreme). In the current analysis, we used item 16 (anxiety) and 20 (depression). In accordance with Liemburg et al. [18], we separated the negative symptoms into two subdomains: expressive negative symptoms (flat affect, poor rapport, lack of spontaneity, mannerisms and posturing, motor retardation, avolition) and social amotivation (emotional withdrawal, passive social withdrawal, active social avoidance). Functional outcome was assessed by the global assessment of functioning (GAF) scale [31] that provides anchor points between 0 and 100 with higher values indicating better global functioning.

All model variables for this analysis were assessed at baseline and after 12 months.

Statistical analyses

Path modelling was applied to test the mediation hypothesis. We tested a basic model first postulating a significant association between the binary predictor variable (i.e. ACCESS vs. SC) and the outcome variables, i.e. functioning and QoL. Next, we included all potential mediator variables (changes in negative symptoms (expressive negative symptoms and social amotivation), anxiety, and depressive symptoms) in the model. As there is clear evidence to support each predictor-mediator-outcome path, no order of the mediators could be hypothesized. Therefore, we started with estimating a saturated model, in which all variables are interrelated. Subsequently, the final model was developed in an iterative procedure by testing nested models with the Chi square difference test and comparison of goodness of fit-indices [32]. Model fit was assessed by the Chi square test (χ^2), the Comparative Fit Index (CFI), the Tucker-Lewis index (TLI), and the Root-Mean-Square Error of Approximation (RMSEA). A good-fitting model should produce a non-significant Chi square test ($P < 0.05$), CFI- and TLI-values higher than 0.95, and a RMSEA-value lower than 0.05 [33–36]. The significance of the indirect effect was tested by calculating bootstrapped, bias-corrected confidence-intervals with 5000 iterations of the indirect effect [37]. In addition, we compared the model fit of the final model with several alternative models, in which we changed the order of each mediator separately while holding all other model variables constant. Furthermore, in a final step potential covariates [age, gender, educational level, number of psychotic episodes, living as well as vocational status, and duration of untreated psychosis (log-transformed)] were included in the model. Moreover, we controlled for the effect of number of treatment contacts in both groups by including it as an additional predictor variable associated with group allocation. We used the mean total score of Q-LES-Q-18 as a manifest, observable variable instead of forming a latent variable. All other model variables had only one indicator and were thereby treated as manifest variables.

As the group membership was generated by catchment area affiliation and not by randomisation, we formed change scores between the assessment after therapy (i.e. after 12 months) and baseline scores of the model variables to account for values at study entry as key predictors with higher values indicating better effects.

All models were tested using Mplus Version 7.2 (Muthén and Muthén 1998–2011) with the weighted least squares mean and variance adjusted estimator (WLSMV), which is recommended for ordinal, non-normally distributed variables [38]. Missing data, e.g. due to drop-out, were missing completely at random (MCAR) and were replaced through multiple imputations by creating 30 complete data-sets based on all estimates of model variables available at each assessment point [39]. The reported results are based on the pooled imputed data-set.

Results

The sample consisted of 120 patients (64 ACCESS/56 SC). The drop-out rate was 15.8% ($n = 19$, 8 ACCESS/11 SC). Patients received a mean quetiapine IR dose of 582.8 mg/day (SD = 293.5) at baseline, which did not differ significantly in both treatment conditions. Patients in the ACCESS-group had a significantly higher number of mean treatment contacts (78.7, SD = 24.7) than patients in the SC-group (11.2, SD = 30.2; $P < 0.001$) due to a shared and lower case-load. Sample characteristics and summary statistics for model variables are shown in Table 1. Changes in all model variables were significantly correlated with each other with correlation coefficients between 0.30 and 0.67 (Table 2). No significant post-therapy group-differences between patients with first- and multi-episode schizophrenia in the ACCESS- and SC-group were present in negative symptoms, depression, and anxiety.

