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ABSTRACT

Objective: Cognitive remediation therapy (CRT) is an evidence-based behavioral intervention that enhances functional outcomes in schizophrenia patients by improving cognition. However, not all patients benefit equally from CRT, and predictors of real-world functional improvement are poorly understood. This study aimed to identify patient-related baseline predictors of functional improvement by evaluating two distinct CRT approaches targeting different types of cognition: social cognition (Integrated Social Cognition and Social Skills Training, ISST) and neurocognition (Neurocognitive Remediation Therapy, NCRT).

Methods: This secondary analysis used data from a large, multicenter randomized controlled trial. Participants with schizophrenia ($N = 174$) were randomly assigned to ISST or NCRT for six months. Multiple linear regression analyses were performed to determine whether baseline demographic, cognitive, clinical, or functional characteristics predicted changes in real-world functioning, as measured by the Social and Occupational Functioning Assessment Scale.

Abbreviations: CDSS, Calgary Depression Rating Scale for Schizophrenia; CGI, Clinical Global Impression; CRT, Cognitive remediation therapy; Db, Digits backward; Df, Digits forward; DRKS, Deutsches Register Klinischer Studien; 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; MINI, Mini International Neuropsychiatric Interview; NC, Neurocognition; NCRT, Neurocognitive Remediation Therapy; PANSS, Positive and Negative Syndrome Scale; PFA, Pictures of Facial Affect; RCT, Randomized Controlled Trial; SAE, Serious adverse event; SC, Social cognition; 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, brief version; VLMT, Auditory Verbal Learning Test; WHOQOL-Bref, World Health Organization Quality of Life scale.

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Results: The Digit Symbol Substitution Test was the strongest and most consistent predictor of functional improvement. Lower baseline functioning also predicted greater gains, although only in multivariable models. Domain-specific predictors were identified for each intervention: better affect recognition predicted better outcomes in ISST, whereas verbal memory did so in NCRT.
Conclusion: The CRT approaches studied here appear to be most effective for individuals with a more preserved baseline level of cognitive performance, especially in terms of processing speed. These findings support the use of brief cognitive assessments to guide CRT implementation and suggest that tailoring interventions to individual cognitive profiles may enhance treatment efficacy.

1. Introduction

Cognitive impairments are one of the core symptoms of schizophrenia (Green et al., 2019, 2004; McCutcheon et al., 2023; Takeda et al., 2024). They show longitudinal stability over the course of disease (McCleery et al., 2016) and respond poorly to antipsychotic medication (Kucharska-Pietura and Mortimer, 2013; Nielsen et al., 2015). Furthermore, they are the main reason why most people with schizophrenia do not reach recovery under current treatment methods (Hansen et al., 2023; Jääskeläinen et al., 2013), and they are associated with poor functioning and psychosocial outcome (Bowie et al., 2006; Kharawala et al., 2022; Vita et al., 2025).

Cognition can be broadly divided into neurocognition (NC) and social cognition (SC) (Green et al., 2019, 2004). Although both domains significantly influence functional outcome in schizophrenia (Takeda et al., 2024), SC is more strongly associated with real-world functioning and moderates the effects of NC on functioning (Fett et al., 2011; Halverson et al., 2019).

Cognitive remediation therapy (CRT) is an effective add-on behavioral intervention for individuals with schizophrenia and improves functional outcome by targeting cognitive impairments (Vita et al., 2021; Wykes et al., 2011). However, CRT is an umbrella term that encompasses diverse approaches that differ in the (1) cognitive approaches used (bottom-up or top-down) (Best and Bowie, 2017), (2) delivery format (which ranges from fully computerized programs to therapist-led interventions) (Wykes et al., 2011), (3) training focus (repetitive drill-and-practice tasks or strategy-based learning) (McGurk et al., 2007), (4) and specific cognitive domains targeted, i.e., NC and/or SC, which may be addressed separately, broadly, or in an integrated manner (Best and Bowie, 2017; Bowie et al., 2020).

Although CRT improves cognition, cognitive enhancement is only an intermediate step toward improved real-world functioning. Furthermore, a competence-performance discrepancy exists (Gupta et al., 2012) in that enhanced cognition does not necessarily translate into corresponding functional improvement.

Research has shown that the positive effects of CRT on real-world functioning can be improved by applying it with broader psychosocial interventions (Vita et al., 2021). In addition, a recent randomized controlled trial (RCT) that compared an SC- and social skill training-based CRT approach with an NC-based one found that even though the two interventions targeted different cognitive domains, they both led to comparable improvements in functioning (Kamp et al., 2025).

Despite the overall positive effects of CRT, not all individuals benefit equally. Therefore, a better understanding of these predictors would be crucial for clinical practice because it may help not only to target CRT to those most likely to benefit, but also to adapt CRT for those patients who do not benefit optimally from current CRT approaches.

Some patient-related predictors of functional improvement have been discussed in the literature to date, but findings across studies remain inconsistent and heterogenous (Barlati et al., 2018; Seccomandi et al., 2020). For instance, meta-analyses have provided mixed evidence regarding the role of age in functional outcomes of CRT: Although CRT appeared to be more effective in older patients in some studies (e.g. McGurk et al., 2007), older age was associated with reduced treatment efficacy in others (e.g. Kurtz and Richardson, 2012). Furthermore, one meta-analysis (Nijman et al., 2020) identified female sex as a positive predictor of social functioning improvements after CRT targeting SC, but a more recent meta-analysis did not replicate this finding (Yeo et al., 2022). Other recent meta-analyses suggested that individuals with fewer years of education and lower premorbid intelligence quotient (IQ) (Vita et al., 2021) and those in a chronic stage of illness (Lejeune et al., 2021) may benefit more in terms of functional improvement after CRT, but another (Kambeitz-Ilankovic et al., 2019) did not find any significant predictors of functional improvement after CRT. A recent secondary moderator analysis of individual patient data from two RCTs found greater improvements in functional capacity after integrative CRT in patients who were older and had fewer years of education, lower baseline cognition and functional scores, and more severe negative symptoms (Sampedro et al., 2023).

