



## Research Paper

## Feasibility of six-month outpatient cognitive remediation in schizophrenia: Experience from the randomized controlled integrated social cognition and social skills therapy study

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## ABSTRACT

Patients with schizophrenia often have cognitive impairments that contribute to diminished psychosocial functioning. Cognitive remediation therapy (CRT) has proven efficacy and is recommended by evidence-based treatment guidelines. Important moderators of efficacy include integration of CRT into a psychiatric rehabilitation concept and patient attendance at a sufficient number of therapy sessions. These conditions can probably best be met in an outpatient setting; however, outpatient treatment is prone to higher rates of treatment discontinuation and outpatient settings are not as well protected as inpatient ones and less closely supervised.

The present study investigated the feasibility of outpatient CRT in schizophrenia over a six-month period. Adherence to scheduled sessions and safety parameters were assessed in 177 patients with schizophrenia randomly assigned to one of two matched CRT programs.

Results showed that 58.8 % of participants completed the CRT (>80 % of scheduled sessions) and 72.9 % completed at least half the sessions. Predictor analysis revealed a high verbal intelligence quotient as favorable for good adherence, but this factor had only low general predictive power. During the six-month treatment phase, serious adverse events occurred in 15.8 % (28/177) of the patients, which is a comparable rate to that reported in the literature.

Our findings support the feasibility of six-month outpatient CRT in schizophrenia in terms of adherence to scheduled sessions and safety.

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## 1. Introduction

The majority of people with schizophrenia exhibit significant cognitive impairments in various functional areas (Keefe et al., 2005), and these impairments, in particular in social cognitive processes, are among the most significant predictors of (psycho-) social functioning and are often subjectively perceived as very distressing (Bellucci et al., 2003; Wexler and Bell, 2005; Wykes et al., 2011). Consequently, cognitive impairments can greatly impact everyday life and may even hinder comprehensive recovery, i.e., symptomatic and functional remission (Harvey and Bellack, 2009).

Treatment approaches for cognitive impairments, in particular cognitive remediation therapy (CRT), have received increasing attention in the past two decades (Vita et al., 2021). Many studies have provided evidence corroborating the efficacy of CRT, e.g., regarding its effects on social-cognitive and neurocognitive processes, occupational reintegration, and psychosocial functioning (Kurtz et al., 2015; Kurtz and Richardson, 2012; Wykes et al., 2011; Vita et al., 2021). Several national guidelines, such as the German S3 Guideline Schizophrenia and the Schizophrenia Treatment Guidelines of the American Psychiatric Association, recommend cognitive remediation as an important part of treatment for schizophrenia (Gaebel et al., 2019; Keepers et al., 2020). However, achieving cognitive and functional gains through CRT requires sufficient intensity and consistency of training (Wykes and Spaulding, 2011). In particular, the number of sessions attended appears to be significantly associated with improvements in neurocognition (Best et al., 2020; Vita et al., 2021), although attendance at enough sessions alone is not sufficient to guarantee the efficacy of a program (Mahncke et al., 2019; Siu et al., 2021). Vita et al. (2021) showed that beyond the number of training sessions, the guidance by an active, trained therapist, the development of cognitive strategies, and the integration of CRT into a psychiatric rehabilitation concept are highly significantly associated with the cognition- and functioning-related outcomes of CRT.

Because the number of attended sessions is essential for the efficacy of CRT, measures have to be taken to reduce treatment nonadherence and dropout from treatment programs, although these events represent general problems in the treatment of individuals with schizophrenia (Gilmer et al., 2004; Kane, 2007; Acosta et al., 2012). Furthermore, nonadherence and dropout may become more common as programs such as CRT are increasingly introduced into outpatient settings. Nevertheless, the outpatient implementation of CRT is supported by meta-analyses that showed superior efficacy of CRT when combined with other rehabilitative treatments (Kurtz et al., 2011; Wykes et al., 2011) and the meta-analysis by Vita et al. (2021), which showed superior efficacy of longer treatment (optimally >20 sessions), because rehabilitative and long-term treatments may not be feasible during inpatient treatment. On the other hand, a higher number of treatment sessions significantly increases dropout rates in neurocognitive interventions (Szymczynska et al., 2017), and inpatient settings improve adherence in CRT (Vita et al., 2022). Taken together, the research suggests that interventions involving a higher number of sessions applied in an outpatient setting may have an increased risk of premature discontinuation of CRT.

