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Cognitive remediation combined with an early intervention service in first episode psychosis

Østergaard Christensen T, Vesterager L, Krarup G, Olsen BB, Melau M, Gluud C, Nordentoft M. Cognitive remediation combined with an early intervention service in first episode psychosis.

Objective: This randomised clinical trial assessed the effects of a 16-week cognitive remediation programme (NEUROCOM) combined with an early intervention service (EIS) vs. EIS alone.
Method: One hundred and seventeen patients with first episode psychosis were randomly assigned to 4 months cognitive remediation combined with EIS vs. EIS alone. Statistical analysis of effect was based on intention to treat.
Results: A total of 98 patients (83.8%) participated in post-training assessments at 4 months and 92 (78.6%) in 12-month follow-up assessments. No effects were found on the primary outcome measure functional capacity. At the post-training assessment, the intervention group had improved significantly on Rosenberg Self-Esteem Scale (Cohen's $d = 0.54$, $P = 0.01$), Positive and Negative Symptoms Scale (PANSS), General Psychopathology Scale (Cohen's $d = 0.51$, $P = 0.05$) and the verbal learning domain (Cohen's $d = 0.46$, $P = 0.02$). At follow-up assessment, the intervention group retained the significant improvements on the verbal learning domain (Cohen's $d = 0.58$, $P < 0.05$). Furthermore, significant improvements were observed on the working memory domain (Cohen's $d = 0.56$, $P = 0.01$) and PANSS positive symptoms (Cohen's $d = 0.44$, $P = 0.04$), while improvement on the composite score was marginally significant (Cohen's $d = 0.34$, $P = 0.05$).
Conclusion: In accordance with other cognitive remediation programmes, this programme demonstrates some immediate and long-term effect on cognitive functioning, symptoms and self-esteem.

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Key words: cognition; remediation; first episode psychosis; early intervention

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Significant outcomes

- A relatively short-termed cognitive remediation programme significantly improved cognitive functioning and psychiatric symptoms.
- Self-esteem was significantly enhanced through the cognitive intervention period.

Limitations

- Possibly due to a measurement ceiling effect, no effect on functional capacity was demonstrated.
- Some method drift cannot be excluded as the cognitive remediation group and the control group received early intervention service treatment in the same clinics.

Introduction

Almost 80 per cent of individuals with schizophrenia show cognitive impairments relative to the general population and probably more have cognitive deficits relative to their premorbid level (1). Within most cognitive domains of attention, learning, memory and executive functioning, the effect

sizes of impairments are moderate to large (2, 3). The deficits are relatively stable during the illness, and nearly all cognitive deficits are comparably impaired across first episode and chronic schizophrenia (4). Cognitive impairments similar to those in schizophrenia are present in other psychotic disorders (5), and today, these impairments are recognised as an inherent part of psychotic illness.

The cognitive deficits of schizophrenia have severe impact on the daily functioning and predict functional outcomes such as employment, social functioning and independent living (6). The predictive power of cognition is even stronger than that of psychotic symptoms (7). Furthermore, there is evidence that clinical factors such as medical compliance are influenced by cognitive functioning (8). Arguments have been raised that memory and learning have special importance for most functional outcomes; however, when multiple neurocognitive domains are included in a summary score, the largest amount of variance appears to be predicted by a global cognitive measure (6). This is probably due to the fact that schizophrenia is associated with multiple cognitive deficits in varying patterns (9).

Cognitive remediation comprises behavioural interventions targeting cognitive deficits that interfere with daily functioning. Several meta-analyses and narrative literature reviews have documented beneficial effects of cognitive remediation for schizophrenia patients on cognitive performance, symptoms and functional capacity. McGurk et al. (10) display effect sizes Cohen's $d = 0.41$ for cognitive function (with a durability effect of Cohen's $d = 0.66$), Cohen's $d = 0.36$ for psychosocial function and Cohen's $d = 0.28$ for symptoms. Furthermore, they conclude that cognitive remediation results in stronger effect sizes for improved psychosocial functioning in studies that provided adjunctive psychiatric rehabilitation (0.47) compared with no psychiatric rehabilitation (0.05; $Q = 5.5$, df = 1, $P < 0.01$.).

