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Efficacy of integrated social cognitive remediation vs neurocognitive remediation in schizophrenia: Results from the multicenter randomized controlled ISST (Integrated Social Cognition And Social Skills Therapy) study

Daniel Kamp [a,*], Agnes Lowe [a], Karolin Weide [a], Mathias Riesbeck [a], Andreas Bechdolf [b,l], Karolina Leopold [b,m], Anke Brockhaus-Dumke [c,d], Bettina Klos [c], René Hurlemann [e,f], Sven Wasserthal [e], Ana Muthesius [g], Joseph Kambeitz [g], Stefan Klingberg [h], Lea Hölz [h], Martin Hellmich [i], Kerstin D. Rosenberger [i], Sabine Sadura [j], Andreas Meyer-Lindenberg [k], Wolfgang Wölwer [a]

[a] Department of Psychiatry and Psychotherapy, Medical Faculty, University of Düsseldorf, Germany
[b] Department of Psychiatry, Psychotherapy and Psychosomatic Medicine, Vivantes Hospital am Urban and Vivantes Hospital im Friedrichshain, Berlin, Germany
[c] Rheinhessen-Fachklinik Alzey, Alzey, Germany
[d] LVR-Klinik Bonn, Bonn, Germany
[e] Division of Medical Psychology, Department of Psychiatry and Psychotherapy, University Hospital of Bonn, Bonn, Germany
[f] Department of Psychiatry, School of Medicine and Health Sciences, University of Oldenburg, Oldenburg, Germany
[g] Department of Psychiatry and Psychotherapy, University of Cologne, Cologne, Germany
[h] Department of Psychiatry and Psychotherapy, University of Tübingen, Tübingen, Germany
[i] Institute of Medical Statistics and Computational Biology, Faculty of Medicine and University Hospital Cologne, University of Cologne, Cologne, Germany
[j] Clinical Trials Centre Cologne (CTCC), Medical Faculty, University of Cologne, Cologne, Germany
[k] Central Institute for Mental Health, Mannheim, Germany
[l] Department of Psychiatry and Psychotherapy, Charité Universitätsmedizin Berlin, Campus Charité Mitte, Berlin, Germany
[m] Department of Psychiatry and Psychotherapy, Carl Gustav Carus University Hospital, TUD Dresden University of Technology, Dresden, Germany

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ABSTRACT

Introduction: Persistent poor psychosocial functioning, which is associated with impairments in cognition, is one of the main barriers to recovery in schizophrenia. Although cognitive remediation therapy (CRT) has shown general efficacy in improving cognition and functioning, simultaneously focusing on social cognition and social behavioural processes may increase its efficacy.

Methods: In a multicenter, rater-blinded, randomized controlled trial, schizophrenia patients (N = 177) were assigned to six months of either Integrated Social Cognitive and Behavioral Skills Therapy (ISST) or, as an active control intervention, Neurocognitive Remediation Therapy (NCRT). The primary endpoint was all-cause discontinuation (ACD) over the 12-month study period. Secondary endpoints were cognition, psychosocial functioning and quality of life, and clinical symptoms.

Results: ACD was not significantly different between the ISST and NCRT groups (43.3 % vs 34.5 %, respectively). More improvement was seen in social cognition (Pictures of Facial Affect; d = 0.83) in the ISST group and in neurocognition (subscores of the Auditory Verbal Learning Test; d = 0.29–0.40) in the NCRT group. Level of functioning, quality of life, and clinical symptoms significantly improved in both groups, with no significant between-group differences.

Discussion: Both therapies differentially improved measures of the cognitive domains they were designed for. Moreover, they both improved social functioning with high effect sizes (d = 0.8–1.0), underlining the important

* Corresponding author at: LVR-Klinikum Düsseldorf, Department of Psychiatry and Psychotherapy, Medical Faculty, University of Düsseldorf, Bergische Landstraße 2, 40629 Düsseldorf, Germany.
E-mail address: Daniel.Kamp@lvr.de (D. Kamp).

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role of CRT in recovery-oriented schizophrenia treatment. However, the absence of a third group without an active intervention limits the interpretability of the results.

1. Introduction

Although the available treatment strategies for schizophrenia are effective in reducing clinical symptoms, psychosocial functioning often remains considerably impaired, and patients with schizophrenia self-rate good psychosocial functioning as their greatest unmet need (Middelboe et al., 2001; Ramsay et al., 2011). Persistent impairments in psychosocial functioning hamper full recovery and make it difficult for patients to lead a satisfying life (Middelboe et al., 2001; Pinkham et al., 2003). Thus, there is an urgent need to improve treatment of psychosocial deficits.

Among the strongest determinants of functional outcome are impairments in basic cognitive processes (such as attention, memory, and executive functions, together often referred to as neurocognition) and social cognitive processes (such as social perception, affect recognition, and theory of mind) (Tsang et al., 2010). In schizophrenia, impairments in social cognition are known to be closely related to impaired psychosocial functioning (Couture et al., 2011; Kharawala et al., 2022; Halverson et al., 2019). In addition, cognitive impairments are also associated with poor adherence to antipsychotic medication (Spiekermann et al., 2011) and less utilization of psychiatric and other psychosocial services (Johansen et al., 2011), with the result that patients often do not benefit from potentially effective treatment.

Over the last two decades, a number of cognitive remediation therapy (CRT) programs have been developed to improve cognitive functioning. All these programs ultimately aim to achieve benefits in social functioning by first improving cognition. However, the programs are very heterogeneous, e.g., they differ in terms of content (i.e., they focus on neurocognitive or social-cognitive processes or both), strategies (e.g., repetitive vs strategy-based learning, bottom-up vs top-down approach), and scope (e.g., number of cognitive functions trained, inclusion of behavior-based exercises, training only in the laboratory or also in everyday situations). Meta-analyses that included all available studies and did not select for the type of remediation approach have shown quite consistently that CRT successfully improves the targeted cognitive domains with small to moderate effect sizes (d = 0.29–0.45) (Wykes et al., 2011; Vita et al., 2021). Larger effect sizes (up to d = 1.35, depending on the social cognitive domain and type of training) were found in meta-analyses that focused on social CRT, although the analyses were based on fewer studies (Kurtz and Richardson, 2012; Kurtz et al., 2016; Nijman et al., 2020). In terms of more distal outcomes of social functioning, meta-analyses revealed rather inconsistent effects, ranging from about d = 0.2 (Vita et al., 2021; Yeo et al., 2021) to about d = 0.8 (Kurtz and Richardson, 2012; Nijman et al., 2020), with larger effects again being found more often for social cognitive remediation. A small head-to-head comparison of social cognitive and neurocognitive remediation by our group also indicated superiority of social cognitive remediation (Wölwer and Frommann, 2011); however, whether social cognitive remediation is generally superior to neurocognitive remediation remains unclear because few other studies have directly compared the two types of program.

The heterogeneity of previous CRT approaches and their results has also contributed to the fact that CRT is not uniformly recommended in international guidelines: Although several scientific societies explicitly recommend (Gaebel et al., 2019; Galletly et al., 2016) or at least suggest CRT (Keepers et al., 2020; Norman et al., 2017; SIGN, 2013), others refrain from doing so (NICE, 2010; Dixon et al., 2010). The latter societies mainly criticize the sparse evidence for long-term effects, especially on social outcomes; the heterogeneity of remediation programs; and the relatively small sample sizes studied. Therefore, scientific societies urgently need and even demand methodologically rigorous, adequately powered randomized controlled trials that have longer follow-up periods and adhere to the recently identified essential treatment elements (see below) (NICE, 2010).

Moderator analyses of recent reviews and meta-analyses (Wykes et al., 2011; Vita et al., 2021; Fiszdon and Reddy, 2012) suggest that the effects of cognitive remediation on functional outcome may be significantly enhanced by combining cognitive remediation with social behavioural skills training or other rehabilitative interventions. However, to date only two studies have tested such combinations in direct experimental comparisons and delivered evidence for a superiority of combined treatment (Bowie et al., 2012; Horan et al., 2018). Reviews have identified a number of treatment elements associated with better treatment success, e.g., strategy-based training, error-free learning, scaffolding, chunking, self-monitoring, model learning, personalization, and contextualization (Wykes et al., 2011; Medalia and Saperstein, 2013), but to date, studies have only partially included these elements.

Therefore, the main aim of the present study was to use rigorous methodology (i.e., randomization, rater-blinded assessments, manualized treatment conditions that were formally broadly comparable, and independent external data management and statistical analyses) in a multicenter design to investigate the hypothesis that integrated social cognitive remediation and social behavioural skills therapy (ISST) is more efficacious than neurocognitive remediation therapy (NCRT) in improving treatment adherence and functional outcome in schizophrenia. In order not to deprive patients of a proven effective therapy, both treatments were designed to incorporate as many of the aforementioned beneficial treatment elements as possible. Furthermore, in contrast to most previous studies, the study was adequately powered a priori to detect the expected moderate treatment effect and included a six-month follow-up after completion of treatment to assess the stability of effects over time.

2. Methods

2.1. Study design

This was a multicenter, prospective, rater-blind, parallel-group, two-arm randomized controlled clinical trial performed according to good clinical practice guidelines. It was part of the ESPRIT (Enhancing Schizophrenia Prevention and Recovery through Innovative Treatments) research network and performed at six psychiatric hospitals (Alzey, Berlin, Bonn, Cologne, Düsseldorf, and Tübingen) in Germany. The study design and methods (Wölwer et al., 2022) and the feasibility and safety data (Schuster et al., 2023) have been published in detail elsewhere.