In the basic model, treatment condition significantly predicted functioning ($\beta = 0.56$, $P < 0.001$) and QoL ($\beta = 0.39$, $P < 0.001$) but explained only 9.1% of the variance of changes in functioning and 8.8% in QoL. The final model (Fig. 1) fit the data well ($\chi^2 = 16.28$, $df = 12$, $P = 0.18$; CFI = 0.99; TLI = 0.98; RMSEA = 0.05). ACCESS significantly predicted improvements in social amotivation. These improvements served as a starting point for two pathways leading to improvements in functioning: One with a direct beneficial effect on functioning (standardised overall indirect effect, IE = 0.20; 95% CIs = 0.11, 0.34; $P = 0.001$) and a second, indirect effect via a reduction in anxiety (IE = 0.11; 95% CIs = 0.04, 0.21; $P = 0.02$). The total effect between treatment condition and changes in functioning including both pathways through social amotivation and/or changes in anxiety was significant (IE = 0.30; 95% CIs = 0.20, 0.46; $P < 0.001$) Thereby, 46.8% of the variance of change in functioning could be explained by this model.

Improvements in functioning also significantly predicted changes in QoL (IE = 0.07; 95% CIs = 0.02, 0.16; $P = 0.03$). Notably, the model fit was decreased when the relationship between functioning and QoL was modelled as a covariance rather than as a regression ($\chi^2 = 21.44$, $df = 12$, $P = 0.04$; CFI = 0.97; TLI = 0.95; RMSEA = 0.08). Furthermore, a sequential path existed leading from changes in social amotivation through two mediators, changes in expressive negative symptoms and depressive symptoms, to changes in QoL (IE = 0.08; 95% CIs = 0.03, 0.16; $P = 0.02$). The mediation model was supported by a significant total effect on QoL including all 3 specific pathways (Fig. 1) running from the treatment condition through changes in social amotivation, anxiety, and functioning as well as through expressive negative symptoms and depressive symptoms (IE = 0.19; 95% CIs = 0.12, 0.30; $P < 0.001$). The model explained 28.0% of the variance of changes in QoL. The relationships identified in the model also remained significant, when potential covariates were included. Age, gender, educational level, living/vocational status, duration of untreated psychosis, and number of psychotic episodes, had no significant association with functioning and QoL. Number of treatment contacts was positively associated with ACCESS ($\beta = 0.88$, $P < 0.001$) but not with any outcome variable ($\beta \leq 0.14$, $P \geq 0.16$). Furthermore, all mediation effects remained stable when the number of treatment-contacts was controlled for. With regard to the order of the mediator variables, changing the position of each mediator separately while holding the others constant resulted in a worse model-fit for every alternative model.

Discussion

Our results extend the current literature by moving beyond the effectiveness of ACT to the investigation of its mechanisms of change with regard to functioning and QoL in first- and multi-episode schizophrenia spectrum patients.

Mediation effects on functioning

Two distinct pathways seem to explain changes in functioning. Both pathways begin with treatment-induced changes in social amotivation and either resulted in changes in functioning directly or indirectly via additional changes in anxiety. Expressive negative symptoms had no significant impact on functioning. This is in line with findings of earlier studies [41–44] indicating that higher levels of social amotivation and anhedonia [19, 43], but not expressive negative symptoms, are associated with more severe impairments in functioning. Recent studies suggest that the strong relationship between social amotivation and functioning may be because patients with schizophrenia generally show low levels of pleasure-seeking behaviour compared to normal controls. This lack of pleasure-seeking behaviour seems to be due to the dysfunctional

Table 1 Sample characteristics and model variables of the total sample, ACCESS and standard care group