Estimated mean dropout rates in CRT derived from the above-mentioned meta-analyses range from about 7 % in purely inpatient studies (Cella et al., 2020) to about 17 % (Vita et al., 2021) to 24 % (Szymczynska et al., 2017) in mixed in- and outpatient studies. However, individual studies show much greater variation, with dropout rates ranging from 0 % to 58 % (Vita et al., 2021). The large difference in dropout rates is probably due to the heterogeneity of patient samples and interventions, differences in therapy settings, and the use of different definitions of dropout (all-cause dropout is used interchangeably with premature discontinuation of treatment). Consistent with the above mentioned importance of an active therapist to treatment success, Wykes et al. (2023) were able to show in a recent multicenter study that

therapist presence also increases adherence, regardless of whether a group or individual setting was used.

Dropout, a dichotomous measure (i.e., yes vs. no), is less suitable for assessing treatment adherence, i.e., the extent to which patients actually attend a treatment program. Instead, adherence is better reflected by the percentage of attended treatment sessions. For instance, Dillon et al. (2016) investigated adherence in an eight-week computerized CRT program in clinically stable outpatients with psychosis. Even though this CRT program was relatively short, only about 23 % of the sample completed it, i.e., attended >80 % of the prescribed treatment sessions (referred to as the full adherence group); another 23 % of the sample partially completed the program by attending to >25 % but <80 % of the sessions (referred to as the partial adherence group). The rest of the sample (23 %) attended <25 % of the sessions or even refused to participate at all (31 %). The authors concluded that 46 % of the sample completed a meaningful number of CRT training sessions (partial and full adherence groups combined), but that the majority of the sample did not attend a sufficient number.

Thus, in the context of growing evidence for the efficacy of CRT for cognitive impairments in schizophrenia, the question of the feasibility of CRT in outpatient settings is very important (Dillon et al., 2016). Therefore, in the scope of a randomized clinical trial (RCT) we aimed to assess the feasibility of six-month outpatient CRT in patients with schizophrenia, mainly in terms of treatment adherence as operationalized by the percentage of sessions attended.

When evaluating the feasibility of a treatment for a severe mental illness, it is essential to investigate adverse and undesirable treatment effects and patient safety (Roberts and Roberts, 1999) and thus was a further aim of the study. This aspect is all the more important because outpatient settings are not as well protected as inpatient ones and are less closely supervised.

There is limited information on individual differences regarding factors that influence or predict adherence. However, demographic variables such as education and premorbid intelligence, as well as clinical variables such as psychopathological status or medication dosage, have been repeatedly described as influencing factors (e.g., Harding et al., 2008; Twamley et al., 2011). In particular, Twamley et al. (2011) reported that participants who completed cognitive training had more formal education and lower daily doses of antipsychotic medications than did participants who dropped out of the study with no exposure to the CT intervention, but completers did not differ in any of the investigated demographic or clinical variables from those participants who started but later discontinued cognitive training. Also, the most recent systematic review from Altman et al. (2023) confirmed educational level and premorbid intelligence as positively related to adherence to CRT programs, besides a number of other variables such as intrinsic motivation, self-efficacy, perceived usefulness, neurocognitive functioning, and therapeutic alliance. However, only few included studies have examined each of these associations and it is unclear to what extent the results are transferable to other programs and settings. Therefore, we examined the association between the aforementioned demographic and clinical variables and adherence as a secondary question in our study.

## 2. Methods

This study was part of a preliminary analysis of a multicenter randomized controlled treatment study. The design and methods of the study have been published in detail elsewhere (Wölwer et al., 2022). Because data clearing and analysis of the main outcome variables are still ongoing, no analyses of treatment differences will be reported here. Instead, this paper focuses on treatment adherence and safety. The differential effects of these interventions will be presented in future articles.