In the most recent meta-analysis, the benefits of adjunctive psychiatric rehabilitation for improved psychosocial functioning in cognitive remediation is emphasised again (11). Particularly, vocational training seems to be a potent enhancement factor (12). In addition, some research suggests that self-esteem might also gain from cognitive remediation (13). Evidence supports that cognitive remediation is equally effective for patients with schizophrenia as well as other psychotic illnesses (14).

Cognitive remediation has been offered to schizophrenia patients since the late 1960s (15); however, today, cognitive remediation is far from a uniform treatment method. Some programmes focus on environmental modifications (16) and others on compensation strategies (17) or restoration/training targeting either single cognitive functions (18), or multiple cognitive functions (19). Some use short programmes with a duration of 3 weeks (20), while other programmes last more than 100 weeks (21). Some use paper and pencil (22) and others computer programs (23) as tools for training.

However, psychotic illness implies several other burdens than cognitive deficits. Different symptoms and social factors also result in poor quality of life for patients and affect outcome (24), and relatives too experience severe distress (25). One way of reducing these burdens and improving outcomes has been to offer early intervention services (EIS) to first episode psychosis patients. This approach focuses on treatment of psychosis during the formative years of the psychotic condition (26, 27). The benefits of the early intervention programme OPUS are well documented (28). OPUS treatment includes medication, social skills training, patient psychoeducation and psychoeducational family treatment adapted to the needs of the individual patient. Whereas psychosocial rehabilitation programmes primarily target reintegration in society, for example, through vocational support, the purpose of OPUS EIS is not contrary to this, but primarily aims to reduce psychotic symptoms and support coping with the illness.

Aims of the study

The aim of this randomised clinical trial was to examine the effects of a 16-week cognitive remediation programme (NEUROCOM) combined with OPUS early intervention service vs. OPUS early intervention service alone on the primary outcome functional capacity and three other outcomes: cognitive functioning, symptoms and self-esteem. To our knowledge, no previous research has addressed these questions.

Material and methods

Participants and consent

All participants were patients at the OPUS clinics at psychiatric departments in Copenhagen and Aarhus, Denmark, and were recruited to the NEUROCOM trial by staff members. Most patients was treated in the OPUS programme for approximately 1 year before inclusion in the NEUROCOM trial and should have at least 6 months left of the 2-year duration of the OPUS programme. Inclusion criteria were a first episode of schizophrenia-spectrum disorders, that is, within the ICD10 F2 spectrum, a stable, postacute phase of

illness for at least 1 month, sufficient comprehension of Danish (i.e. did not need an interpreter) and written informed consent. The diagnosis was determined using the Present State Examination (PSE) interview. The interviews were conducted by experienced psychiatrists prior to the study. Exclusion criteria were rejection of participation, organic disorder or substance dependence.

Participation was voluntary, and all participants were informed both verbally and in written form that they could withdraw from the trial at any time, without having any consequences for their continued OPUS treatment.

Randomisation and blinding

The participants were randomly allocated to either the experimental intervention, that is, cognitive remediation combined with continued OPUS treatment, or control intervention, that is, continued OPUS treatment. A centralised, stratified block-randomisation 1 : 1 was carried out by Copenhagen Trial Unit (CTU) following two stratification criteria: either good (total raw score ≥16) or poor (total raw score <16) performance level on the brief version of University of California San Diego Performance Skills Assessment (UPSA-B) and participation in OPUS group treatment, for example social skills training or psychoeducation (yes or no). The generation of allocation sequence was computerised. Allocation concealment was achieved through centralised randomisation with a block size unknown to investigators.

Each investigator used an individual four-digit pin code when calling CTU requesting a randomisation. The CTU did not inform the investigators, but the cognitive trainers about the randomisation result using a telefax. The cognitive trainers informed the individual participant about the randomisation result. The trial was not blinded in regard to participants, cognitive trainers and OPUS teams. The blinding applied only to the investigators engaged in baseline, post-training and follow-up assessment. The blindness of the investigators was endeavoured by instructing the participants in advance not to reveal what type of interventions they had received. The randomised intervention allocation was concealed until the statistical analyses of the data were completed (29).