	Total sample	Access group	Standard care group	*P* value[b]
Socio-demographic data[a]				
Age (years), mean (SD)	34.3 (11.2)	31.4 (9.9)	37.6 (11.7)	0.002
Gender, *n* (%) male	68 (56.7)	36 (56.3)	32 (57.1)	ns
Partnership, *n* (%), single	92 (76.7)	49 (76.6)	43 (76.8)	ns
Education, years in school, median (quartiles)	10.0 (9.0;13.0)	10.0 (10.0;13.0)	10.0 (9.0;12.0)	0.031
Employed, *n* (%)	30 (25.0)	22 (34.4)	8 (14.3)	0.011
Independent living, *n* (%)	71 (59.2)	41 (64.1)	30 (53.6)	ns
Clinical data[a]				
Diagnosis of psychosis, *n* (%)				ns
Schizophrenia	66 (55.0)	34 (53.1)	32 (57.1)	
Schizoaffective disorder	23 (19.2)	14 (21.9)	9 (16.1)	
Schizophreniform disorder	17 (14.2)	8 (12.5)	9 (16.1)	
Delusional disorder	7 (5.8)	4 (6.3)	3 (5.4)	
Psychotic disorder NOS	7 (5.8)	4 (6.3)	3 (5.4)	
First-episode psychosis, *n* (%)	49 (40.8)	28 (43.8)	21 (37.5)	ns
Comorbid psychiatric disorder at entry, *n* (%)				ns
Comorbid disorder (without SUD)	44 (36.7)	23 (35.9)	21 (37.5)	
Substance use disorder	50 (41.7)	33 (51.6)	17 (30.4)	
Duration of untreated psychosis, median (quartiles)	24.6 (8.7;52.3)	21.9 (8.3;65.3)	27.6 (8.7;52.1)	ns
PANSS score, mean (SD)				
Positive	22.2 (6.4)	23.1 (7.5)	21.3 (4.8)	ns
Negative	24.6 (5.9)	25.2 (6.7)	24.0 (4.7)	ns
General	48.9 (9.8)	48.7 (9.2)	49.0 (10.6)	ns
Model variables				
Social amotivation, mean (SD), baseline	12.3 (2.9)	12.4 (3.2)	12.2 (2.5)	ns
Social amotivation, mean (SD), 12 months	8.5 (3.4)	7.1 (3.3)	10.3 (2.4)	<0.001
Expressive negative symptoms, mean (SD), baseline	17.6 (4.3)	17.4 (4.7)	17.8 (3.9)	ns
Expressive negative symptoms, mean (SD), 12 months	14.5 (4.9)	12.4 (4.8)	17.1 (3.6)	<0.001
Depressive symptoms, *n* (%), baseline				ns
Absent	3 (2.5)	3 (4.7)	0 (0.0)	
Minimal	2 (1.7)	1 (1.6)	1 (1.8)	
Mild	29 (24.2)	13 (20.3)	16 (28.6)	
Moderate	52 (43.3)	29 (45.3)	23 (41.4)	
Moderate–severe	27 (22.5)	12 (18.8)	15 (26.8)	
Severe	7 (5.8)	6 (9.4)	1 (1.8)	
Depressive symptoms, *n* (%), 12 months				0.010
Absent	16 (13.3)	13 (20.3)	3 (5.4)	
Minimal	15 (12.5)	13 (20.3)	2 (3.6)	
Mild	38 (31.7)	19 (29.7)	19 (33.9)	
Moderate	24 (20.0)	9 (14.1)	15 (26.8)	
Moderate–severe	6 (5.0)	2 (3.1)	4 (7.1)	
Severe	1 (0.8)	0 (0.0)	1 (1.8)	
Anxiety, *n* (%), baseline				ns
Absent	1 (0.8)	1 (1.6)	0 (0.0)	
Minimal	2 (1.7)	0 (0.0)	2 (3.6)	
Mild	28 (23.3)	16 (25.0)	12 (21.4)	
Moderate	46 (38.3)	20 (31.3)	26 (46.4)	
Moderate–severe	25 (20.8)	15 (23.4)	10 (17.9)	
Severe	18 (15.0)	12 (18.8)	6 (10.7)	

Table 1 continued

	Total sample	Access group	Standard care group	*P* value[b]
Anxiety, *n* (%), 12 months				0.010
Absent	9 (7.5)	6 (9.4)	3 (5.4)	
Minimal	20 (16.7)	17 (26.6)	3 (5.4)	
Mild	57 (47.5)	29 (45.3)	28 (50.0)	
Moderate	12 (10.0)	4 (6.3)	8 (14.3)	
Moderate–Severe	3 (2.5)	0 (0.0)	3 (5.4)	
Severe	0 (0.0)	0 (0.0)	0 (0.0)	
GAF score, mean (SD), baseline	44.8 (11.8)	45.0 (12.0)	44.5 (11.7)	ns
GAF score, mean (SD), 12 months	64.4 (12.1)	69.4 (10.7)	58.5 (11.3)	<0.001
Q-LES-Q-18, mean (SD), baseline	3.0 (0.02)	3.1 (0.2)	3.0 (0.2)	ns
Q-LES-Q-18, mean (SD), 12 months	3.6 (0.5)	3.8 (0.4)	3.4 (0.5)	<0.001

GAF global assessment of functioning scale, *PANSS* positive and negative syndrome scale, *Q-LES-Q-18* quality of life enjoyment and satisfaction questionnaire (18 items), *SUD* substance use disorder