## 2.1. Design

This was a multicenter randomized controlled trial performed according to good clinical practice guidelines at the outpatient facilities of six psychiatric hospitals (Alzey, Berlin, Bonn, Cologne, Düsseldorf, and Tübingen) in Germany. The main inclusion criteria were a diagnosis of schizophrenia confirmed by the Mini-International Neuropsychiatric Interview (version 6) (Sheehan et al., 1998), a total score on the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987) of less than or equal to 75, and proficiency in German. Patients were excluded from the study if they had a lack of capacity to consent; a positive drug screen during the inclusion phase (excluding cannabinoids and benzodiazepines); severe suicidality; other relevant psychiatric, neurological, and somatic disorders; or a verbal intelligence quotient (IQ) below 80 (according to the multiple-choice vocabulary test).

Participants were randomly assigned to one of two six-month outpatient CRT programs that targeted either social cognition and skills (Integrated Social Cognition and Social Skills Therapy, ISST) or neurocognition (Neurocognitive Remediation Therapy, NCRT). The programs comprised 18 sessions each (50 min per session) and were closely matched in terms of the application regimen. Both programs started with ten weekly individual sessions addressing social cognitive (ISST) or neurocognitive (NCRT) impairments. This phase was followed by five group sessions every two weeks for practice and two sessions in everyday “real life” situations to improve transfer. Both programs were guided by trained therapists and applied as an add-on to routine drug and psychosocial treatment according to the individual's clinical needs and standard clinical outpatient treatment procedures in Germany (Wölwer et al., 2022).

After obtaining written informed consent from participants, inclusion and exclusion criteria were checked, and eligible patients were randomly allocated to one of the two CRT programs. Subsequently, clinical status and cognitive and social functioning were assessed at baseline (before the first treatment session, V1), at the end of the six-month treatment period (V6), and after six months of follow-up (V12). Moreover, during the treatment period safety parameters and reasons for prematurely discontinuing therapy were recorded monthly (V1-V6).

## 2.2. Sample

A total of 177 outpatients with schizophrenia, including 75 women (41.1 %) and 99 men (56.9 %), participated in the study (Table 1). The mean age of the participants was 31.9 (SD = 10.9; median = 27), and the mean illness duration was 57.4 months (SD = 79.5; median = 27 months). The time since onset of schizophrenia was less than seven years in 129 of the patients (79.6 %).

## 2.3. Outcome variables

Treatment adherence was assessed as the number of CRT sessions attended. Similar to the definition of Dillon et al. (2016), we calculated participation in the 18 CRT sessions as a percentage and categorized attendance as follows: refusal to participate in any session (i.e., 0 % participation), poor adherence (attending 1–9 sessions, i.e., up to 50 %), partial adherence (attending 10–14 sessions, i.e., up to 80 %), and full adherence (attending 15–18 sessions, i.e., >80 %). In contrast to the classification made by Dillon et al. (2016), the threshold for poor adherence was set at 50 % instead of 25 %. Considering that the first ten sessions of each CRT program comprised basic and indispensable training contents, comparable forms of which have been shown in previous studies to be effective on their own (Wölwer et al., 2005; Klingberg et al., 2011), participants who attended more than half of the sessions (i.e., those with partial or full adherence) can be assumed to have completed a meaningful and effective part of the treatment. Therefore, we combined partial and full treatment adherence and refusal and poor treatment adherence into the two superordinate categories *meaningful*

**Table 1**

Baseline characteristics of study participants (by adherence classification).