Assessment

The assessment at baseline, post-training and follow-up were conducted by two trained psychologists (LV and TØC) or supervised assistants. LV and TØC were trained by certified Positive and Negative Symptoms Scale (PANSS) trainers. All investigators were introduced to MCCB and UPSA, but no reliability tests were conducted, as these cognitive test outcomes are specifically designed to exclude the effects of rater bias (11).

Experimental intervention

The cognitive training part of the NEUROCOM remediation programme was offered on an individual basis, 1 h twice a week for 16 weeks. The cognitive training was based on a manual developed through a pilot study. The cognitive trainers were psychologists and occupational therapists with professional psychiatric experience and basic knowledge of cognitive psychology. The cognitive training consisted of four modules: The first three modules covered domains of attention, executive functions and learning/memory. The last module focused on cognitive domains that the participant needed to improve. Thus, the participant and the trainer based the content of module four on a combined evaluation.

The training contained computer exercises of focused, divided, and sustained attention, planning, strategy learning and problem solving, as well as interaction-based exercises of working memory, verbal and visual recall, and recognition memory. The whole of the first module and the first half of the second module were based on cognitive tasks on a gradually increasing level of difficulty, using COGNIsoft computer tasks (http://www.cognisoft.dk), while the second half of the second module and module three included training of practical everyday tasks (e.g. preparing and making a meal) and compensatory training. Module four involved an individually designed combination of computer exercises and practical everyday tasks.

The rationale of the training programme was an eclectic combination of a mainly bottom-up approach, that is, all participants did repetitive drills and practice with identical exercises to make cognitive processing more effective and automatic, but a top-down approach was also used, that is, strategy learning and guided problem-solving training adapted to participants individual resources. Compensatory strategies were also applied, as calendar training was a central part of the learning/memory module. The cognitive trainer approach relied on a combination of errorless learning and scaffolding principles (30, 31).

As an innovative element, the participants engaged in a competence dialogue 1 h every other week. The dialogues were designed as semistructured interviews. The competence dialogues functioned in part as a method for developing and

maintaining motivation and in part as a bridge between the cognitive training and three everyday skills: work competencies (e.g. following rules and agreements), self-experienced cognitive competencies (e.g. attention) and social competencies (e.g. interpersonal skills). The competence dialogues were in line with recommendations for addressing motivation and providing bridging facilities that allow participants to apply skills beyond the cognitive exercises (32).

The mean weekly time offered for the total remediation programme, including the competence dialogues, was two and a half hour, and the total number of hours was 38.

Both the intervention group and the control group were treated in OPUS before, during and after the trial.

Outcomes

Danish versions of the following measures were used for outcome assessment:

Functional capacity. University of California San Diego Performance Skills Assessment (UPSA-B) (33).

Cognitive functioning. MATRICS Consensus Cognitive Battery (MCCB): speed of processing (BACS Symbol Coding, Category Fluency and Trail Making A), attention (Continuous Performance Test-IP), working memory (Wechsler Memory Scale-III, Letter–Number Sequencing), verbal learning – Hopkins verbal learning test-revised (HVLT-R), visual learning (Brief Visuospatial Memory Test – Revised), problem solving (Neuropsychological Assessment Battery, NAB Mazes), social cognition (Mayer–Salovey–Caruso Emotional Intelligence Test – MSCEIT) (34).

Additional cognitive tests. Trail Making Test: Part B, the recall and recognition parts of Hopkins verbal learning test–revised (HVLT–R) and Danish Adult Reading Test (DART; i.e. Danish version of NART) (35).

Symptoms. Positive and Negative Symptom Scale (PANSS) (36).

Self-Esteem. The Rosenberg Self-Esteem Scale (RSE) (37).