The present study aimed to identify baseline predictors of real-world functional improvement after two distinct CRT approaches in individuals with schizophrenia by analyzing data from a large, methodologically rigorous multicenter RCT (Kamp et al., 2025). On the basis of the research described above, we hypothesized that individuals with fewer years of education, lower baseline cognitive and functional performance levels, and more severe clinical symptoms at baseline may derive the greatest functional benefit from CRT.

2. Method

2.1. Study design

The present study was a secondary predictor analysis of a multicenter, prospective, rater-blinded, parallel-group, two-arm clinical RCT. The design and methods (Wölwer et al., 2022), feasibility and safety (Schuster et al., 2023), and primary and secondary endpoints (Kamp et al., 2025) of this RCT have been published elsewhere.

The RCT was part of the ESPRIT (Enhancing Schizophrenia Prevention and Recovery through Innovative Treatments) research network and performed according to good clinical practice guidelines at six German psychiatric hospitals (Alzey, Berlin, Bonn, Cologne, Düsseldorf, and Tübingen). It compared the efficacy of Integrated Social Cognition and Social Skills Therapy (ISST, which targets SC and social skills) as the active intervention with that of Neurocognitive Remediation Therapy (NCRT, which targets NC) as the control intervention in improving treatment adherence, cognition, and clinical and functional outcomes in individuals with schizophrenia.

Outcome measures were assessed at baseline (V1), the end of the six-month treatment period (V6), and the six-month post-treatment follow-up (V12). For the present analysis, baseline measures (V1) were used to predict the change in social functioning from V1 to V6.

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

Table 1
Description of the psychometric, cognitive, and functional measures used in the present study.

Variable	Description	Reference
Calgary Depression Rating Scale for Schizophrenia (CDSS)	Clinician-rated scale that assesses the severity of depressive symptoms in individuals with schizophrenia.	Addington et al., 1993
Clinical Global Impression (CGI)	Single-item clinician rating that evaluates overall symptom severity in psychiatric patients.	Hamilton and Guy, 1976
Digits backward (Db)	Task requiring the recall of digit sequences in reverse order. Primarily assesses working memory and attention control.	Wechsler, 1981
Digits forward (Df)	Task requiring the recall of digit sequences in the same order as presented. Measures short-term verbal memory and attention span.	Wechsler, 1981
Digit-Symbol Substitution Test (DSST)	Timed substitution task in which participants match symbols to numbers. Mainly evaluates processing speed.	Wechsler, 1981
Functional Remission of General Schizophrenia (FROGS)	Questionnaire that assesses social and occupational functioning across multiple functional domains in people with schizophrenia.	Llorca et al., 2009
Movie for the Assessment of Social Cognition (MASC)	Video-based test that measures theory of mind by having participants infer the mental states of characters in short film clips.	Dziobek et al., 2006
Positive and Negative Syndrome Scale (PANSS)	Clinician-administered instrument that assesses positive, negative, and general psychopathology symptoms in schizophrenia.	Kay et al., 1987
Pictures of Facial Affect (PFA)	Test that evaluates the ability to recognize and label basic emotions from standardized pictures of faces.	Ekman and Friesen, 1976
Social and Occupational Functioning Assessment Scale (SOFAS)	Single-item clinician rating scale that assesses real-world social and occupational functioning independently of symptom severity.	Morosini et al., 2000
Trail-Making Test Version A (TMT-A)	Timed paper-and-pencil task that measures visual attention and processing speed by asking participants to connect numbered dots in sequence.	Reitan, 1956
Trail-Making Test Version B (TMT-B)	Timed paper-and-pencil task that measures cognitive flexibility, task switching, and executive functioning by asking participants to alternate between numbers and letters.	Reitan, 1956
University of California Performance-based Skills Assessment, brief version (UPSA-Brief)	Role play-based test that evaluates practical everyday functioning in domains such as communication and financial management.	Mausbach et al., 2007
Auditory Verbal Learning Test (VLMT)	Task that assesses verbal learning and memory by using a list-learning paradigm with multiple trials and interference.	Helmstaedter et al., 2001
World Health Organization Quality of Life scale (WHOQOL-Bref)	Self-report questionnaire that measures perceived quality of life across various domains.	WHO, 1996

Caption: The table gives a brief description of the measures used in the present study and provides the respective references.
Abbreviations: 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; PANSS = Positive and Negative Syndrome Scale; PFA = Pictures of Facial Affect; SOFAS = Social and Occupational Functioning Assessment Scale; TMT = Trail Making Test; UPSA-Brief = University of California Performance-based Skills Assessment – Brief; VLMT = Verbaler Lern- und Merkfähigkeitstest; WHOQOL-BREF = World Health Organization Quality of Life – Brief Version.

2.2. Interventions

After providing written informed consent, eligible patients were randomly assigned to one of the two CRT interventions. The interventions were administered for six months, closely matched in their administration protocols, and delivered by specially trained therapists according to comprehensive treatment manuals. Each intervention provided an equivalent amount of group interaction and community engagement.

The CRT interventions were delivered as an add-on to routine pharmacological and psychosocial treatment according to each patient's clinical needs and standard clinical treatment procedures in Germany.

Each intervention consisted of 18 sessions, each lasting 50 min. The programs began with 10 weekly individual sessions, followed by five biweekly group sessions for practice, two sessions conducted in real-life settings to facilitate transfer, and a final session during which the therapist and participant provided feedback. A brief overview of each intervention is provided below, and a more comprehensive description can be found elsewhere (Wölwer et al., 2022).