The study evaluated the efficacy of ISST as the active intervention vs NCRT as the control invention in improving treatment adherence and functional outcome in schizophrenia. ISST targets social cognition and skills, whereas NCRT targets neurocognition. Outcomes were assessed at baseline before randomization (V1), at the end of the six-month treatment period (V6), and at the six-month follow-up (V12). Moreover, during the treatment period (i.e., from V1-V6), serious adverse events and reasons for premature discontinuation of therapy were recorded monthly. Table 1 gives an overview of the schedule of enrolment, interventions, and main assessments.

All study procedures complied with the Declaration of Helsinki and were approved by the local ethics committees of the participating centers. Before recruitment started, the study was registered at ClinicalTrials.gov (NCT 02678858) and in the German Clinical Trials Register (DRKS 00010033). All participants gave written informed consent to participate.

Table 1
Schedule of enrolment, interventions, and main assessments of the Integrated Social Cognition and Social Skills Therapy study.

Variables	Screening visit	Treatment period		Follow-up
	Day −7 to −1	Day 0	Day 182 ± 14	≈Day 365 ± 28
	V0	V1	V6	V12
Informed consent	X			
Inclusion/exclusion criteria + Mini International Neuropsychiatric Interview, Version 6	X			
Randomization		X		
Efficacy (primary endpoint): study discontinuation				
All-cause discontinuation[a]		X	X	X
Efficacy (secondary endpoint): cognitive performance				
Social cognition: Pictures of Facial Affect, Movie for the Assessment of Social Cognition (MASC)		X	X	X
Neurocognition: Auditory Verbal Learning Test, Digit-Symbol Substitution Test, Digits forward + backward, Trail-Making Test A and B		X	X	X
Efficacy (secondary endpoint): psychosocial functioning/quality of life				
Social and Occupational Functioning Assessment Scale[a]		X	X	X
Functional Remission of General Schizophrenia		X	X	X
University of California Performance-based Skills Assessment		X	X	X
Quality of Life (WHOQOL-Bref)		X	X	X
Efficacy (secondary endpoint): clinical symptoms				
Positive and Negative Syndrome Scale	X	X	X	X
Calgary Depression Scale for Schizophrenia		X	X	X
Clinical Global Impression[a]		X	X	X
Safety				
Serious adverse events[a]		X	X	X

WHOQOL-Bref: World Health Organization Quality of Life scale.
[a] All-cause discontinuation, Social and Occupational Functioning Assessment Scale, Clinical Global Impression, and serious adverse events were assessed monthly.

2.2. Interventions

Both interventions were six-month CRT programs, and they were closely matched in terms of the application regimen. After providing written informed consent, eligible patients were randomly allocated to one of the two programs. The programs were applied as an add-on to routine drug and psychosocial treatment according to each patient's clinical needs and standard clinical treatment procedures in Germany. Furthermore, both were conducted in accordance with detailed treatment manuals. All study therapists were specially trained in applying the therapies, and after each treatment session, they recorded adherence to the manual by completing protocol forms.

Each intervention comprised 18 sessions (each lasting 50 min). Both interventions started with 10 weekly individual sessions, which were followed by five group sessions every two weeks for practice, two sessions in everyday real life situations to improve transfer, and a final session in which the therapist and patient gave feedback and together evaluated whether the patient's individual goals had been achieved. Both interventions provided the same amount of group interaction and guided community activity. The interventions are briefly described below, but a more detailed description can be found in Wölwer et al. (Wölwer et al., 2022).

2.2.1. ISST

ISST targets expressive and interactional behavior skills and the respective social cognitive domains. It is based primarily on the social cognitive remediation program Training in Affect Recognition (TAR), which was developed at the coordinating site (Department of Psychiatry and Psychotherapy, University of Düsseldorf, Düsseldorf, Germany). TAR primarily aims to enhance affect recognition and has already shown its efficacy in schizophrenia (Wölwer and Frommann, 2011; Wölwer et al., 2005; Luckhaus et al., 2013). For the present study, the TAR program was extended by integrating several behavioural exercises from typical social skills training programs to produce additional benefits.

ISST aims to facilitate the transfer and implementation of skills into problem areas in real life (which are identified in the first treatment session). To enhance transfer, it uses strategy training, personalization, and contextualization. Thus, ISST strives to integrate social behavioural with social cognitive training and specifically to foster cognitive comprehension of behavioural skills exercises.

2.2.2. NCRT

NCRT targets impairments in neurocognition, in particular attention, memory, and executive functions. It was used as the active control intervention to ensure that the amount of therapeutic attention and commitment to therapy was comparable in both groups. NCRT not only targets a different subset of cognitive processes than ISST but also follows a different kind of treatment strategy: In contrast to ISST, NCRT primarily uses a drill and practice approach that, according to the results of a previous study (Wölwer and Frommann, 2011), has no significant impact on social functioning.

2.3. Participants

The study included male and female in- and outpatients aged 18 to 65 years with a primary diagnosis of schizophrenia, as confirmed by the Mini International Neuropsychiatric Interview (Version 6.0.0) (Sheehan et al., 1998), and a total score on the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1992) of less than or equal to 75.

Further inclusion criteria were stable treatment with one or two antipsychotics and proficiency in German.

Exclusion criteria included severe suicidality; other relevant psychiatric, neurological, and somatic disorders; a verbal intelligence quotient below 80 (according to the multiple-choice vocabulary test MWT-B (Lehrl, 2005)); and current drug abuse. All inclusion and exclusion criteria were assessed after participants provided written informed consent at V0 (1–7 days before V1). Further details can be found in the study protocol (Wölwer et al., 2022).

2.4. Endpoints

2.4.1. Primary endpoint

As in all ESPRIT research network studies, the primary endpoint was ACD across the 12-month study period. The use of ACD as a common primary endpoint enables cross-comparisons and data pooling of the ESPRIT trials. In the psychiatric treatment and care of patients with

Table 2
Description of the secondary outcome measures.

Secondary outcome	Abbreviation	Description
Calgary Depression Rating Scale for Schizophrenia (Addington et al., 1993)	CDSS	A clinician-rated measure of depression in people with schizophrenia.
Clinical Global Impression (Guy, 1976)	CGI	Comprises single-item external assessment rating scales that measure the severity of symptoms in psychiatric patients.
Digits backward (Wechsler, 1981)	Db	Reproduction of digits in reverse order to test working memory
Digits forward (Wechsler, 1981)	Df	Reproduction of digits in their original order to test working memory
Digit-Symbol Substitution Test (Wechsler, 1981)	DSST	Replacing digits with symbols to test processing speed
Functional Remission of General Schizophrenia (Llorca et al., 2009)	FROGS	Assessments of improvements in social and occupational functioning
Movie for the Assessment of Social Cognition (Dziobek et al., 2006)	MASC	Video-based questionnaire for the evaluation of theory of mind
Positive and Negative Syndrome Scale (Kay et al., 1992)	PANSS	A clinician-rated measure of symptom severity for different symptoms in people with schizophrenia
Pictures of Facial Affect (Ekman and Friesen, 1976)	PFA	Test of ability to detect basic emotions from people's faces
Social and Occupational Functioning Assessment Scale (Morosini et al., 2000)	SOFAS	Single-item assessments of improvements in social and occupational functioning
Trail-Making Test Version A (Reitan, 1956)	TMT-A	Paper-pencil test for the assessment of attention
Trail-Making Test Version B (Reitan, 1956)	TMT-B	Paper-pencil test for the assessment of executive dysfunctions
University of California Performance-based Skills Assessment (Mausbach et al., 2007)	UPSA-Brief	Role-play and performance-based skills assessment of financial and communication skills
Auditory Verbal Learning Test (Helmstaedter et al., 2001)	VLMT	A test of learning and memory skills that uses serial list learning with subsequent distraction.
World Health Organization Quality of Life scale (WHO, 1996)	WHOQOL-Bref	Questionnaire to measure quality of life as a subjective assessment embedded in a cultural, social, and environmental context

The table gives a brief description of the secondary outcome measures used in the present study, their abbreviations and the respective references.

schizophrenia, non-adherence is a major problem that prevents patients from receiving effective treatment. Consequently, ACD has become a commonly used endpoint in landmark psychiatric treatment trials, e.g., the Clinical Antipsychotics Trials of Intervention Effectiveness (CATIE; Keefe et al., 2007; Lieberman et al., 2005) and the European First Episode Schizophrenia Trial (EUFEST; Kahn et al., 2008). ACD is also justified as an outcome in the context of improvements in cognition because patients with more pronounced cognitive impairment show poor adherence and low engagement with services.

ACD was evaluated at each study visit and defined as (1) not keeping appointments for treatment sessions or diagnostic assessments as scheduled for >6 weeks; (2) an inability to reach the participant despite extensive efforts by the study team; (3) termination of study participation by the patient or (4) study staff (e.g., for clinical reasons); (5) non-compliance with prescribed drug treatment for >14 consecutive days; and/or (6) relevant worsening of symptoms (PANSS total score $\geq$ 75 on consecutive visits over >14 days).

2.4.2. Secondary endpoints

Secondary endpoints included ratings of (1) cognitive performance, (2) psychosocial functioning and quality of life, and (3) clinical symptoms, as summarized in Tables 1 and 2 (see also (Wölwer et al., 2022)).