Statistical analyses

Most data were analysed with the SPSS (PASW Statistics for Windows, version 18, SPSS Inc., Chicago, IL, USA) software program. Alfa was set at 0.05. The power of the study was set at 90 per cent, that is, $\beta = 0.1$. The minimal relevant difference (MIREDIF) was set at 1 point on UPSA-B total score (Mean = 17.63 points, SD = 1.66). The SD was assumed to be 1.66. To be able to detect a difference of 1 point on UPSA-B mean total score between the two groups, the required number of participants in each group was 31. Estimated drop-out of 45 per cent necessitated recruitment of about 120 participants, 60 in each intervention group.

Effect sizes (Cohen's *d*) for post-training and follow-up compared with baseline were calculated as the mean differences between the intervention group (NEUROCOM) and the control group, divided by the pooled standard deviation.

At baseline, chi-squared tests and independent-samples *t*-tests were conducted to investigate sociodemographic characteristics and to compare performances on the rating scales and neuropsychological tests. As all data showed a statistically acceptable normal distribution, no nonparametric or logarithmic transformations were applied.

Data sets on non-completing participants were included in the data analyses on an intention-to-treat basis. Non-existent outcome measures (due to non-carried out testing, withdrawal or drop-out) were subjected to further analysis using a mixed-model analysis with a repeated-measurement model with unstructured variance matrix. The condition for using this method is the assumption that data were missing at random when taking into consideration the information extracted from baseline results and information about the other patients in the database. As covariate, the sites (Aarhus/Copenhagen) were applied. The values from baseline test and rating were included automatically, because they are included in the model (38).

Results

Assessment flow

Two hundred and thirty-five patients were assessed for eligibility. 118 (42%) patients were not included due to either not meeting inclusion criteria ($n = 69$, 29%) or other reasons ($n = 49$, 21%), for example, they lived too far from the clinics. In all, 117 patients were included. The flow chart (Fig. 1) shows reasons for ineligibility as well as attrition at post-training and follow-up assessments. 15 per cent from the intervention group and 17.5 per cent from the control group did not attend at the post-training assessment. Regarding the follow-up assessment, the attrition was slightly