2.2.1. ISST

ISST is primarily based on the social cognitive remediation program Training in Affect Recognition (TAR), which was developed at the coordinating site of the RCT (Department of Psychiatry and Psychotherapy, University of Düsseldorf, Düsseldorf, Germany) and has previously shown efficacy in schizophrenia (Luckhaus et al., 2013; Wölwer et al., 2005; Wölwer and Frommann, 2011). ISST targets expressive and interactional behavior skills and the corresponding social cognitive domains. To achieve additional benefits, it also integrates several behavioral exercises from typical social skills training programs. Furthermore, it enhances transfer by incorporating strategy training, personalization, and contextualization.

2.2.2. NCRT

NCRT, the active control condition, addresses deficits in NC, particularly in the areas of memory, attention, and executive processes. It not only addresses a different subset of cognitive functions than ISST, but also uses a fundamentally different treatment strategy: Unlike ISST, which emphasizes strategy-based interventions, NCRT relies primarily on repetitive drill-and-practice methods.

2.3. Participants

Participants were 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 (MINI) (Version 6.0.0) (Sheehan et al., 1998) and a total score of 75 or less on the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987). Additional inclusion criteria were stable treatment with one or two antipsychotics and sufficient knowledge of German. Exclusion criteria were relevant psychiatric, neurological, or somatic comorbidities; severe suicidality; a verbal IQ below 80 as assessed by the multiple-choice vocabulary test MWT-B (Lehrl, 2005); and current substance abuse. Further details are provided elsewhere (Wölwer et al., 2022).

2.4. Assessment

The following variables were assessed: (1) patient characteristics; measures of (2) cognitive performance and (3) psychosocial functioning and quality of life; and (4) clinical symptoms (see also (Wölwer et al., 2022) and (Kamp et al., 2025)). Table 1 provides a brief description of

the respective measures.

2.5. Data analysis

The entire ESPRIT study sample comprised 177 patients. However, 3 patients were excluded from the analysis because they had no values at all, so the final analysis sample (intention-to-treat [ITT] sample) comprised 174 patients. All data were analyzed with SPSS Statistics (Version 29; IBM Corp., Armonk, NY, USA). Descriptive statistics included frequency and proportions for categorical data and mean and standard deviation (SD) for continuous data. The significance level was set in advance as a p value of less than.05. No adjustments for multiple comparisons were made because of the exploratory nature of the study.

Predictors of change in social functioning – defined as the difference in the Social and Occupational Functioning Assessment Scale (SOFAS) scores (Morosini et al., 2000) between V6 and V1 - were identified by (multiple) linear regression analyses. The baseline values of the following variables were considered as potential predictors:

- Patient characteristics: age, sex, years of education, verbal IQ, illness duration, number of psychotic episodes
- Treatment characteristics: treatment group
- Cognition: Auditory Verbal Learning Test (VLMT) scores, i.e., number of immediately recalled items after the first ($VLMT_1$) and fifth trials ($VLMT_5$), sum of recalled items across the first to fifth trials ($VLMT_{sum\ 1–5}$), and delayed recall after the seventh trial ($VLMT_7$); Digit-Symbol Substitution Test (DSST); Digits forward (Df) and Digits backward (Db); Pictures of Facial Affect (PFA); Movie for the Assessment of Social Cognition (MASC) sum score; Trail-Making Test versions A (TMT-A) and B (TMT-B); and University of California Performance-based Skills Assessment, brief version (UPSA-Brief) sum score
- Symptoms: Clinical Global Impression (CGI) severity; PANSS positive, negative, and general psychopathology scores (positive, negative, and general psychopathology severity scores were derived from the original PANSS subscales (Kay et al., 1987), calculated as the unweighted sum of items P1–P7, N1–N7, and G1–G16, respectively); Calgary Depression Rating Scale for Schizophrenia (CDSS) sum score
- Quality of life: World Health Organization Quality of Life scale (WHOQOL-Bref) G1: Quality of Life, WHOQOL-Bref G2: Health
- Social functioning: Functional Remission of General Schizophrenia sum score, SOFAS

In participants with missing values for baseline predictors and for the SOFAS at V6, values were imputed by using an estimation-maximization algorithm (Dempster et al., 1977). To assess the robustness of the findings regarding the handling of missing data, we performed an additional sensitivity analysis only in participants with complete baseline and outcome data ($n = 122$, completer sample).

All cognitive measures were transformed into z-scores (mean, 0; SD, 1) according to the distribution of observed values (deviation from the sample mean divided by the sample SD). The z-scores for the time to complete the TMT-A and TMT-B were inverted (i.e., multiplied by −1) to enable a uniform interpretation of scores (i.e., so that for all scales, higher scores meant better performance). The assumptions for the multiple linear regression were checked in advance, and residuals were found to be approximately normally distributed according to both visual inspection and formal testing (Kolmogorov-Smirnov test; $p > .2$). No relevant multicollinearity was detected among the potential predictors.

In an initial step, to evaluate the univariate relationship within the framework of the general linear model we calculated bivariate correlations for each predictor, i.e., Pearson correlation coefficients for continuous predictors and point-biserial coefficients for dichotomous measures (sex, treatment group). Then, to obtain a final model we used a stepwise forward procedure to identify multiple predictors (inclusion criterion, $p \leq .05$; exclusion criterion, $p \geq .10$). An additional regression

Table 2
Sample characteristics of all patients (intention-to-treat sample, $N = 174$).