2.4.3. Safety measures

The safety of the interventions was assessed by evaluating the number of serious adverse events (SAEs), i.e., rehospitalizations, symptom exacerbations, suicidal crises, suicide attempts, and suicides, which occurred during the twelve-month treatment period.

2.5. Statistical analyses

Data were analyzed with IBM SPSS Statistics for Windows Version 28 (28.0.1.1). To avoid bias, analyses were performed primarily in the intention-to-treat (ITT) sample. However, a per protocol (PP) analysis was also performed with the data from all patients who fulfilled the predefined criteria of receiving at least 13 sessions of therapy of sufficient length and with sufficient motivation (according to the evaluation of the treating therapist) and who participated in the study at least until V6.

The main statistical analyses were performed by independent statisticians (authors MH and KR), and effect sizes were calculated by author MR. While transforming and analyzing the data, all statisticians were blinded to group assignments. The sample size was calculated according to the requirements of the primary endpoint. According to that calculation, each study arm has to include a total of 90 participants (see (Wölwer et al., 2022) for details). It should be noted that the alpha error was not controlled for in the analysis of the secondary endpoints.

2.5.1. Primary endpoint

To examine group differences in the primary endpoint, i.e., ACD over the 12-month study period, Kaplan-Meier curves were stratified by treatment group and compared by a log-rank test and a Cox regression. The Cox regression was stratified by study site, with the main effects group (ISST vs. NCRT), chlorpromazine (CPZ) equivalents at baseline, age, and sex. In 10 patients, invalid or missing CPZ equivalents values were estimated by an expectation maximization algorithm that included CPZ equivalents, age, sex, and secondary outcome scale scores (except for change in Clinical Global Impression [CGI]) at V1. A two-sided significance level of 5 % was applied, and adjusted hazard ratios with 95 % confidence intervals were calculated.

2.5.2. Secondary endpoints

A mixed model for repeated measures (MMRM) was used to test for group differences in secondary endpoint variables over time, with the fixed effects *intervention* (ISST vs NCRT), *time* (V6, and V12), the interaction of *intervention* and *time* (intervention*time), and the respective baseline score (V1) as covariates (with a heterogeneous first-order autoregressive variance-covariance matrix).

In addition, we used MMRM estimated marginal means to calculate effect sizes (according to Cohen's d) for the change from baseline to V6 and V12 in each group by using the pooled standard deviations (SDs) of both groups at baseline.

For descriptive measures, we calculated group means and SDs of observed values and MMRM estimated marginal means and standard errors. To evaluate for group differences at baseline, we analyzed frequencies and proportions by chi^2 tests and continuous measures by *t*-tests; in case of missing statistical prerequisites (normal distribution, homogeneity of variances), we examined continuous measures also by (non-parametric) Mann-Whitney tests.

The p values for a group-specific change from V1 to V6 and V1 to V12 can be calculated in two ways. Either based on the model of the post scores by subtracting the mean baseline value from the group-specific

estimated marginal means at V6 and V12 or directly by modelling the change score of the considered outcome variable. In both cases, the mean difference from baseline is divided by the standard error to calculate a t-statistic, which can then be transformed to a p value by using the corresponding degrees of freedom of the estimated marginal mean.

3. Results

3.1. Sample

Study participants were recruited from April 2016 to March 2020, and data acquisition, including follow-up, was completed in March 2021. As shown in the CONSORT chart (Fig. 1), the six participating trial centers together pre-screened 1436 individuals with schizophrenia for study eligibility. A total of 1259 individuals could not be included in the study because of a lack of consent to participate (n = 237), insufficient treatment compliance (n = 130), or fulfilment of at least one of the exclusion criteria (n = 892). Thus, 177 patients (76 women [42.9 %] and 101 men [57.1 %]) participated in the study.

Ninety patients were randomly allocated to ISST, and 87 to NCRT. Only rudimentary data were available for three participants because despite giving informed consent at the time of the screening examination (V0), they did not participate in the baseline assessment (V1) or attend subsequent study visits.

Participant baseline demographic and clinical characteristics are shown in Table 3. The mean age of the participants was 31.9 years (SD = 10.9; median = 27), and mean illness duration was 57.4 months (SD = 79.5; median, 27 months). These variables were not significantly different between the groups (Table 3).

Although the sex ratio appeared to be numerically less balanced in the ISST group (61 % men, n = 55) than in the NCRT group (53 % men, n = 46), the difference was not statistically significant (p = 0.27). Participants in the ISST group had a significantly lower mean number of own children (p = 0.02). They also tended to have a higher number of relatives with mental disorders, but the difference was not significant (p = 0.09). The two groups did not differ in any other demographic or clinical variables at the baseline assessment. In both groups, the number of patients receiving psychotherapy was relatively small: In the ISST group, six patients were receiving cognitive behavioural therapy and five patients, another form of psychotherapy, and in the NCRT group, seven patients were receiving cognitive behavioural therapy and eight patients, another form of psychotherapy. These numbers were not significantly different between the groups. As part of their regular treatment, all inpatients also participated in various day-structuring therapies, such as occupational therapy, sports therapy, and art therapy.

Of the planned 18 therapy sessions per participant, participants completed an overall mean of 13.3 sessions (median, 17; for more details, see (Schuster et al., 2023)). The formal criteria for treatment according to the study protocol (PP sample, i.e., participation in at least 13 of the planned 18 therapy sessions with sufficient length and motivation and participation in V6) were met by 110 of the 177 study participants. Six individuals did not participate in any of the therapy sessions. In the six-month treatment period, 31.1 % of patients fulfilled the ACD criteria. The criteria for PP treatment were met by a tendentially lower proportion of participants in the ISST group than in the NCRT group (ISST, 56 %, n = 50; NCRT, 69 %, n = 60; p = 0.07). This numerical difference was also reflected in a tendency for the ISST group to attend a lower mean number of therapy sessions (ISST, 12.5 sessions, SD, 6.3; NCRT, 14.1 sessions, SD, 5.7; p = 0.08).

Compared with the PP sample (n = 110), patients not included in the PP sample (n = 67) more often had a migration background (p = 0.04) and had fewer years of education (p = 0.02) and a higher score for depressive symptoms (CDSS, p = 0.01).

3.2. Primary endpoint

According to the Kaplan-Meier analysis in the ITT sample, ACD over the 12-month study was not significantly different between the ISST and NCRT groups (43.3 % vs 34.5 %, respectively; hazard ratio [HR] 1.33, 95 % CI 0.82–2.15; p = 0.248) (Fig. 2).

The ACD rate was significantly higher in men (46.5 %) than in women (28.9 %; p = 0.018). In the Cox regression, the hazard ratio for female versus male patients was 0.597 (95 % CI: 0.351–1.016; p = 0.057).

When the factors age and CPZ equivalents at baseline were included in the Cox regression, neither showed a significant contribution.

The reasons for dropout were not significantly different between the groups and were related to withdrawal of consent by participants (n = 30, 16.9 %), failure of participants to keep scheduled appointments for study treatment or assessments (n = 18, 10.2 %), inability of study staff to contact participants despite extensive efforts (n = 15, 8.5 %), and other reasons (n = 6, 3.4 %).

3.3. Secondary endpoints

The following results refer to the ITT sample. The results for the PP sample (N = 110) were similar to those for the ITT sample and therefore are not shown.

3.3.1. Cognition

The MMRM results on cognition and additional statistical parameters for all variables are presented in Table 4. The MMRM with the group factor *intervention* (ISST vs NCRT), the repeated measures factor *time* (V6 and V12), and the respective baseline score (V1) as covariates revealed significant group effects but no interactions. ISST had significantly greater effects than NCRT in the PFA test (p < 0.001), whereas NCRT had significantly greater effects than ISST in the $VLMT_1$ (p = 0.002), $VLMT_5$ (p = 0.031), and $VLMT_{sum1–5}$ (p = 0.021).

Additionally, the MMRM showed tendencies for a group effect in that NCRT tended to have a greater effect than ISST on DSST (p = 0.081) and DS-b (p = 0.075); no interactions were found. MMRM revealed no significant effect of the intervention for any of the other measures of cognition (all p > 0.1).

The analysis of the changes from baseline to V6 revealed a significant improvement in the PFA test for the ISST group (p < 0.001; d = 0.83) and the NCRT group, although the effect size was much lower in the latter group (p = 0.032; d = 0.22) (Fig. 3). Concerning neurocognition, significant improvements occurred only in the NCRT group, in particular in the $VLMT_1$ (p = 0.005; d = 0.40), $VLMT_5$ (p = 0.028; d = 0.29), $VLMT_{sum1–5}$ (p = 0.017; d = 0.30), and DSST (p < 0.001; d = 0.29) (Fig. 3); no improvements were found in Db.

3.3.2. Level of functioning

The MMRM results and additional statistical parameters for all level of functioning measures are presented in Table 5. The MMRM revealed significant group effects only for the WHO Quality of Life scale (WHO-QOL-Bref) *social relationships* domain (p = 0.046), which favored NCRT; no interactions were found. The analysis of the changes from baseline to V6 revealed that NCRT significantly improved the WHOQOL-Bref social relationships domain (p < 0.001; d = 0.41).