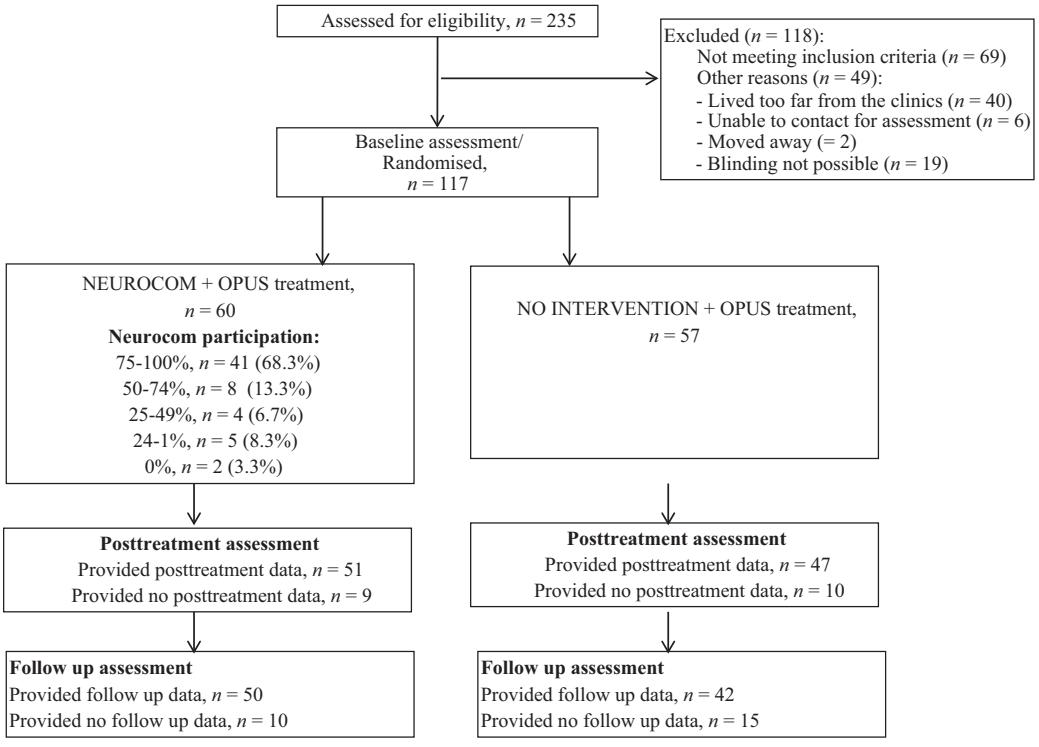

Fig. 1. Flowchart: Assessment and treatment of the NEUROCOM group and the control group.

skewed; 17% and 26% from the intervention and the control group did not participate, respectively. These differences were not statistically significant. The planned times to make post-training and follow-up assessments were 120 and 300 days following the baseline assessment. However, the effective mean time from baseline to post-training was 163.7 (SD 44.1) days and to follow-up assessment 377.5 (SD: 87.4) days, but without significant differences between the two groups (post-training: $t = 425$, df = 61, $P = 0.67$; follow -up: $t = -0.166$, df = 51, $P = 0.87$). The assessment delays were due to prolonged treatment, illness relapse, delayed attendance and other factors.

Randomisation

Baseline data for patients in both the groups are shown in Table 1. There were no significant differences in baseline data between the two groups.

Programme fidelity

A total of 28.3 per cent completed the programme within 16 weeks; another 28.3 per cent exceeded by less than 4 weeks; 23.3 per cent exceeded by more than 4 weeks; and 20.0 per cent terminated prematurely. The reasons for exceeding varied, but many were related to illness exacerbation, in some cases including readmission, while a few were due to practical circumstances, for example, vacation. The mean number of total hours used by participants on the remediation programme was 28.7 (SD: 11.2) hours. There were no centre differences regarding hours of participation in the remediation programme ($t = 0.252$, df = 58, $P = 0.80$). Two (3.3%) participants did not participate in the programme despite randomisation for treatment, while 12 (20%) participated in all sessions of the programme.

Functional capacity

Although the intervention group showed improvements at both post-training and follow-up, the UPSA-B measures of functional capacity revealed no significant benefits of the cognitive remediation programme (See Table 2). At post-training and at follow-up, ceiling effects were found on UPSA-B (range 1–100): 75th percentile at post-training: 94.4, 75th percentile at follow-up: 90.91 (for the entire sample).

Cognition

The MCCB scores were converted to domain T-scores by contrasting the intervention- and control groups domain scores with the original MCCB standardisation group (39). Analysis showed no significant baseline domain differences between the

Table 1. Baseline characteristics of the randomized 117 patients with first episode psychosis, participating in the NEUROCOM trial