Variable	Observed values		After imputation of missing data (N = 174)
	N (%)	Mean (SD)	Mean (SD)
Sociodemographic and Clinical Variables			
Sex			
- Male, n (%)	99 (56.9)		
- Female, n (%)	75 (43.1)		
CRT group			
- ISST, n (%)	88 (50.6)		
- NCRT, n (%)	86 (49.4)		
Age, y	174	31.9 (10.9)	31.9 (10.9)
Duration of illness, mo	162	57.4 (79.5)	61.8 (79.7)
Psychotic episodes, n	165	3.0 (5.6)	3.1 (5.6)
Years of education	173	12.4 (2.7)	12.4 (2.7)
Verbal IQ	173	103.0 (11.4)	103.0 (11.3)
Clinical Symptom Measures			
CGI severity of illness	174	4.2 (1.0)	4.2 (1.0)
PANSS positive scale score	174	11.6 (3.7)	11.6 (3.7)
PANSS negative scale score	174	13.8 (4.8)	13.8 (4.8)
PANSS general psychopathology score	174	26.1 (5.0)	26.1 (5.0)
CDSS total score	174	4.2 (3.6)	4.2 (3.6)
Cognitive Measures			
PFA sum score	173	20.5 (3.4)	20.4 (3.4)
MASC sum score	170	29.0 (6.8)	29.0 (6.7)
$VLMT_1$	173	6.6 (2.0)	6.6 (2.0)
$VLMT_5$	172	11.7 (2.5)	11.6 (2.5)
$VLMT_{sum\ 1–5}$	173	48.4 (10.6)	48.4 (10.6)
$VLMT_7$	172	9.7 (3.4)	9.7 (3.4)
DSST	174	44.1 (12.3)	44.1 (12.3)
Df	172	7.4 (2.1)	7.4 (2.1)
Db	172	6.0 (1.9)	6.0 (1.9)
TMT-A, s	174	33.2 (13.2)	33.2 (13.2)
TMT-B, s	173	81.2 (41.0)	81.9 (41.7)
UPSA-Brief sum score	169	12.3 (2.1)	12.3 (2.1)
Functioning and Quality of Life			
FROGS sum score	174	63.6 (10.6)	63.6 (10.6)
SOFAS score at baseline	174	53.3 (11.8)	53.3 (11.8)
SOFAS score at V6	122	62.8 (14.6)	61.3 (14.9)
Δ SOFAS score (V6-V1)	122	8.5 (11.6)	8.0 (10.2)
WHOQOL-Bref G1: Quality of life	170	3.3 (0.9)	3.3 (0.9)
WHOQOL-Bref G2: Health	170	3.2 (1.0)	3.2 (1.0)

Caption: The table shows baseline characteristics of the patients, including observed values (including missing values) and values after missing data imputation using the expectation-maximization algorithm. Continuous variables are presented as mean (SD), and categorical variables as number (percentage). ΔSOFAS indicates the change in the SOFAS score from baseline to the six-month visit (V6).
Abbreviations: CDSS, Calgary Depression Rating Scale for Schizophrenia; CGI,

Clinical Global Impression; CRT, cognitive remediation therapy; Db, Digits backward; Df, Digits forward; DSST, Digit-Symbol Substitution Test; FROGS, Functional Remission of General Schizophrenia; IQ, intelligence quotient; MASC, Movie for the Assessment of Social Cognition; PANSS, Positive and Negative Syndrome Scale; PFA, Pictures of Facial Affect; SOFAS, Social and Occupational Functioning Assessment Scale; TMT-A, Trail-Making Test A; TMT-B, Trail-Making Test B; UPSA-Brief, University of California Performance-based Skills Assessment, brief version; $VLMT_1$, 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; WHOQOL-Bref, World Health Organization Quality of Life scale.

with backward elimination performed to validate the model produced exactly the same set of predictors; therefore, detailed results are not reported.

To test for differences in predictive parameters between the treatment groups (ISST vs NCRT), we performed the respective analyses for each group with the ITT sample data ($N = 174$).

To examine whether predictors of these two models differed significantly from each other, we included all of them in a multiple regression model (computed separately for each group) and compared any two coefficients by using the z-statistic $(b_1 - b_2)/\sqrt{se_1^2 + se_2^2}$.

3. Results

The baseline sample characteristics and statistics for all variables included in the predictor analyses are presented in Table 2. The table shows measured values and values after imputation of missing data and includes the SOFAS score at baseline and V6 (after the six-month treatment phase) and the change in SOFAS score from baseline (V6-V1).

In the complete sample (N = 174), 11 out of 28 bivariate correlations between the putative predictors and the change in SOFAS score from V1 to V6 reached statistical significance. The strongest correlation coefficients were found for DSST ($r = 0.38$, $p < .001$), MASC sum score ($r = 0.29$, $p < .001$), and UPSA-Brief sum score ($r = 0.25$, $p < .001$). A multiple linear regression model constructed with nine significant predictors explained 36% of the variance in the change in SOFAS score. The strongest single predictor was DSST ($R^2 = 0.14$, $p \leq 0.001$), followed by the baseline SOFAS score ($\Delta R^2 = 0.03$, $p \leq 0.001$) and the WHOQOL-Bref G1: Quality of Life score ($\Delta R^2 = 0.05$. $p \leq 0.001$). Table 3 summarizes the results of the bivariate correlations and multiple linear regression. The sensitivity analysis in the completer sample ($n = 122$; see Supplementary Table S1) produced a similar pattern of results, with DSST and baseline SOFAS score remaining the strongest and most consistent predictors of functional improvement, confirming the robustness of the main findings.

In the ISST subsample ($n = 88$), five bivariate correlations reached

Table 3
Regression analysis predicting change in the Social and Occupational Functioning Assessment Scale score from baseline to six months (V6) in the whole sample (N = 174).