For all other measures of functioning (including the SOFAS and FROGS sum scores), MMRM showed no significant differences between the intervention groups (all p > 0.1). However, functioning (i.e., the SOFAS and FROGS sum scores) significantly improved from baseline to V6 and V12 in both groups, with comparatively high effect sizes in the SOFAS (d = 0.67–1.0). Fig. 4 shows the changes in SOFAS score, FROGS sum score, and the WHOQOL-Bref *psychological* and *social relationships* domains.

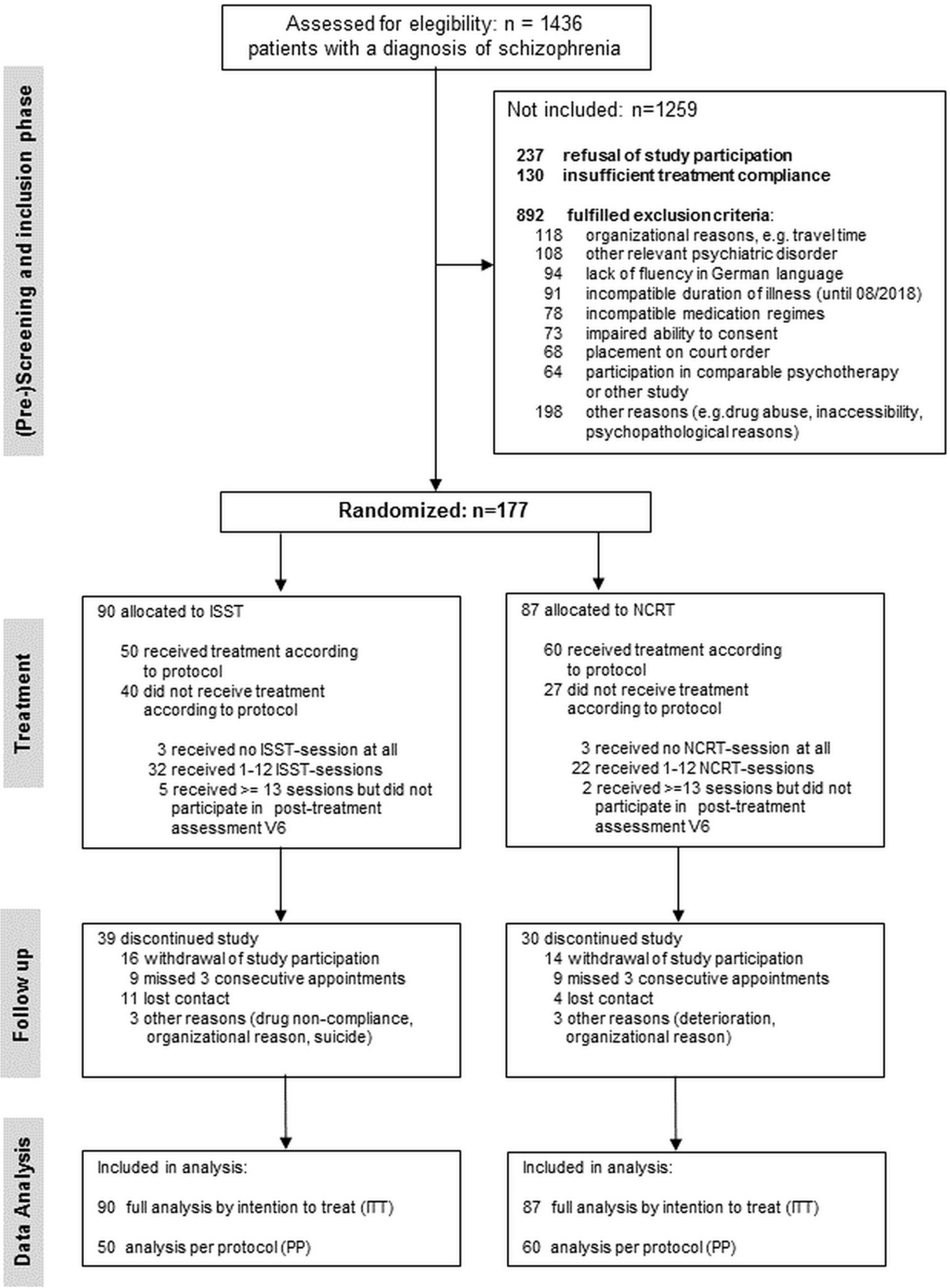

Fig. 1. CONSORT chart. Caption: Flow of patients through the study. ISST, Integrated Social Cognitive and Behavioural Skills Therapy; NCRT, Neurocognitive Remediation Therapy.

Table 3
Demographic and clinical characteristics at baseline of patients with schizophrenia treated by Integrated Social Cognitive and Behavioural Skills Therapy or Neurocognitive Remediation Therapy.

Characteristics	Total	ISST	NCRT	p[a]
Total, no. (%)	177 (100)	90 (50.8)	87 (49.2)	
Age, mean (SD), y[b]	32.1 (11.0)	31.9 (10.7)	32.2 (11.3)	0.84
Sex (male), no. (%)[b]	101 (57.1)	55 (61.1)	46 (52.9)	0.27
Body mass index, mean (SD)	26.5 (5.2)	26.2 (5.1)	26.8 (5.4)	0.46
Migration background (yes), No. (%)	62 (35.6)	32 (36.4)	30 (34.9)	0.84
Native language (German), No. (%)	147 (83.1)	73 (81.1)	74 (85.1)	0.48
Family status no. (%)				0.60
Married, living together	26 (14.9)	11 (12.5)	15 (17.4)	
Married, living separated	5 (2.9)	1 (1.1)	4 (4.7)	
Single	135 (77.6)	71 (80.7)	64 (74.4)	
Divorced	7 (4)	4 (4.5)	3 (3.5)	
Widowed	1 (0.6)	1 (1.1)	0 (0)	
Number of children, mean (SD)	0.2 (0.7)	0.1 (0.4)	0.4 (0.8)	**0.02**
Number of siblings, mean (SD)	1.7 (1.4)	1.7 (1.5)	1.7 (1.4)	0.90
Relatives with mental disorders, no. (%)	116 (66.7)	64 (72.7)	52 (60.5)	0.09
Living situation (alone), no. (%)	69 (39.7)	31 (35.2)	38 (44.2)	0.23
Years of education, mean (SD)	12.4 (2.7)	12.2 (3.1)	12.6 (2.2)	0.32
Occupation (not working), no. (%)	69 (40.4)	37 (43)	32 (37.6)	0.47
Duration of illness, mean (SD), mo	57.4 (79.5)	55.1 (79.8)	59.8 (79.5)	0.71
Number of psychotic episodes, mean (SD)	2.9 (5.6)	2.7 (2.6)	3.2 (7.5)	0.53
CGI severity of illness at baseline, mean (SD)	4.1 (1)	4.1 (1.1)	4.2 (0.9)	0.86
Past suicidal attempt (yes), No. (%)	37 (21.3)	18 (20.5)	19 (22.1)	0.79
CDSS total score, mean (SD)	4.1 (3.6)	4.3 (3.7)	4 (3.5)	0.65
PANSS total score, mean (SD)	51.5 (10.3)	52.5 (9.9)	50.5 (10.7)	0.20
Participants at each center, no. (% of total participants)				0.97
Alzey	19 (10.7)	9 (10)	10 (11.5)	
Berlin	13 (7.3)	8 (8.9)	5 (5.7)	
Bonn	11 (6.2)	6 (6.7)	5 (5.7)	
Cologne	48 (27.1)	23 (25.6)	25 (28.7)	
Düsseldorf	44 (24.9)	22 (24.4)	22 (25.3)	
Tübingen	42 (23.7)	22 (24.4)	20 (23)	
Antipsychotic dose in CPZ equivalents, mean (SD)	393.1 (232.5)	399.4 (212.1)	386.3 (254.1)	0.62

CDSS, Calgary Depression Rating Scale for Schizophrenia; CGI, Clinical Global Impression; CPZ, chlorpromazine; ISST, Integrated Social Cognition and Social Skills Therapy; NCRT, Neurocognitive Remediation Therapy; PANSS, Positive and Negative Syndrome Scale.

[a] Significance level for group differences; for frequencies and proportions, chi^2 test; for continuous measures, *t*-test, and in case of missing statistical prerequisites (normal distribution, homogeneity of variances), (non-parametric) Mann-Whitney test (indicated by #).

[b] For n = 3 patients, the missing age and sex in the database were calculated by using the entries in the randomization file. Significant results are shown in bold.

3.3.3. Clinical symptoms

Table 6 presents the MMRM results and additional statistical parameters for all measures of clinical symptoms. MMRM revealed no significant group or time effects or interactions. For all these measures, the analysis of the changes from baseline to V6 revealed a significant improvement with both interventions.

3.3.4. Safety measures

During the 12 month study period, 48 SAEs were documented, the majority of which were temporary rehospitalizations because of psychiatric conditions (31/48, 64.6 %). One patient committed suicide. The number of SAEs was not significantly different between the groups (ISST, n = 27; NCRT, n = 21, $chi^2 = 0.62$ [df = 1]; p = 0.43).

4. Discussion

The present study was designed to test the hypothesis that in patients with schizophrenia, a combination of social-cognitive remediation and social behavioural skills training (i.e., ISST) is associated with lower ACD, i.e., a lower dropout rate, than neurocognitive remediation (i.e., NCRT) and is more effective in improving functional outcomes.