		NEUROCOM (n = 60)		Control (n = 57)	
Domain	Variable	n	%	n	%
Sociodemographics	Male	35	58.3	28	49.1
	Schizophrenia	52	86.7	46	80.7
	High school completed	33	55.0	26	45.6
	Living independently	53	88.3	49	86.0
	Substance abuse during the trial period	4	7.0	6	11.0
	Previous psychological testing	24	40.0	28	49.1
Concurrent OPUS treatment	Antipsychotic medication	56	93.3	48	84.2
	Group treatment	5	8.3	5	8.8
	Case manager – weekly contact	39	65.0	45	78.9
	Case manager – monthly contact	20	33.3	12	21.1
	Contact with job consultant	9	15.0	11	19.3
	Multi-family group	9	15.0	3	5.3
		Mean	SD	Mean	SD
	Age (years)	25.0	3.3	24.9	3.7
	Hospitalisation (days) since diagnosis	50.1	87.7	67.9	108.2
	GAF	47.4	10.2	45.7	10.8
Functional capacity	UPSA-B	78.9	11.7	76.1	14.9
Self-esteem	Rosenberg Self-Esteem Scale	22.3	5.5	23.9	5.5
Symptoms	Positive Scale	11.9	4.0	11.8	4.2
	Negative Scale	15.6	5.7	15.1	6.0
	General Psychopathology Scale	26.4	6.1	27.7	7.0
	PANSS total	53.9	11.8	54.6	13.1
Cognition	DART	25.2	8.0	26.4	7.4
	Trail making test A*	30.1	12.9	30.0	10.3
	BACS symbol coding task	51.5	10.8	49.9	10.6
	WMS spatial span	17.4	3.3	16.6	3.0
	HVLT-R immediate recall	25.5	5.1	25.8	5.6
	HVLT-R delayed recall	9.0	2.8	9.0	2.8
	HVLT-R recognition	11.4	1.1	11.3	1.3
	Letter-number sequencing	13.6	2.9	14.2	3.3
	BVMT-R	22.2	6.8	23.1	7.3
	Semantic fluency	21.0	5.4	20.6	5.0
	NAB mazes	21.3	4.6	21.1	4.7
	Trail making test B*	64.2	21.1	73.5	40.7
	CPT-IP	2.46	0.60	2.27	0.66
	MSCEIT managing emotions	89.0	10.5	90.5	10.0
MCCB domains	Speed of processing†	43.93	10.5	42.88	9.8
	Attention/vigilance†	42.05	9.0	39.20	9.9
	Working memory†	47.45	9.4	46.82	9.4
	Verbal learning†	44.58	9.7	45.65	11.1
	Visual learning	44.82	10.7	46.18	11.3
	Reasoning and problem solving†	53.13	9.2	52.65	9.0
	Social cognition†	40.82	12.0	42.64	11.5
	Cognitive composite T-scores†	42.6	9.5	43.1	10.1

GAF, global assessment of functioning; DART, Danish Adult Reading Test; UPSA, University of California Performance Skills Assessment; PANSS, Positive and Negative Syndrome Scale; TMT, trail making test; BACS SC, brief assessment of cognition in schizophrenia; CPT IP, continuous performance test – identical pairs; WMS, Wechsler Memory Scale; LNS, letter-number span; HVLT-R, Hopkins verbal learning test-Revised; BVMT-R, brief visuospatial memory test-revised; NAB mazes, neuropsychological assessment battery: mazes; MSCEIT ME, Mayer–Salovey–Caruso emotional intelligence test: managing emotions.

*Measure of time to completion.

†T-scores derived from the MCCB normative scores.

two groups. All baseline–domain scores were between 40 and 50, with the exception of reasoning and problem solving, which for both the groups were larger than 50, and attention/vigilance, which for the control group was just below 40, suggesting that the cognitive profiles of both the groups were close to one standard deviation below normal. When analysing neuropsychological test data and domain scores with the repeated measure model, all significant effect sizes were in favour of the experimental intervention group. At post-training assessment, the experimental intervention group showed significant improvements with medium effects sizes on the HVLT-R (0.42, $P = 0.04$) and the corresponding MCCB domain verbal learning (0.46, $P = 0.03$) compared with the control group.

Table 2. Post-training and follow-up effects of cognitive remediation among the randomized 117 patients with first episode psychosis on functional outcome (UPSA), and cognitive function assessed with MCCB domains and three additional cognitive tests