Variable	Univariate analysis		Multiple linear regression analysis				
	r[1]	p	b	Standard. beta	p	R^2	Step-No.[2]
DSST, *Z*-score	**0.38**	**< 0.001**	**4.19**	**0.41**	**< 0.001**	**0.14**	**1**
MASC sum score, Z-score	0.29	< 0.001	1.32	0.13	0.047	0.29	5
UPSA-Brief sum score	**0.25**	**< 0.001**	**0.90**	**0.19**	**0.013**	**0.33**	**7**
$VLMT_1$, Z-score	**0.24**	**0.001**					
PFA sum score, *Z*-score	**0.24**	**0.001**	**1.45**	**0.14**	**0.042**	**0.36**	**9**
Duration of illness, mo	−0.23	0.003					
Psychotic episodes, n	−0.23	0.003					
Age, y	−0.22	0.004					
Db, Z-score	0.21	0.006					
$VLMT_{sum\ 1-5}$, Z-score	0.18	0.019					
WHOQOL-Bref G1: Quality of life	0.17	0.024	3.50	0.32	< 0.001	0.22	3
Df, Z-score	0.15	0.051					
TMT-B, inverted Z-score	0.14	0.073					
$VLMT_7$, Z-score	0.13	0.095					
$VLMT_5$, Z-score	0.12	0.124					
FROGS sum score	0.12	0.124					
TMT-A, inverted Z-score	0.11	0.151	−1.88	−0.18	0.017	0.35	8
CDSS total score	0.11	0.159	0.68	0.24	< 0.001	0.26	4
Sex	0.09	0.224					
Verbal IQ	−0.08	0.271	−0.13	−0.15	0.022	0.31	6
SOFAS score at baseline	**−0.08**	**0.288**	**−0.21**	**−0.24**	**< 0.001**	**0.17**	**2**
Years of education	0.07	0.352					
PANSS positive scale score	0.06	0.464					
Treatment group	0.06	0.470					
PANSS general psychopathology score	−0.04	0.607					
PANSS negative scale score	−0.04	0.635					
WHOQOL-Bref G2: Health	−0.02	0.818					
CGI severity of illness	0.01	0.851					

Caption: The table shows the results of univariate and stepwise forward multiple regression analyses predicting change in the SOFAS score, including imputed missing values. For the multiple regression analyses, the following are shown: unstandardized (b) and standardized (β) coefficients, significance (p), explained variance (R^2), and step of entry. Predictors are sorted by absolute univariate association. Selected predictors (DSST, SOFAS score at baseline, UPSA-Brief sum score, PFA sum score and $VLMT_1$) are highlighted in bold to enhance readability.

Abbreviations: CDSS, Calgary Depression Rating Scale for Schizophrenia; CGI, Clinical Global Impression; Db, Digits backward; Df, Digits forward; DSST, Digit-Symbol Substitution Test; FROGS, Functional Remission of General Schizophrenia; IQ, intelligence quotient; MASC, Movie for the Assessment of Social Cognition; PANSS, Positive and Negative Syndrome Scale; PFA, Pictures of Facial Affect; SOFAS, Social and Occupational Functioning Assessment Scale; TMT-A, Trail-Making Test A; TMT—B, Trail-Making Test B; UPSA-Brief, University of California Performance-based Skills Assessment, brief version; $VLMT_1$, 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; WHOQOL-Bref, World Health Organization Quality of Life scale.

[1] Pearson correlation coefficients were used for continuous predictors, and point-biserial coefficients for dichotomous measures (sex, treatment group).

[2] Step-No. indicates the order of entry in the stepwise forward multiple regression model.

Table 4
Regression analysis predicting change in the Social and Occupational Functioning Assessment Scale score in the Integrated Social Cognition and Social Skills Training subgroup ($n = 88$).

Variable	Univariate analysis		Multiple analysis				
	r[1]	p	b	Standard. beta	p	R^2	Step-No.[2]
DSST, *Z*-score	**0.35**	**< 0.001**	**3.19**	**0.34**	**< 0.001**	**0.12**	**1**
MASC sum score, Z-score	0.29	0.006					
Age, y	−0.29	0.007	−0.23	−0.26	0.008	0.18	2
PFA sum score, Z-score	**0.25**	**0.019**	**1.90**	**0.22**	**0.025**	**0.23**	**3**
Db, Z-score	0.22	0.041					
$VLMT_{sum\ 1–5}$, Z-score	0.19	0.078					
Duration of illness, mo	−0.18	0.092					
$VLMT_1$, Z-score	**0.18**	**0.100**					
TMT-B, inverted Z-score	0.16	0.15					
SOFAS score at baseline	**−0.14**	**0.207**	**−0.17**	**−0.22**	**0.028**	**0.28**	**4**
$VLMT_7$, Z-score	0.13	0.221					
WHOQOL-Bref G1: Quality of life	0.13	0.220					
Verbal IQ	−0.13	0.248					
$VLMT_5$, Z-score	0.12	0.281					
WHOQOL-Bref G2: Health	−0.10	0.338					
Psychotic episodes, n	−0.10	0.355					
UPSA-Brief sum score	**0.10**	**0.355**					
Years of education	0.09	0.426					
CGI severity of illness	0.07	0.539					
PANSS general psychopathology score	−0.05	0.671					
CDSS total score	0.03	0.763					
PANSS positive scale score	−0.03	0.762					
Df, Z-score	0.03	0.794					
Sex	−0.03	0.804					
PANSS negative scale score	0.02	0.868					
TMT-A, inverted Z-score	0.01	0.920					
FROGS sum score	0.00	0.974					