[a] Assessed at baseline; non-imputed data

[b] Chi square test for categorical variables, *U* test for non-normally distributed and/or not interval-scaled variables

Table 2 Correlations between model variables for imputed data

	1	2	3	4	5	6	7
Treatment condition	–						
Δ Social amotivation	0.55***	–					
Δ Expressive negative symptoms	0.48***	0.67***	–				
Δ Anxiety	0.41***	0.50***	0.47***	–			
Δ Depression	0.30***	0.51***	0.58***	0.46***	–		
Δ Functioning	0.38***	0.52***	0.53***	0.55***	0.46***	–	
Δ Quality of life	0.37***	0.37***	0.41***	0.43***	0.41***	0.44***	–

*** $P < 0.001$

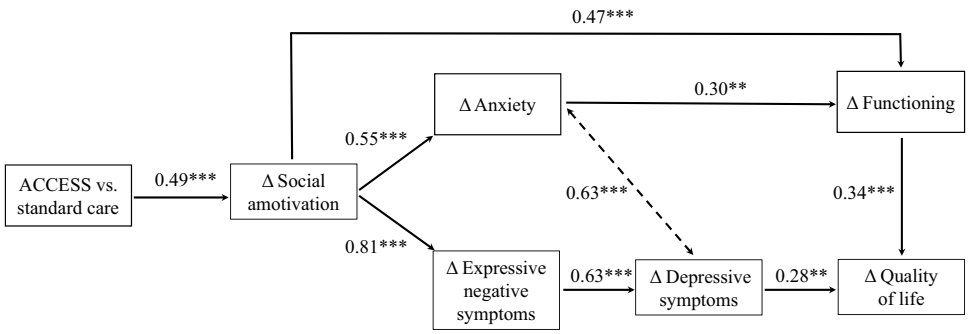

Fig. 1 Final mediation model between treatment condition and changes in functional outcome and quality of life. *Rectangles* present observed, manifest variables; values are standardised partial regression coefficients (*single-headed arrows*) or correlation coefficients (*double-headed arrow*, *dotted line*). All pathways remained significant when the influence of potential covariates (age, gender, level of education, living/vocational status, duration of untreated psychosis, number of psychotic episodes and treatment contacts) on functioning and quality of life was controlled for. ** $P < 0.01$, *** $P < 0.001$

belief that specific activities, such as social interactions, do not result in positive, rewarding experiences (i.e. negative pleasure beliefs) [44, 45]. Therefore, they are less motivated to expend the effort for goal-directed activities, which will prevent them from obtaining potentially beneficial functional outcomes [46, 47]. Furthermore, high levels of social amotivation as indicated by negative pleasure-beliefs may also result in high levels of negative emotions, in particular anxiety and depression [48]. This may be because patients with schizophrenia often experience discouraging life-experiences, which contributes to the avoidance of potentially threatening, but also pleasurable situations [44, 48]. Thereby, social amotivation may serve as a dysfunctional coping strategy to avoid such anxiety-provoking situations, which ultimately leads to poor functioning [40, 49]. As social amotivation in schizophrenia is characterised and maintained by an impairment to retrieve positive experiences and to translate them into future action [44], ACT may be an appropriate therapy option, as it allows to shape and positively reinforce goal-directed, pleasurable behaviour directly by the therapist in a patient's natural environment.

Mediation effects on quality of life

An additional distinct pathway seems to exist for changes in QoL. This path involved changes in social amotivation as a common starting point as well as changes in depressive and expressive negative symptoms. In contrast to the domain of social amotivation, which is inherently a subjective psychological state, the expressive subdomain of negative symptoms reflects behaviours that are directly observable and thereby prone to social feedback [50]. High levels of social amotivation with dysfunctional pleasure-beliefs may prevent patients from initiating adequate verbal and nonverbal communication behaviours [51]. As such expressive behaviours are critical for successful social interactions [52], deficits in these skills may cause negative feedback from the patient`s social environment [53, 54], which is known to be linked to the development and severity of depressive symptoms [55]. In line with previous studies, depressive symptoms were predictive of poor QoL in our path-model [3, 56]. Regarding the effects of ACCESS, the small client-staff ratio, continuity of care, and extended availability may have supported the formation of a strong therapeutic alliance and may have provided a better apprehension and involvement of the social environment of a patient during therapy than SC [57]. This may have facilitated the experience of positive social events and corrective social feedback for the patient, followed by a reduction in depressive symptoms and improvements in QoL.