The study did not confirm the hypothesis that ACD is lower with ISST than with NCRT; however, the mean overall dropout rate of 39 % across both groups was considerably lower than the dropout rate of 68 % in the pharmacological studies on early schizophrenia that were used for the power calculation (Gaebel et al., 2007). The numbers are roughly comparable with the results of two former studies on comprehensive psychosocial rehabilitation programs featuring cognitive remediation, which reported dropout rates of 37 % (Kurtz et al., 2013) and 43 % (Twamley et al., 2011).

The present study confirmed the higher dropout rate described in the literature in men with schizophrenia, i.e., the ACD rate was significantly higher in men (46.5 %) than in women (28.9 %).

The effects of the study interventions on functional outcome must be considered at different levels: According to the definition of cognitive remediation, effects in proximal variables of cognitive performance must be considered as a prerequisite for the ultimately targeted effects in more distal measures of social functioning and quality of life (Bowie et al., 2020).

Overall, the effects on cognitive performance suggest that both treatment conditions essentially achieved the expected differential improvements in many, but not all, of the cognitive domains they targeted. As expected from our own preliminary results on studies of the precursors of the two treatment conditions (Wölwer et al., 2005; Luckhaus et al., 2013), facial affect recognition (PFA) improved significantly more with ISST than with NCRT. The effect size in the treatment period V1 to V6 was comparatively high in the ISST group (d = 0.83) compared with the NCRT group (d = 0.22). This training effect of ISST was also maintained in the six-month follow-up period, i.e., V6 to V12. Nevertheless, theory of mind showed no significant group difference between ISST and NCRT, which may be because the interventions did not improve theory of mind or the Movie for the Assessment of Social Cognition test was insensitive.

As expected, neurocognitive improvements were more pronounced in the NCRT group. The MMRM of the period V6 to V12 revealed significant group differences in VLMT short-term memory ($VLMT_1$) and learning components ($VLMT_5$, and $VLMT_{sum1-5}$). In both these components, in the period V1 to V6 the improvement in performance was more

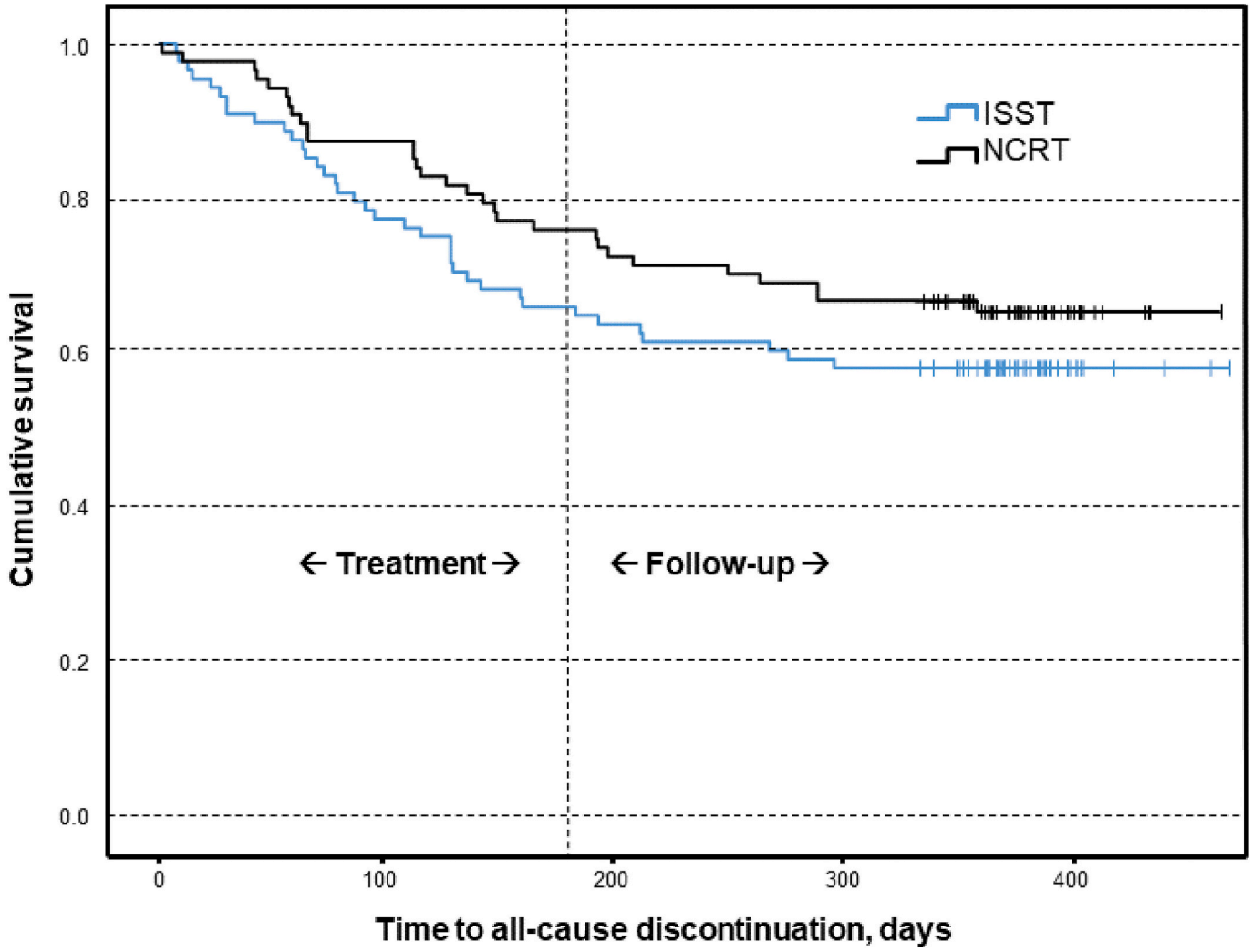

Fig. 2. All-cause discontinuation rates in patients with schizophrenia treated by Integrated Social Cognitive and Behavioural Skills Therapy (n = 90) or Neurocognitive Remediation Therapy (n = 87). Caption: The figure shows Kaplan-Meier curves for all-cause discontinuation (ACD) rates in the intention-to-treat sample. Results from the Integrated Social Cognition and Social Skills therapy group are shown in blue, and those from the Neurocognitive Remediation Therapy control group in black. The x-axis represents the time until ACD in days, and the y-axis, the participation probability. The vertical dotted bar indicates the end of the active treatment period at 180 days.
ISST, Integrated Social Cognition and Social Skills therapy; NCRT, Neurocognitive Remediation Therapy. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

pronounced with NCRT ($VLMT_1$, d = 0.40; $VLMT_5$, d = 0.28; $VLMT_{sum1–5}$, d = 0.30) than with ISST ($VLMT_1$, d = 0.07; $VLMT_5$, d = −0.01; $VLMT_{sum1–5}$, d = 0.03). Numerically different but non-significant effects were found for NCRT in working memory (Db) and cognitive processing speed (DSST). Although these effects must be interpreted with caution because of the large number of comparisons, the lack of alpha adjustment, and null findings on other outcome variables, the overall pattern of the results may suggest that ISST essentially achieved the targeted improvement in social cognition and NCRT that in neurocognition. Therefore, in principle both treatment conditions can be considered to be effective. To put it in a nutshell, we found no change from V6 to V12 but significant improvement from baseline to V6 and V12. The finding that the effects persisted even after the end of treatment is consistent with the results of a recently published meta-analysis (Vita et al., 2024).

Contrary to expectations, the MMRMs of the follow-up period V6 to V12 showed no statistically significant difference between the two groups in almost all parameters of the level of functioning (SOFAS, FROGS), social capacity (UPSA), and subjective quality of life (WHO-QOL-Bref). A group effect was found only for satisfaction with social relationships (WHOQOL-Bref D3), where satisfaction was significantly higher in the NCRT group. Nevertheless, from V1 to V6 both treatment groups showed clinically significant improvements in social functioning (SOFAS) (ISST, d = 0.67; NCRT, d = 0.79), which even increased slightly after the end of treatment (V1 vs V12: ISST, d = 0.80; NCRT, d = 1.00). The improvement after the end of treatment formed the basis of the tendency for a time effect seen in the MMRM for the follow-up period V6 to V12 (p = 0.057). Such a tendency for a time effect was also evident in the FROGS sum score (p = 0.086) despite the lower effect sizes in the change scores over the observation period.

To date, meta-analyses have reported effect sizes of the magnitude achieved for SOFAS almost exclusively for cognitive remediation procedures but generally not for therapies without cognitive remediation. For example, only small to moderate effects (d = 0.2–0.5) on global measures of functioning in schizophrenia were reported for treatments aimed at symptom reduction, such as antipsychotic drugs (Swartz et al., 2007) or behavioural therapy (Wykes et al., 2008) and for social skills training aimed at promoting social skills (Kurtz and Mueser, 2008). Among the various CRT procedures, large effect sizes (d ≈ 0.8) were most likely to be reported for social-cognitive remediation approaches,

Table 4
Mixed model estimated means and test statistics for effects on cognitive outcomes in patients with schizophrenia treated by Integrated Social Cognitive and Behavioural Skills Therapy (n = 90) or Neurocognitive Remediation Therapy (n = 87).