Caption: The table shows the results of univariate and stepwise forward multiple regression analyses predicting change in the SOFAS score in the ISST subgroup, including imputed missing values. For the multiple regression analyses, the following are shown: unstandardized (b) and standardized (β) coefficients, significance (p), explained variance (R^2), and step of entry. Predictors are sorted by absolute univariate association. Selected predictors (DSST, SOFAS score at baseline, UPSA-Brief sum score, PFA sum score and $VLMT_1$) are highlighted in bold to enhance readability.
Abbreviations: CDSS, Calgary Depression Rating Scale for Schizophrenia; CGI, Clinical Global Impression; Db, Digits backward; Df, Digits forward; DSST, Digit-Symbol Substitution Test; FROGS, Functional Remission of General Schizophrenia; IQ, intelligence quotient; MASC, Movie for the Assessment of Social Cognition; PANSS, Positive and Negative Syndrome Scale; PFA, Pictures of Facial Affect; SOFAS, Social and Occupational Functioning Assessment Scale; TMT-A, Trail-Making Test A; TMT—B, Trail-Making Test B; UPSA-Brief, University of California Performance-based Skills Assessment, brief version; $VLMT_1$, 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; WHOQOL-Bref, World Health Organization Quality of Life scale.
[1] Pearson correlation coefficients were used for continuous predictors, and point-biserial coefficients for dichotomous measures (sex, treatment group).
[2] Step-No. indicates the order of entry in the stepwise forward multiple regression model.

statistical significance, with the strongest effect for DSST ($r = 0.35$, p < .001), MASC sum score (r = 0.29, $p = .006$), and age ($r = −0.29$, $p = .007$). The corresponding multiple regression model included four significant predictors and explained 28% of the variance. Again, DSST emerged as the strongest predictor ($R^2 = 0.12$, p < .001), followed by age ($\Delta R^2 = 0.05$, $p = .008$) and PFA sum score ($\Delta R^2 = 0.06$, $p = .025$). Table 4 summarizes the results.

In the NCRT subsample ($n = 86$), 10 bivariate correlations reached statistical significance, most notably DSST ($r = 0.39$, p < .001), UPSA-Brief sum score ($r = 0.36$, p < .001), and $VLMT_1$ ($r = −0.30$, $p = .005$). The multiple regression model for this group included seven significant predictors with a total explained variance of 44%. The strongest predictor was DSST ($R^2 = 0.15$, p < .001), followed by the UPSA-Brief sum score ($\Delta R^2 = 0.06$. $p = .01$) and PANSS positive scale score ($\Delta R^2 = 0.06$, $p = .013$). Details are presented in Table 5.

As shown in Table 6, none of the z-tests comparing the regression coefficients between the ISST and NCRT models reached statistical significance. Thus, the influence of the predictors on SOFAS change did not differ significantly between the two treatment groups.

4. Discussion

This secondary analysis of a rigorously designed multicenter RCT investigated baseline predictors of real-world functional improvement in individuals with schizophrenia treated with two distinct CRT approaches.

Across both treatment groups, the DSST, which assesses processing speed, consistently emerged as the strongest predictor of functional improvement. In terms of raw scores, this relationship between DSST and SOFAS means, that a 10-point better performance in DSST at baseline predicts an increase of 3.11 points in SOFAS after treatment. Additionally, baseline social functioning as assessed by the SOFAS was also a significant predictor in all final multivariate models. Facial affect recognition (as assessed by the PFA) was significant only in the ISST group, and verbal short-term memory (as assessed by $VLMT_1$) only in the NCRT group.

These results underscore the importance of preserved cognitive baseline performance for successful outcomes with the two CRT approaches, irrespective of the specific therapeutic focus (i.e., the NC or SC domain). Patients who had faster processing speed at the start of CRT appeared to benefit more from both types of interventions. Processing speed is considered to be one of the most affected NC domains in schizophrenia (Dickinson et al., 2010; Kern et al., 2011; Knowles et al., 2010) and the finding that is plays an important role in predicting functional improvement is in line with previous studies. Prior research has shown that processing speed mediates the effect of verbal memory and fluency on functional outcomes in schizophrenia (Ojeda et al., 2008) and also predicts long-term changes in functioning in the course of disease (Sánchez et al., 2009). Nevertheless, this result challenges meta-analytic findings that suggested that individuals with more severe

Table 5
Regression analysis predicting change in the Social and Occupational Functioning Assessment Scale score in the Neurocognitive Remediation Therapy subgroup (n = 86).

Variable	Univariate analysis		Multiple analysis				
	r[1]	p	b	Standard. beta	p	R^2	Step-No.[2]
DSST, Z-score	**0.39**	**< 0.001**	**3.62**	**0.33**	**< 0.001**	**0.15**	**1**
UPSA-Brief sum score	**0.36**	**< 0.001**	**1.25**	**0.26**	**0.01**	**0.21**	**2**
$VLMT_1$, Z-score	**0.30**	**0.005**	**2.34**	**0.22**	**0.017**	**0.41**	**6**
Psychotic episodes, n	−0.29	0.006					
MASC sum score, Z-score	0.29	0.006					
Duration of illness, mo	−0.27	0.011					
Df, Z-score	0.25	0.019					
FROGS sum score	0.23	0.033					
PFA sum score, Z-score	**0.23**	**0.035**					
Db, Z-score	0.21	0.049					
WHOQOL-Bref G1: Quality of life	0.21	0.051	4.20	0.34	< 0.001	0.31	4
TMT-A, inverted Z-score	0.19	0.078					
Sex	0.19	0.080					
CDSS total score	0.19	0.087	0.77	0.25	0.011	0.37	5
Age, y	−0.17	0.119					
$VLMT_{sum\ 1–5}$, Z-score	0.17	0.123					
PANSS positive scale score	0.14	0.185	0.42	0.15	0.013	0.27	3
$VLMT_7$, Z-score	0.12	0.279					
$VLMT_5$, Z-score	0.12	0.284					
TMT-B, inverted Z-score	0.11	0.303					
PANSS negative scale score	−0.08	0.462					
WHOQOL-Bref G2: Health	0.07	0.538					
Verbal IQ	−0.05	0.631					
Years of education	0.05	0.673					
CGI severity of illness	−0.04	0.704					
SOFAS score at baseline	**−0.03**	**0.774**	**−0.20**	**−0.22**	**0.049**	**0.44**	**7**
PANSS general psychopathology score	−0.03	0.813					