	Total (N = 177)	Adherence group <sup>a</sup>				p <sup>b</sup>
		Refusal (n = 6)	Poor (n = 42)	Partial (n = 25)	Full (n = 104)	
Age, mean (SD), y	31.9 (10.9)	39 (7.2)	30.9 (11.4)	31.2 (12.3)	32.3 (10.5)	0.89
Sex, n (%)						0.14
Male	99 (56.9)	3 (100)	26 (61.9)	17 (68.0)	53 (51.0)	
Female	75 (43.1)	0 (0)	16 (38.1)	8 (32.0)	51 (49.0)	
Migration history, n (%)	62 (35.6)	0 (0)	19 (45.2)	10 (40.0)	33 (31.7)	0.42
Education, n (%)						0.05
Passed secondary (high) school examination	94 (54.0)	0 (0)	20 (47.6)	10 (40.0)	64 (61.5)	
Less education	80 (46.0)	3 (100)	22 (52.4)	15 (60.0)	40 (38.6)	
Verbal IQ, mean (SD)	102.9 (11.4)	99.8 (11.8)	99.5 (9.6)	105.0 (10.7)	104.0 (11.9)	0.07
Illness duration in months mean (SD)	57.4 (79.5)	104.5 (47.4)	53.1 (76.4)	53.6 (84.1)	59.1 (80.6)	0.99
Number of episodes per patient, mean (SD)	2.9 (5.6)	3.0 (0)	2.6 (2.2)	2.3 (2.7)	3.2 (6.9)	0.87
PANSS, mean (SD)						
Positive symptoms	11.6 (3.7)	12.7 (3.3)	11.5 (4.0)	12.8 (3.8)	11.3 (3.6)	0.27
Negative symptoms	13.9 (4.8)	13.2 (3.4)	13.6 (4.3)	14.1 (4.5)	13.9 (5.2)	0.85
General symptoms	26.1 (5.0)	25.3 (6.3)	26.7 (5.2)	27.9 (5.9)	25.4 (4.5)	0.06
Total score	51.5 (10.3)	51.2 (9.4)	51.9 (11.1)	54.7 (10)	50.6 (10.1)	0.23
Sessions participated in per patient, mean (SD)	13.3 (6.1)	0 (0)	4.8 (2.5)	12.5 (1.2)	17.7 (0.8)	–

<sup>a</sup> Refusal: 0 % participation (no data at all were available for 3 persons); poor: up to 50 % participation (1–9 sessions); partial: up to 80 % participation (10–14 sessions); full: >80 % participation (15 to 18 sessions).

<sup>b</sup> p for differences between adherence groups; due to low frequency of ‘refusals’, they were grouped together with ‘poor’; Chi2 for proportions, ANOVA for metric measures.

*number of treatment sessions (>50 %) and insufficient number of treatment sessions (≤50 %), respectively.*

The safety of the CRT programs was assessed by evaluating the number of serious adverse events (SAEs), i.e., symptom exacerbations, rehospitalizations, suicidal crises, suicide attempts, or suicides, that occurred during the six-month outpatient treatment.

## 2.4. Analyses

Treatment adherence, safety parameters, and sample characteristics were analyzed descriptively as frequencies and percentages in the whole sample and in each treatment adherence subgroup.

To identify general predictors of treatment adherence, we performed logistic regression analysis based on the two superordinate categories described above: *meaningful number of treatment sessions* and *insufficient number of treatment sessions*.

Patient characteristics (age, sex, migration history, education level, verbal IQ, social function according to the Social and Occupational Functioning Assessment Scale, illness duration, number of episodes, and symptom severity according to Clinical Global Impression (CGI) and the

positive, negative and general scores of the Positive and Negative Syndrome Scale (PANSS)) were considered as potential predictors in an exploratory logistic regression analysis with a stepwise forward procedure.

All analyses were performed with IBM SPSS Statistics (Version 25) with a significance level of  $\alpha = 0.05$ .

### 3. Results

The baseline characteristics of the 177 participants (subdivided into adherence categories) are presented in [Table 1](#).

The numbers of patients in the adherence subgroups were as follows: full adherence, 104 (58.8 %); partial adherence, 25 (14.1 %); poor adherence, 42 (23.7 %); and refusal, six (3.4 %). Thus, 72.9 % of participants completed a meaningful number of treatment sessions, i.e., they had full or partial adherence. The mean percentage of attendance at therapy sessions was 93 % in the patients with full adherence and 77 % in the whole group of participants. For different sample characteristics as given in [Table 1](#) only marginal group differences were found for level of education ( $p = 0.05$ ), verbal IQ ( $p = 0.07$ ) and PANSS-general score ( $p = 0.06$ ) with somewhat more favorable scores in each variable in the 'full adherence' group.

The exploratory logistic regression analyses of the relationship between better adherence and participant characteristics identified only higher verbal IQ as a significant predictor (odds ratio. 1.039;  $p = 0.039$ ; 95 % CI 1.004–1.076); however, the multivariate model had only low explanatory power (Nagelkerke  $R^2 = 0.045$ ).