Variable	Group	V1	V6	V12	Effect size		Change from baseline per group		MMRM overall effects (V6 to V12)		
		Mean	Mean (SE)	Mean (SE)	V1-V6	V1-V12	p (time)		p (time)	p (group)	p (g × t)
							V1-V6	V1-V12			
PFA sum score	ISST	20.7	23.5 (0.4)	23.5 (0.5)	0.83	0.84	**<0.001**	**<0.001**	0.669	**<0.001**	0.697
	NCRT		21.4 (0.3)	21.6 (0.4)	0.22	0.28	**0.032**	**0.034**			
MASC sum score	ISST	29.6	31.9 (0.6)	32.9 (0.7)	0.34	0.47	**<0.001**	**<0.001**	**0.005**	0.476	0.617
	NCRT		32.3 (0.6)	33.6 (0.7)	0.38	0.58	**<0.001**	**<0.001**			
$Vlmt_1$	ISST	6.6	6.8 (0.3)	5.6 (0.3)	0.07	−0.49	0.603	**0.001**	**0.003**	**0.002**	0.109
	NCRT		7.4 (0.3)	7.0 (0.3)	0.40	0.17	**0.005**	0.224			
$Vlmt_5$	ISST	11.9	11.9 (0.3)	11.8 (0.3)	−0.01	−0.06	0.926	0.642	0.911	**0.031**	0.589
	NCRT		12.6 (0.3)	12.7 (0.3)	0.28	0.31	**0.029**	**0.014**			
$Vlmt_{sum\ 1–5}$	ISST	49.5	49.7 (1.4)	47.0 (1.4)	0.03	−0.23	0.849	0.074	**0.015**	**0.021**	0.315
	NCRT		52.6 (1.3)	51.5 (1.3)	0.30	0.19	**0.017**	0.135			
$Vlmt_7$	ISST	10.0	10.0 (0.4)	8.9 (0.5)	0.00	−0.32	0.998	**0.023**	**0.013**	0.414	0.155
	NCRT		10.1 (0.4)	9.8 (0.5)	0.01	−0.08	0.951	0.547			
DSST	ISST	45.3	46.3 (1.0)	47.4 (1.1)	0.08	0.17	0.303	0.057	0.327	0.081	0.371
	NCRT		48.9 (0.9)	49.0 (1.0)	0.29	0.30	**<0.001**	**0.001**			
Df	ISST	7.5	7.3 (0.2)	7.5 (0.2)	−0.12	−0.01	0.250	0.928	0.197	0.186	0.73
	NCRT		7.7 (0.2)	7.8 (0.2)	0.07	0.13	0.475	0.239			
Db	ISST	6.2	5.9 (0.2)	5.7 (0.3)	−0.18	−0.24	0.156	0.064	0.866	0.075	0.382
	NCRT		6.2 (0.2)	6.4 (0.2)	−0.02	0.08	0.880	0.519			
TMT-A	ISST	31.6	30.4 (1.5)	27.2 (1.3)	−0.09	−0.34	0.416	**0.001**	**0.007**	0.269	0.148
	NCRT		27.6 (1.4)	26.6 (1.2)	−0.31	−0.38	**0.004**	**<0.001**			
TMT-B	ISST	77.2	77.8 (3.5)	67.7 (3.5)	0.03	−0.27	0.749	**0.012**	**0.001**	0.344	0.079
	NCRT		70.6 (3.3)	67.3 (3.3)	−0.18	−0.28	0.070	**0.006**			

The table shows test statistics for the cognitive measures in the mixed models repeated measure analysis with the group factor *intervention* (Integrated Social Cognitive and Behavioural Skills Therapy vs Neurocognitive Remediation Therapy), the repeated measures factor *time* (V6 and V12), and the respective baseline score (V1) as covariate. Significant results are shown in bold.
Db, digits backward; Df, digits forward; DSST, Digit-Symbol Substitution Test; FROGS, Functional Remission of General Schizophrenia; MASC, Movie for the Assessment of Social Cognition; MMRM, mixed models for repeated measures; TMT-A and -B, Trail-Making Test A and B; $VLMT_1$, Auditory Verbal Learning Test, first trial; $VLMT_5$, Auditory Verbal Learning Test, fifth trial; $VLMT_{sum\ 1–5}$, Auditory Verbal Learning Test, sum of first, second, third, fourth, and fifth trials; $VLMT_7$, Auditory Verbal Learning Test, seventh trial.

especially when therapy was guided by a therapist and used strategy-oriented training (Kurtz and Richardson, 2012; Nijman et al., 2020). In contrast, more exercise-oriented neurocognitive approaches, especially those that used only PC-based repetitive training, tended to achieve smaller effect sizes (d ≈ 0.2) (Prikken et al., 2019). In this respect, the finding that social functioning and quality of life did not improve more with the social-cognitive and social-behavioural remediation program ISST than with the neurocognitive-oriented remediation program NCRT was contrary to expectations. The finding can most likely be interpreted as a sign that both treatment approaches showed high efficacy and as indicating that the active control intervention NCRT was more effective than expected. The better-than-expected efficacy of NCRT may have been due to the strong methodological and formal parallelization of the treatment conditions, which aimed to avoid differences related to non-specific factors (e.g., therapeutic attention). Thus, the close matching of procedures in both treatment arms may have attenuated the differences in effect size obtained for functioning.

Because of the careful design of the treatment session protocols, we can assume that the two study interventions were implemented as planned. However, the ISST group completed a mean of only 12.5 sessions, which was slightly fewer than the mean number in the NCRT group (14.1 sessions). The lower number of ISST sessions is in line with the lower proportion of PP treatments in the ISST group than in the NCRT group (56 % vs 69 %), which in turn can be interpreted as a consequence of the numerically higher (but not statistically significant) discontinuation rate between V1 and V12 in the ISST group (43 %) than in the NCRT group (35 %). A higher discontinuation rate was recorded in particular for male participants, who were assigned slightly (although not statistically significantly) more often to the ISST group than to the NCRT group (61.1 % vs 52.9 %). However, a comparison of the results of the ITT analysis with those of the PP analysis, which obtained very similar results despite the exclusion of patients who discontinued treatment, indicates that the difference in discontinuation rate does not explain the lack of the expected group differences.

As expected, we found no group-specific effects on participants' psychopathological condition. However, in the treatment period V1 to V6 the results showed a group-independent improvement in almost all clinical variables, with absolute medium effect sizes ranging from 0.25 (for the PANSS negative scale) to 0.77 for the global assessment of severity (CGI). In the follow-up period (V6-V12), the clinical condition of both groups remained stable, so the MMRMs showed no time or interaction effects.

The safety data on SAEs indicated that neither of the study treatments had a higher risk because the results showed no significant group difference in the number of SAEs (total n = 48) during the study period V1 to V12. Overall, the SAE rate was comparable to or even lower than the values to be expected in people with schizophrenia and reported in the literature (see (Schuster et al., 2023)).

This ISST study is one of the most comprehensive and methodologically rigorous clinical trials on the efficacy of cognitive remediation approaches in schizophrenia. To enhance transfer into real life, both the ISST and NCRT interventions included recently identified, essential treatment elements, such as guidance by a trained therapist, strategy training, personalization, and contextualization. Another strength of the study is the use of an active control treatment (i.e., NCRT) that almost perfectly controlled non-specific treatment effects. However, in retrospect the active control intervention appears to have been more of a limitation because the specific treatment effects of ISST were smaller than expected and the results did not show the expected group differences. We expected to find differences between the treatments because evidence from other studies indicates that social cognitive remediation and social behavioural training have beneficial effects on functional outcome (Kurtz and Richardson, 2012; Nijman et al., 2020; Kurtz and Mueser, 2008) whereas drill- and practice-based neurocognitive