Caption: The table shows the results of univariate and stepwise forward multiple regression analyses predicting change in the SOFAS score in the NCRT subgroup, including imputed missing values. For the multiple regression analyses, the following are shown: unstandardized (b) and standardized (β) coefficients, significance (p), explained variance (R^2), and step of entry. Predictors are sorted by absolute univariate association. Selected predictors (DSST, SOFAS score at baseline, UPSA-Brief sum score, PFA sum score and $VLMT_1$) are highlighted in bold to enhance readability.
Abbreviations: CDSS, Calgary Depression Rating Scale for Schizophrenia; CGI, Clinical Global Impression; Db, Digits backward; Df, Digits forward; DSST, Digit-Symbol Substitution Test; FROGS, Functional Remission of General Schizophrenia; IQ, intelligence quotient; MASC, Movie for the Assessment of Social Cognition; PANSS, Positive and Negative Syndrome Scale; PFA, Pictures of Facial Affect; SOFAS, Social and Occupational Functioning Assessment Scale; TMT-A, Trail-Making Test A; TMT—B, Trail-Making Test B; UPSA-Brief, University of California Performance-based Skills Assessment, brief version; $VLMT_1$, 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; WHOQOL-Bref, World Health Organization Quality of Life scale.
[1] Pearson correlations were used for continuous predictors, and point-biserial coefficients for dichotomous measures (sex, treatment group).
[2] Step-No. indicates the order of entry in the stepwise forward multiple regression model.

impairments (e.g., lower premorbid IQ or educational attainment) may benefit more from CRT (Vita et al., 2021; Lejeune et al., 2021). Our findings also stand in contrast to those reported by Sampedro et al. (2023), who found that lower cognition scores at baseline predicted greater gains in functional capacity (in the UPSA). Several factors may explain these discrepancies. First, the UPSA evaluates functional capacity in a structured testing environment and does not directly capture real-world functioning as the SOFAS does. Second, the interventions analyzed by Sampedro et al. were considerably longer in duration (60 sessions in total) than in the present study (18 sessions in total), which may have allowed patients with lower cognitive scores at baseline more time to engage in and benefit from CRT. Previous meta-analyses have identified treatment duration and overall training dose as potential moderators of CRT outcome, with longer interventions tending to yield larger cognitive gains (McGurk et al., 2007; Vita et al., 2021). Accordingly, individuals with more severe baseline impairments may require greater treatment exposure, whereas shorter protocols, such as the present one, may primarily benefit participants with higher baseline cognition, suggesting an interaction between baseline ability and treatment dose.

In contrast to the above discrepancies, our results are in line with those of Lindenmayer et al. (2017), who reported that patients with faster processing speed at baseline showed greater gains in cognition after 36 sessions of CRT.

Our findings suggest that baseline social functioning level (as measured by the SOFAS) predicts improvement in functioning independently of treatment group. Patients with higher baseline functioning showed less improvement in functioning, which may have been because they started from a higher level and therefore had less room for improvement. Thus, while schizophrenia patients with a higher level of real-world functioning may still benefit from CRT, the therapy may not specifically target their needs. The association between baseline functioning and functional improvement became apparent only in the multivariate regression models, indicating a suppressor effect. Controlling for shared variance with other predictors—such as processing speed—revealed that baseline real-world functioning uniquely contributed to functional gains. Clinically, this finding may suggest that baseline cognitive performance and social functioning influence functional outcome after CRT through partly overlapping but distinct pathways.

The sensitivity analysis in the completer sample produced a very similar pattern of predictors and identified processing speed and baseline social functioning as the strongest determinants of functional improvement. This finding indicates that the main results were not substantially affected by the imputation procedure. However, the similarity of findings between the completer and imputed samples further suggests that differences in treatment completion, such as motivation or ability to adhere to therapy, appear not to have substantially influenced the observed predictors of improvement in functioning.

Although baseline processing speed and social functioning were common predictors across both treatment arms, other predictors were

Table 6
Comparison of multiple regression analyses predicting change in the Social and Occupational Functioning Assessment Scale score in the Integrated Social Cognition and Social Skills Therapy versus Neurocognitive Remediation Therapy groups.

Predictor	Treatment group	b[1]	p	95% CI		z[2]	p[2]
				Lower limit	Upper limit		
DSST, Z-score	ISST	3.35	0.001	1.36	5.33	0.09	0.397
	NCRT	3.21	0.006	0.96	5.45		
SOFAS score at baseline	ISST	−0.16	0.066	−0.34	0.01	0.26	0.385
	NCRT	−0.20	0.051	−0.40	0.00		
Age, y	ISST	−0.22	0.015	−0.39	−0.04	−1.32	0.166
	NCRT	−0.05	0.537	−0.23	0.12		
PFA sum score, Z-score	ISST	1.80	0.042	0.07	3.53	0.64	0.325
	NCRT	0.89	0.430	−1.34	3.12		
UPSA-Brief sum score	ISST	−0.14	0.808	−1.27	0.99	−1.88	0.069
	NCRT	1.26	0.010	0.30	2.21		
PANSS positive scale score	ISST	−0.09	0.750	−0.61	0.44	−1.40	0.150
	NCRT	0.45	0.108	−0.10	1.01		
WHOQOL-Bref G1: Quality of life	ISST	2.22	0.055	−0.05	4.48	−1.25	0.182
	NCRT	4.27	< 0.001	1.92	6.61		
CDSS total score	ISST	0.47	0.129	−0.14	1.08	−0.66	0.321
	NCRT	0.75	0.014	0.16	1.35		
$VLMT_1$, Z-score	ISST	0.45	0.669	−1.63	2.52	−1.16	0.205
	NCRT	2.11	0.037	0.13	4.10		

Caption: The table shows a comparison of multiple regression coefficients predicting change in the SOFAS score for the ISST and NCRT subgroups. Shown are unstandardized coefficients (b) from the multiple regression, significance (p), and 95% confidence intervals (CI). Only predictors entering the model in either subgroup are displayed.