Clinical implications

Our mediation model indicates that an integrated treatment, which targets all mediators, should produce the best generalisation effects on functioning and QoL [58]. The order of the mediators in the model suggests that the ACT therapist should ideally target each mechanism of change in the following sequence, i.e. begin with the treatment of social amotivation, which may then trigger or at least facilitate improvements in anxiety as well as expressive negative symptoms and depressive symptoms that will finally enhance improvements in functioning and QoL. Moreover, our model implies two therapeutic strategies to optimise the effects on functioning and QoL: First, one could identify and target the most deficient mechanisms of change, particularly those early in the causal order, with the aim to interrupt the detrimental consequences of the respective pathway. Second, the ACT therapist could identify those mechanisms of change already existing in order to use them as a resource to initiate a treatment-induced cascading effect of change on the subsequent mediators [26].

Strengths and limitations

The main strength of this study refers to the fact that there are only few studies, in which ACT was exclusively offered to patients with schizophrenia. Furthermore, within this context this is one of the first mediation analyses that investigated potential mechanisms of change so far.

As our results may have important clinical implications, our exploratory model needs to be confirmed in another sample. A limitation refers to the measures we used. All variables were measured by only one indicator. Therefore, we needed to use manifest instead of latent variables, which may have underestimated the path coefficients and the amount of explained variance in each dependent variable [59]. Furthermore, the use of the GAF scale to assess functioning is problematic given that it is confounded with the current level of psychiatric symptoms. Together with the fact that both negative symptom subdomains as well as anxiety and depression were assessed with the same measurement scale, i.e., the PANSS, this may have boosted the associations between them. Another limitation refers to the fact that mediation analysis inherently implies a causal relationship between the variables of interest. Due to the sample size, we used only change scores of potential mediators and outcomes, which does not allow firm conclusions to be drawn on the temporal order between them. However, testing several models with an alternative order of the mediators allowed us to exclude alternative models with a better fit to the data. Our treatment allocation was not based on randomisation but on catchment area affiliation. Therefore, we

cannot rule out potential group-differences in addition to the treatment condition that may have affected the mediation effects but the model remained stable when potential covariates and group-differences in the number of treatment contacts were taken into account and a broad range of baseline variables was assessed to control for differences between the two treatment arms. Both treatment conditions differed in several methodological aspects that were assumed to be responsible for the beneficial treatment effects of ACCESS (e.g. shared vs. individual caseload, carried out in the natural environment vs. office). Therefore, it was impossible to investigate the relative efficacy of these ACT-characteristics as potential mechanisms of change. This should be investigated in future RCTs by direct head-to-head comparisons of various forms of ACT that only differ in the characteristic of interest. Furthermore, future studies should also include other antipsychotic agents as treating all patients with the same antipsychotic medication limits the generalisability of our results. However, this procedure allowed us to directly compare the two psychosocial interventions with minimal confounding through different antipsychotic agents.

In summary, our results suggest that both subdomains of negative symptoms, social amotivation and expressive negative symptoms, depression, and anxiety may function as mediators, and thereby, as potential mechanisms of change of ACT on functioning and QoL for patients with schizophrenia. A combined and sequential treatment focusing on the most powerful mediators that best fit the individual patient may optimise the treatment effects on functioning and QoL produced by ACT.

Compliance with ethical standards

Financial support This study was supported by Astra Zeneca. The sponsor was not involved in designing and conducting the study, analysing as well as interpreting the data or writing up the manuscript.

Conflict of interest Dr Schmidt and Dr Lange have no conflict of interest to declare. Dr Schöttle has received honoraria from Astra Zeneca. Dr Karow has received honoraria from and serves on speakers boards of Astra Zeneca. Dr Schimmelmann has served as paid speaker for Eli Lilly and Shire. Dr Lambert has received grant/research support from and served on speakers or advisory boards of Astra Zeneca and has received honoraria from Astra Zeneca, Eli Lilly, Janssen-Cilag, and Bristol-Myers Squibb.

Ethical standards The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008. The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional guides on the care and use of laboratory animals.

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