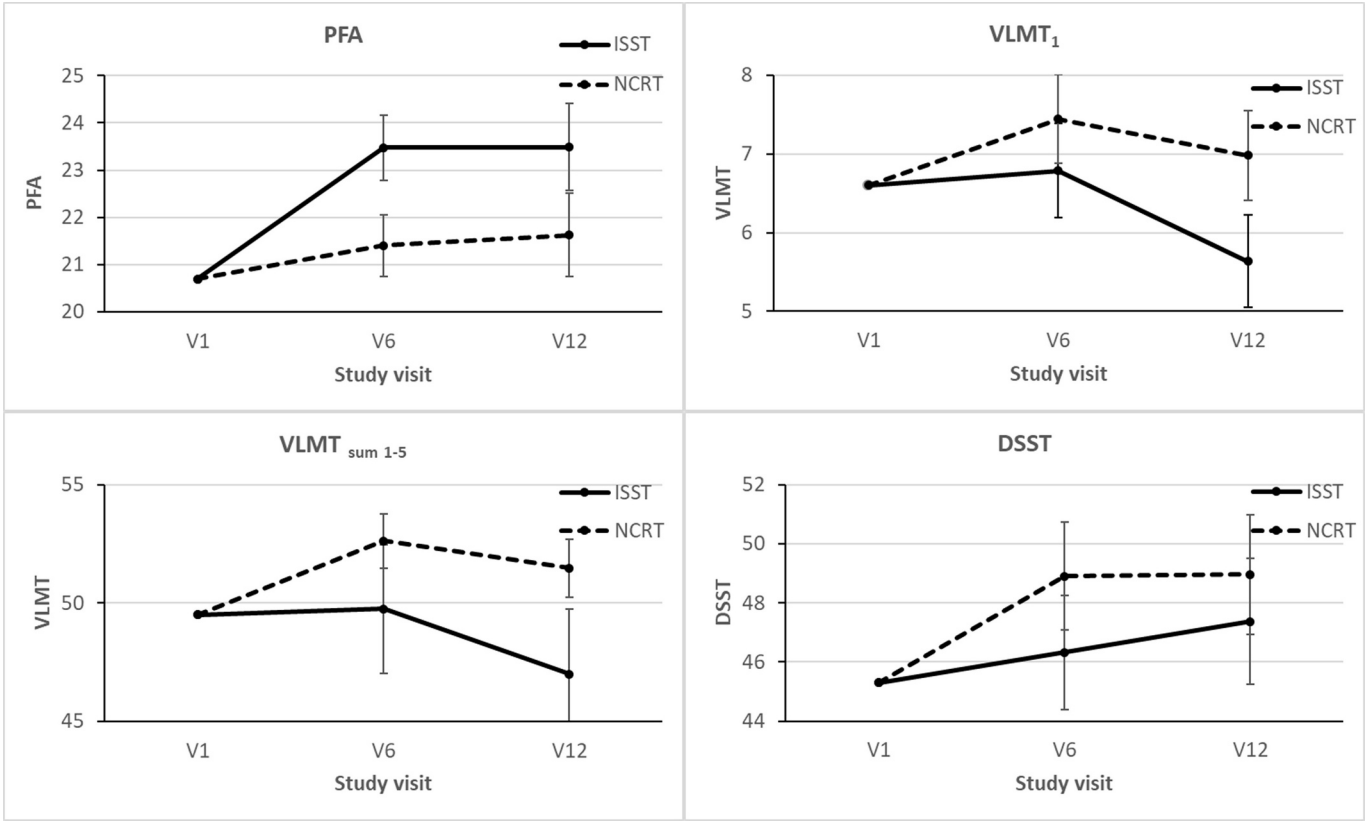

Fig. 3. Time course of cognitive measures in patients with schizophrenia treated by Integrated Social Cognitive and Behavioural Skills Therapy (n = 90) or Neurocognitive Remediation Therapy (n = 87). Caption: Pictures of Facial Affect recognition improved more in the Integrated Social Cognitive and Behavioural Skills Therapy group, whereas neurocognitive measures such as the Auditory Verbal Learning Test and Digit-Symbol Substitution Test improved more in the Neurocognitive Remediation Therapy.
DSST, Digit-Symbol Substitution Test; ISST, Integrated Social Cognitive and Behavioural Skills Therapy; NCRT, Neurocognitive Remediation Therapy; PFA, Pictures of Facial Affect; VLMT, Auditory Verbal Learning Test.

remediation has only marginal effects (Prikken et al., 2019).

The inclusion of a third treatment condition comprising treatment as usual without cognitive remediation and social skills training may have helped to clarify whether both treatments were equally effective or whether there was no treatment effect at all. However, both pragmatic and ethical reasons precluded the use of such a three-group approach because patient availability was limited and we considered it inappropriate to deprive patients of treatment components such as cognitive and social skills training, which are already established in many hospitals.

Overall, the results of this study indicate that ISST and NCRT support social functioning in people with schizophrenia and can serve as important components in the overall treatment concept for schizophrenic disorders with the aim to achieve the desired level of "recovery."

Abbreviations

ACD	All-cause discontinuation
CDSS	Calgary Depression Rating Scale for Schizophrenia
CGI	Clinical Global Impression
CPZ	Chlorpromazine
CRT	Cognitive remediation therapy
Db	Digits backward
Df	Digits forward
DSST	Digit-Symbol Substitution Test
ESPRIT	Enhancing Schizophrenia Prevention and Recovery through Innovative Treatments
FROGS	Functional Remission of General Schizophrenia
ISST	Integrated Social Cognition and Social Skills Therapy
ITT	Intention-to-treat
MASC	Movie for the Assessment of Social Cognition
MMRM	Mixed models for repeated measures
NCRT	Neurocognitive Remediation Therapy
PANSS	Positive and Negative Syndrome Scale
PFA	Pictures of Facial Affect
PP	Per protocol
SAE	Serious adverse event
SD	Standard deviation
SOFAS	Social and Occupational Functioning Assessment Scale
TAR	Training in Affect Recognition
TMT-A and -B	Trail-Making Test Versions A and B
UPSA-Brief	University of California Performance-based Skills Assessment
VLMT	Auditory Verbal Learning Test
WHOQOL-Bref	World Health Organization Quality of Life scale

ISST Study Group

The study was performed by the ISST study group, which consists of the following people: W. Wölwer, S. Abresch, N. Frommann, A. Lowe, D. Kamp, P. Ockenfelds, K. Weide, F. Pessanha, and S. Dinse (Düsseldorf); A. Philipsen, R. Hurlemann, J. Schultz, N. Striepens, U. Darrelmann, C. Kloss, S. Wasserthal, H. Högenauer, and N. Schumacher (Bonn); F. Jessen, J. Kambeitz, C. Baldermann, A. Muthesius, C. Doll, H. Schneegans, A. Ferrari, G. Kolb, T. Haidl, D. Zeus, T. Pilgram, M. Rohde, P. Albert-Porcar, S. Hölzer, M. Hellmich, K. Kuhr, K. Rosenberger, S. Hamacher, D. Kraus, S. Sadura, U. Bergmann, F. Scheckenbach, and A. Montada (Cologne); S. Klingberg, D. Wildgruber, U. Hermanutz, J. Richter, J. Vonderschmitt, and L. Hölz (Tübingen); A. Bechdolf, K. Leopold, S.

Table 5
Mixed model estimated means and test statistics for effects on level of functioning and quality of life in patients with schizophrenia treated by Integrated Social Cognitive and Behavioural Skills Therapy (n = 90) or Neurocognitive Remediation Therapy (n = 87).

Variable	Group	V1	V6	V12	Effect size		Change from baseline per group		MMRM overall effects (V6 to V12)		
		Mean	Mean (SE)	Mean (SE)	V1-V6	V1-V12	p (time)		p (time)	p (group)	p (g × t)
							V1-V6	V1-V12			
SOFAS	ISST	54.1	61.6 (1.5)	62.7 (1.7)	0.67	0.80	**<0.001**	**<0.001**	0.057	0.350	0.417
	NCRT		62.6 (1.4)	65.1 (1.6)	0.79	1.00	**<0.001**	**<0.001**			
FROGS sum score	ISST	65.6	68.3 (1.2)	69.6 (1.3)	0.26	0.38	**0.018**	**0.002**	0.086	0.551	0.901
	NCRT		69.3 (1.1)	70.3 (1.2)	0.35	0.45	**0.001**	**<0.001**			
UPSA sum score part 1	ISST	7.4	7.8 (0.2)	7.9 (0.2)	0.28	0.33	**0.017**	**0.008**	0.377	0.724	0.81
	NCRT		7.8 (0.2)	8.0 (0.2)	0.30	0.39	**0.005**	**0.001**			
UPSA sum score part 2	ISST	5.0	5.0 (0.2)	5.2 (0.1)	−0.08	0.16	0.622	0.160	0.056	0.861	0.805
	NCRT		5.0 (0.1)	5.2 (0.1)	−0.03	0.15	0.847	0.154			
WHOQOL-Bref G1: Quality of life	ISST	3.3	3.6 (0.1)	3.7 (0.1)	0.27	0.38	**0.015**	**0.003**	0.212	0.687	0.981
	NCRT		3.5 (0.1)	3.6 (0.1)	0.22	0.33	**0.036**	**0.005**			
WHOQOL-Bref G2: Health	ISST	3.2	3.5 (0.1)	3.4 (0.1)	0.25	0.13	**0.032**	0.310	0.59	0.527	0.503
	NCRT		3.5 (0.1)	3.5 (0.1)	0.26	0.27	**0.018**	**0.023**			
WHOQOL-Bref D1: Physical	ISST	24.6	26.5 (0.5)	26.5 (0.6)	0.41	0.43	**0.001**	**0.002**	0.239	0.936	0.309
	NCRT		26.1 (0.5)	26.8 (0.6)	0.32	0.49	**0.004**	**<0.001**			
WHOQOL-Bref D2: Psychological	ISST	19.8	21.2 (0.5)	20.5 (0.6)	0.29	0.15	**0.008**	0.234	0.751	0.139	0.068
	NCRT		21.5 (0.5)	21.9 (0.5)	0.36	0.47	**0.001**	**<0.001**			
WHOQOL-Bref D3: Social relationships	ISST	9.8	10.1 (0.3)	10.4 (0.3)	0.15	0.25	0.180	**0.071**	0.183	**0.046**	0.922
	NCRT		10.8 (0.2)	11.1 (0.3)	0.41	0.53	**<0.001**	**<0.001**			
WHOQOL-Bref D4: Environment	ISST	30.6	32.6 (0.5)	32.3 (0.6)	0.46	0.38	**<0.001**	**0.007**	0.932	0.905	0.306
	NCRT		32.2 (0.5)	32.6 (0.6)	0.36	0.45	**0.002**	**0.001**			

Results are shown for mixed models for repeated measures with the group factor *intervention* (ISST vs NCRT), the repeated measures factor *time* (V6 and V12), and the respective baseline score (V1) as covariates. Significant results are shown in bold.
FROGS, Functional Remission of General Schizophrenia; ISST, Integrated Social Cognitive and Behavioural Skills Therapy; MMRM, mixed models for repeated measures; NRT, Neurocognitive Remediation Therapy; SOFAS, Social and Occupational Functioning Assessment Scale; UPSA-Brief, University of California Performance-based Skills Assessment; WHOQOL-Bref, World Health Organization Quality of Life scale.