Abbreviation: CDSS, Calgary Depression Rating Scale for Schizophrenia; CI, confidence intervals; DSST, Digit-Symbol Substitution Test; ISST, Integrated Social Cognition and Social Skills Therapy; NCRT, Neurocognitive Remediation Therapy; PANSS, Positive and Negative Syndrome Scale; PFA, Pictures of Facial Affect; SOFAS, Social and Occupational Functioning Assessment Scale; UPSA-Brief, University of California Performance-based Skills Assessment, brief version; $VLMT_1$, Auditory Verbal Learning Test, first trial; WHOQOL-Bref, World Health Organization Quality of Life scale.

[1] Regression coefficient in multiple regression analysis of all predictors.

[2] Test for significant differences in b values between groups.

more treatment specific: In the ISST group, facial affect recognition abilities were a significant predictor, whereas in the NCRT group, verbal short-term memory was. The association between better baseline social cognitive abilities (assessed as the ability to recognize facial affect) and greater functional gains during ISST was to be expected because the ISST directly targets this domain. The finding is in line with the above-mentioned overall effect of processing speed and suggests that higher baseline domain-specific cognition may be necessary to engage meaningfully with domain-specific training. Also, in the NCRT group, better baseline cognitive performance in domains targeted by the intervention predicted better outcomes.

Given the exploratory nature of this analysis, a few limitations warrant consideration. First, no correction for multiple testing was performed, so the analyses have a higher risk of a type I error. Second, although our sample size was comparatively large and based on a high-quality multicenter RCT, the exploratory nature of the analysis and the large number of candidate predictors increase the risk of overfitting. Third, when comparing predictors across treatment modalities the statistical power of this post hoc comparison may not have been sufficient to detect small differences. Additionally, clinical symptom dimensions were derived from the original PANSS subscales (Kay et al., 1987), in accordance with the preregistered analysis plan, but these have been suggested to not optimally capture symptom dimensions in factor-analytic studies (Wallwork et al., 2012). Thus, the use of factor-based operationalizations of PANSS item sets (van der Gaag et al., 2006) or more recent second-generation rating approaches may have provided a more differentiated representation of symptom dimensions (Galderisi et al., 2021). Last, the results of the present study may not be fully generalizable to other CRT approaches: The time required for the two CRT programs evaluated in this study, together with other factors, make the programs more demanding for patients than other CRT programs, so patients required higher cognitive baseline performance to achieve optimal benefits. However, the two programs are representative of contemporary, cognitively demanding CRT formats that require sustained engagement and effort. Thus, although some caution is warranted in generalizing the findings, they may be relevant to a broader range of CRT interventions with similar structural and cognitive demands. Against this background, the present study provides novel evidence that baseline cognitive performance—especially processing speed—may play a crucial role in predicting real-world functional improvements after such CRT approaches in schizophrenia.

Our findings suggest two important considerations for optimizing CRT implementation in clinical practice: First, patient selection through pre-treatment assessments may enhance the effectiveness of CRT by identifying individuals with preserved cognitive functions, particularly those with higher processing speed, who are most likely to benefit from the therapy; and second, performing preparatory modules prior to CRT interventions could help equip patients with foundational cognitive skills and thereby improve the outcomes of the core CRT. The second approach could evolve toward a more modular structure, in which entry-level modules are applied as needed to prepare patients for CRT or omitted if not required. Although this concept is not new (Roder, 1988), our study provides empirical support for the idea that without such preparatory steps, some patients may not fully benefit from CRT interventions.

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. Siebert, F. Seidel, and E.S. Blanke (Berlin); A. Brockhaus-Dumke, X.

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Declaration of competing interest

KL has been a consultant and/or advisor to or has received honoraria from Boehringer-Ingelheim, Janssen/J&J, Lundbeck, Otsuka, Recordati, and ROVI, and she and has received grant support from Janssen/J&J and Otsuka. AML has been a consultant and/or advisor to or has received honoraria from AbbVie, Boehringer-Ingelheim, Clarivate Analytics, ECNP, Elsevier, French Program in Precision Psychiatry, Joint Federal Committee/Innovation Committee, Hector Foundation, Heinrich-Lanz-Foundation, Helmut Horten Foundation, Janssen-Cilag GmbH, Johnson & Johnson, State Medical Association, Lundbeckfonden, The Loop Zürich, Medical Research Council/UKRI, Lausanne University, Association for Mental Wellbeing, Wellcome Trust, Forum for Medical Continuing Education, Clinic Ingolstadt, MCNP (Consorcio Mexiano de Neuropsicofarmacologia), ÖGKJP Vienna/Austria, Norwalk University/USA, Vitos Clinic Rheingau, Neuroscience Applied/ECNP, Japan Society for the Promotion Science (JSPS), Beltz Publ., Kohlhammer Publ., and Thieme Publ. None of the other authors has a competing interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.schres.2026.03.027.

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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