The main reasons for not participating in a meaningful number of sessions, i.e., <10 sessions (48/177 patients. 27.1 %) were active withdrawal from participation by the patient ( $n = 26$ ), non-appearance at scheduled appointments for study treatment or diagnosis for more than six weeks ( $n = 11$ ), and failure to contact the patient during the treatment period despite extensive efforts by the team ( $n = 6$ ).

#### 3.1. Safety

During the six-month treatment period, 35 SAEs were documented in 28/177 patients (15.8 %). Most SAEs were rehospitalizations because of psychiatric conditions (23/35 SAEs. 65.7 %) or non-psychiatric conditions (1/35. 2.8 %). Other SAEs were increased suicidality (8/35. 22.9 %) and temporary severe drug abuse (3/35. 8.8 %). Six SAEs (17.1 %) were rated as severe (five rehospitalizations and one drug abuse), 22 (62.9 %) as moderate, and seven (20 %) as mild.

### 4. Discussion

In the last two decades, CRT has proved to be effective in improving cognition, occupational reintegration, and psychosocial functioning in schizophrenia (Kurtz et al., 2015; Kurtz and Richardson, 2012; Wykes et al., 2011; Vita et al., 2021). The integration of CRT into a psychiatric rehabilitation concept and participant attendance at sufficient sessions (preferably >20) are two important moderators enhancing efficacy (Bowie et al., 2020; Wykes et al., 2011; Vita et al., 2021). These moderators can probably best be implemented in an outpatient setting. However, outpatient treatment is prone to higher rates of treatment discontinuation (Szymczyńska et al., 2017; Vita et al., 2022) and has to be performed in a less protected and supervised setting than inpatient treatment, raising the question of the feasibility of more extensive CRT in outpatient settings in terms of therapy adherence and safety. Moreover, only a small number of studies explore factors that affect or predict treatment adherence (Altman et al., 2023).

The present study primarily investigated therapy adherence and safety, which are both aspects of feasibility, and showed that the mean percentage of attendance at therapy sessions in the whole group of participants is 77 %. This result is consistent with a large systematic review by Sedgwick et al. (2021), in which the mean percentage of

therapy adherence to various group interventions for the treatment of psychosis was 76.4 % (SD = 17.4).

Referring only to those patients who completed >80 % of the scheduled sessions in the six-month outpatient treatment period (full adherence), our study shows that 58.8 % of participants reached that score. When combined with those participants who attended 50 % or more of the scheduled sessions, a total of 72.9 % of participants completed a meaningful number of sessions (i.e., 10 or more sessions). Compared with similar CRT programs, the finding that 58.8 % of participants fully completed can be considered as positive and exceeds the rate of 23 % reported by Dillon et al. (2016). García-Fernández et al. (2019) reported a slightly higher rate of fully adherent patients (66.7 %). i.e., those who completed >80 % of a 24-session computer-assisted CRT, but their study had a much shorter intervention phase (12 weeks). The percentage of participants who did not complete a sufficient number of sessions in the present study (27.7 %) is comparable to the percentage who did not fully complete a three-month CRT (30.3 %, 10/33 patients) in a study by Twamley et al. (2011) and the mean percentage of intervention dropouts (24 %) reported by Szymczyńska et al. (2017) for cognitive and neurocognitive interventions in schizophrenia. The encouraging results of the present study were obtained for a longer treatment period (six months) with a more demanding training, which included computer-based and non-computer-based training elements under the guidance of a therapist.

At the same time, the data on SAEs indicated that CRT does not have an increased safety risk: SAEs occurred in 15.8 % of the 177 patients during the six-month treatment phase (i.e., until V6). The vast majority of SAEs were inpatient or day-care readmissions in connection with psychopathological exacerbations and/or for readjustment of medication. Although no safety-relevant adverse effects were expected, experience has shown that the population of individuals with schizophrenia has a fundamentally increased risk of suicide compared with non-psychiatric patients and a relatively high risk of relapse. The rate of SAEs in this study is comparable to expected rates in schizophrenia as reported in the literature. For example, a psychotherapeutic trial with 18-month follow-up by Tarrier et al. (2004) found three confirmed and one suspected suicide in a study sample of 225 patients. Wykes et al. (2023) reported SAEs in 11.7 % of patients who participated in various CRT programs over 15 weeks. Data on the annual rate of rehospitalization in patients with schizophrenia vary from 12.1 % in first-episode patients (Üçok et al., 2006) to 39 % in a naturalistic sample of patients with a mean of 3.4 previous schizophrenia episodes or inpatient treatment for schizophrenia (Schennach et al., 2012). The CRT studied here can therefore be considered to be safe.