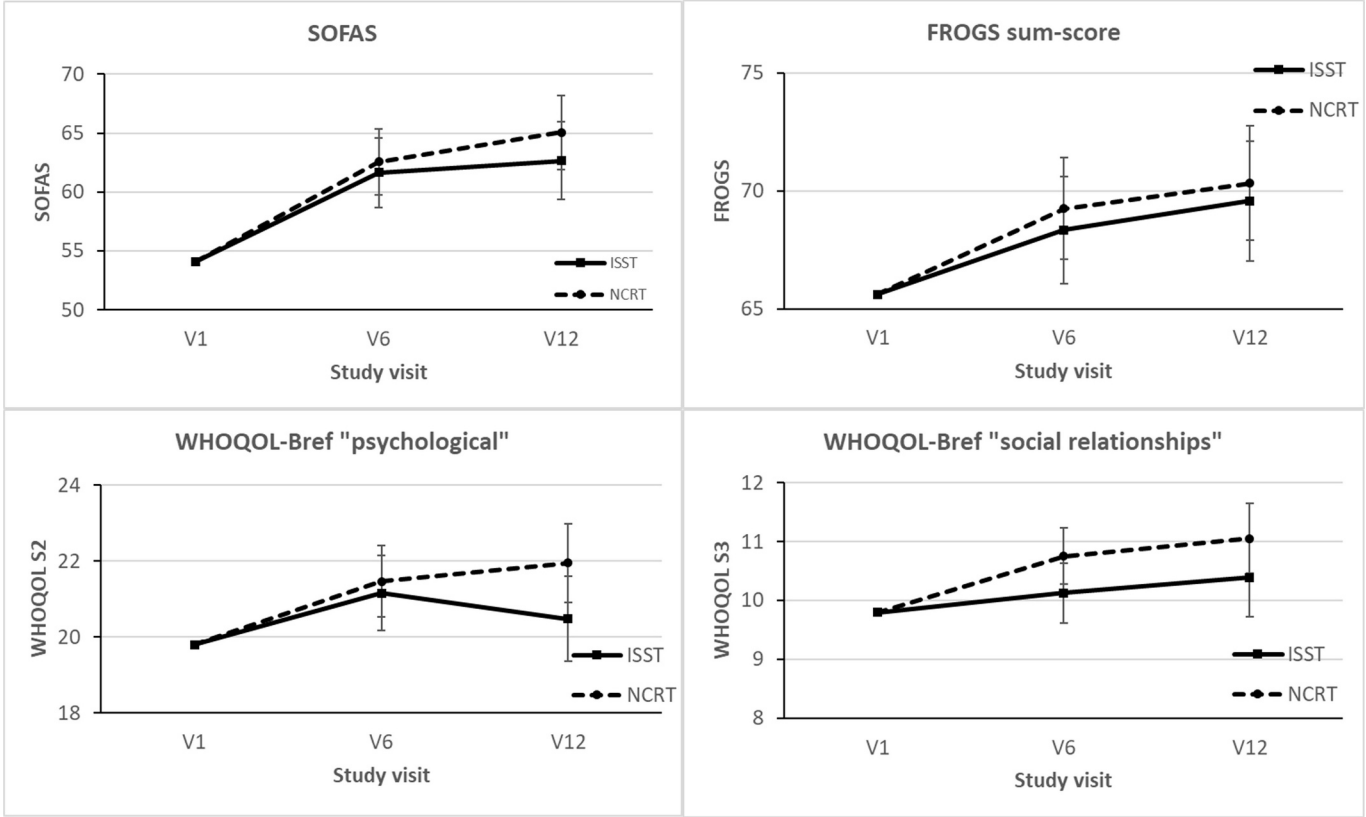

Fig. 4. Time course of level of functioning and quality of life in patients with schizophrenia treated by Integrated Social Cognitive and Behavioural Skills Therapy (n = 90) or Neurocognitive Remediation Therapy (n = 87). Caption: The only significant difference between the groups was in the World Health Organization Quality of Life scale *Social relationships* domain. However, a consistent improvement over time was seen with both interventions. FROGS, Functional Remission of General Schizophrenia; ISST, Integrated Social Cognitive and Behavioural Skills Therapy; NRT, Neurocognitive Remediation Therapy; SOFAS, Social and Occupational Functioning Assessment Scale; WHOQOL-Bref, World Health Organization Quality of Life.

Table 6
Mixed model estimated means and test statistics for effects on clinical symptoms in patients with schizophrenia treated by Integrated Social Cognitive and Behavioural Skills Therapy (n = 90) or Neurocognitive Remediation Therapy (n = 87).

Variable	Group	V1	V6	V12	Effect size		Change from baseline per group		MMRM overall effects (V6 to V12)		
		Mean	Mean (SE)	Mean (SE)	V1-V6	V1-V12	p (time)		p (time)	p (group)	p (g × t)
							V1-V6	V1-V12			
PANSS sum score	ISST	50.5	45.1 (1.3)	45.9 (1.3)	−0.52	−0.45	**<0.001**	**0.001**	0.97	0.798	0.379
	NCRT		46.2 (1.2)	45.6 (1.3)	−0.42	−0.48	**0.001**	**<0.001**			
PANSS positive scale	ISST	11.4	10.1 (0.4)	9.8 (0.5)	−0.35	−0.42	**0.004**	**0.001**	0.451	0.741	0.753
	NCRT		9.8 (0.4)	9.7 (0.4)	−0.42	−0.45	**<0.001**	**<0.001**			
PANSS negative scale	ISST	13.6	11.7 (0.5)	12.2 (0.6)	−0.39	−0.31	**0.001**	**0.013**	0.342	0.407	0.649
	NCRT		12.4 (0.5)	12.6 (0.6)	−0.25	−0.22	**0.017**	0.058			
PANSS general psychopathology	ISST	25.5	23.4 (0.7)	23.9 (0.7)	−0.43	−0.33	**0.003**	**0.025**	0.835	0.986	0.201
	NCRT		24 (0.7)	23.3 (0.7)	−0.31	−0.45	**0.023**	**0.001**			
CDSS sum score	ISST	3.8	2.4 (0.4)	2.9 (0.4)	−0.38	−0.26	**0.001**	**0.033**	0.922	0.64	0.17
	NCRT		2.6 (0.4)	2.3 (0.4)	−0.33	−0.43	**0.002**	**<0.001**			
CGI_severity	ISST	4.1	3.5 (0.1)	3.5 (0.2)	−0.58	−0.68	**<0.001**	**<0.001**	0.281	0.285	0.569
	NCRT		3.4 (0.1)	3.3 (0.1)	−0.77	−0.92	**<0.001**	**<0.001**			

Results of the mixed models for repeated measures with the group factor *intervention* (Integrated Social Cognitive and Behavioural Skills Therapy vs Neurocognitive Remediation Therapy), the repeated measures factor *time* (V6 and V12), and the respective baseline score (V1) as covariates. Significant results are shown in bold. CDSS, Calgary Depression Rating Scale for Schizophrenia; CGI, Clinical Global Impression; ISST, Integrated Social Cognitive and Behavioural Skills Therapy; MMRM, mixed models for repeated measures; NRT, Neurocognitive Remediation Therapy; PANSS, Positive and Negative Syndrome Scale.

Siebert, F. Seidel, and E.S. Blanke (Berlin); A. Brockhaus-Dumke, X. Solojenkina, B. Klos, E. Rosenbauer, S. Cinar, L. Herdt, F. Henrich, and S. Neff (Alzey); and A. Meyer-Lindenberg (Mannheim).

CRediT authorship contribution statement

Daniel Kamp: Writing – review & editing, Writing – original draft, Methodology, Investigation, Conceptualization. **Agnes Lowe:** Writing – review & editing, Methodology, Investigation, Conceptualization. **Karolin Weide:** Writing – review & editing, Methodology, Investigation, Conceptualization. **Mathias Riesbeck:** Writing – review & editing, Formal analysis. **Andreas Bechdolf:** Writing – review & editing, Supervision, Investigation. **Karolina Leopold:** Writing – review & editing, Investigation. **Anke Brockhaus-Dumke:** Writing – review & editing, Supervision, Investigation. **Bettina Klos:** Writing – review & editing, Investigation. **René Hurlemann:** Writing – review & editing, Supervision, Investigation. **Sven Wasserthal:** Writing – review & editing, Investigation. **Ana Muthesius:** Writing – review & editing, Supervision, Investigation. **Joseph Kambeitz:** Writing – review & editing, Investigation. **Stefan Klingberg:** Writing – review & editing, Supervision, Investigation. **Lea Hölz:** Writing – review & editing, Investigation. **Martin Hellmich:** Writing – review & editing, Formal analysis. **Kerstin D. Rosenberger:** Writing – review & editing, Formal analysis. **Sabine Sadura:** Writing – review & editing, Data curation. **Andreas Meyer-Lindenberg:** Writing – review & editing, Conceptualization. **Wolfgang Wölwer:** Writing – review & editing, Writing – original draft, Supervision, Project administration, Methodology, Funding acquisition, Conceptualization.

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Declaration of competing interest

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Data availability

Scripts for the whole analysis and deidentified participant data can be made available upon reasonable request (email to daniel.kamp@lvr.de).

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