With regard to the secondary question on the demographic and clinical factors influencing adherence, the respective regression analysis identified only one significant predictor, i.e., higher verbal IQ as favorable. At the same time, the 'full adherence'-group showed a slightly higher educational level and premorbid IQ in the univariate comparisons than the remaining groups. These results confirm earlier previous findings on the relationship between education or IQ and adherence (e.g., Twamley et al., 2011; Altman et al., 2023). The fact, that no other variable showed a significant relationship to adherence may indicate, that there is no patient group in which poor adherence can be expected a priori.

Some limitations must be considered when interpreting the results. First, the results were obtained under the special conditions of an RCT; as described by Medalia et al. (2019), patients who agreed to participate in a comprehensive clinical trial may be more motivated than typical patients, which may positively influence the results. Likewise, the inclusion and exclusion criteria of an RCT may lead to a positive sample selection. On the other hand, study requirements such as the regular diagnostic assessments and the strict adherence to a treatment manual instead of orientation towards individual needs could have been perceived as burdensome or artificial by some participants, which could have increased the risk for dropout from the study and thus from



CRT—two events that could not be distinguished in each individual case. Last, the study evaluated the feasibility of two different CRT programs (ISST and NCRT). Differences between the programs were not considered here because such differences are part of the main research question. i.e., whether the efficacy of the two programs is different; the data regarding this question will be published elsewhere in the context of the differential effects on cognitive and functional outcomes. However, the inclusion of two different programs can also be seen as a strength of the study in terms of the generalizability of the results for CRT. The generalizability is also strengthened by the comparatively large sample of 177 patients treated at six sites by different therapists and under different local outpatient care conditions. The conditions of an RCT also ensured the necessary standardization and methodological quality in the implementation of the study, especially in the application of CRT according to specified manuals. In addition, the CRT programs incorporated all core elements and methodologies recommended as conducive for successful training by the consensus statement of the expert working group on CRT (Bowie et al., 2020).

In conclusion, our findings support the feasibility of outpatient cognitive remediation in schizophrenia over a period of six months in terms of adherence to scheduled sessions and safety. In Germany, CRT in schizophrenia is predominantly implemented in an inpatient setting over comparatively short periods of a few weeks during the hospital stay, so our findings are an encouraging signal for the necessary extension of such therapy to outpatient care in the future.

### Ethical approval

The study received initial approval from the ethics committee of the Medical Faculty, University of Düsseldorf (reference number: 5333R) and subsequently from the local ethics committees of each study center. The study was performed in accordance with the latest version of the Declaration of Helsinki. Patients were only included in the study after giving written informed consent.

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### CRediT authorship contribution statement

**Tim Schuster:** Analyses and interpretation of data. Writing – original draft. **Agnes Lowe:** Investigation, Writing – original draft. **Karolin Weide:** Investigation, Writing – original draft. **Daniel Kamp:** Conceptualization, Investigation. **Mathias Riesbeck:** Analyses and interpretation of data. **Andreas Bechdorf.** **Anke Brockhaus-Dumke.** **René Hurlmann.** **Ana Muthesius.** **Stefan Klingberg:** Investigation. **Martin Hellmich:** Methodology, Design and supervision of statistical analyses. **Sabine Schmied:** Data base development, Data Management. **Andreas Meyer-Lindenberg:** Methodology, Funding acquisition, Supervision. **Wolfgang Wölwer:** Conceptualization, Methodology, Funding acquisition, Supervision, Writing – original draft. **All authors** were involved in revising the article, read and approved the final version of the manuscript.

### Conflict of interest

None of the authors has any financial or personal conflicts of interest to declare.

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