	Post-training				Follow-up			
Measures	NEUROCOM (n = 51) Mean (SD)	Control (n = 47) Mean (SD)	Between group difference	Effect size	NEUROCOM (n = 50) Mean (SD)	Control (n = 42) Mean (SD)	Between group difference	Effect size
UPSA-B total	85.4 (10.7)	82.6 (14.8)	2.8 (−2.4 to 7.9)	0.22	85.2 (9.9)	83.7 (14.1)	1.6 (−3.4 to 6.6)	0.13
Speed of processing (MCCB)	48.0 (6.9)	46.9 (7.0)	1.1 (−1.7 to 3.9)	0.16	50.78 (7.4)	48.23 (7.2)	2.6 (−5 to 5.6)	0.35
Attention/vigilance (MCCB)	42.4 (6.3)	43.4 (6.4)	−1.1 (−3.6 to 1.5)	−0.17	43.7 (7.1)	43.7 (7.0)	−0.0 (−3.0 to 3.0)	0.00
Working memory (MCCB)	50.7 (7.0)	48.7 (7.0)	1.9 (−0.9 to 4.8)	0.28	52.7 (6.6)	49.1 (6.5)	3.7 (0.9 to 6.4)	0.56*
Verbal learning (MCCB)	50.1 (8.9)	46.0 (9.1)	4.1 (0.5–7.7)	0.46*	52.0 (8.9)	46.9 (8.9)	5.2 (1.4–9.0)	0.58*
Visual learning (MCCB)	49.7 (8.6)	48.2 (8.7)	1.5 (−2.0 to 5.0)	0.18	51.5 (7.2)	50.4 (7.1)	1.0 (−2.0 to 4.0)	0.15
Reasoning and problem solving (MCCB)	54.7 (6.4)	53.3 (5.9)	1.4 (−1.2 to 4.0)	0.23	57.4 (6.5)	56.2 (5.8)	1.2 (−1.2 to 3.7)	0.20
Social cognition (MCCB)	43.5 (10.8)	42.1 (11.2)	1.4 (−3.0 to 5.8)	0.12	43.00 (10.3)	44.6 (11.5)	−1.6 (−6.4 to 3.2)	−0.12
Composite (MCCB)	47.5 (6.7)	45.2 (6.9)	2.30 (−0.4 to 5.0)	0.34	50.2 (5.8)	47.8 (5.8)	2.4 (−0.3 to 4.8)	0.34
HVLT-R recall	9.80 (1.8)	9.5 (1.9)	0.3 (−0.4 to 1.1)	0.17	10.5 (1.8)	9.51 (1.8)	1.0 (0.3–1.8)	0.56*
HVLT-R recognition-true positive	11.5 (0.9)	11.5 (1.0)	0 (−0.4 to 0.4)	0	11.8 (1.0)	11.7 (0.7)	0.1 (0.1–0.4)	0.16
TMT A†	26.1 (6.7)	28.2 (6.7)	−2.1 (−4.8 to 0.6)	−0.32	24.3 (6.7)	26.8 (6.5)	−2.5 (−5.2 to 0.3)	−0.37

*$P < 0.05$.

†Measure of time to completion.

At follow-up assessment, the experimental intervention group retained the significant improvements on the HVLT-R and the verbal learning domain and showed significant improvements with medium to large effects sizes on letter-number span (LNS; 0.77, $P = 0.01$) and the corresponding MCCB domain working memory (0.56, $P = 0.01$) and the HVLT-R recall (0.56, $P = 0.01$). A small improvement for the intervention group in the MCCB Composite Score was marginally significant (Cohen's $d = 0.34$, $P = 0.06$; See 2).

Self-esteem and psychopathology

At post-training, significant improvements with medium effect sizes were found on Rosenberg Self-Esteem Scale (0.54) and PANSS General psychopathology (−0.51) in the experimental intervention group. At follow-up, the post-training difference between the two groups on Rosenberg Self-Esteem Scale and PANSS General psychopathology disappeared. However, the experimental intervention group showed significant improvements with medium to large effects sizes on PANSS positive symptoms (−0.44, $P = 0.04$) at follow-up (See Table 3). At baseline, many patients had full or partial remission of psychotic symptoms, which was probably because many of them had already completed a substantial part of their OPUS treatment.

Medical compliance

At follow-up, 75.5 per cent of the intervention group and 62 per cent of the control group took their antipsychotic medication regularly. This difference was not significant ($\chi^2 = 6.54$, df = 3 $P = 0.09$).

Table 3. Post-training and follow-up effects of measures for self-esteem (The Rosenbergs Self-esteem Scale) and psychopathology (PANSS) among the randomized 117 patients with first episode psychosis on functional outcome (UPSA), and cognitive function assessed with MCCB domains and three additional cognitive tests

	Post-training				Follow-up			
Measures	NEUROCOM (n = 51) Mean (SD)	Control (n = 47) Mean (SD)	Est. mean difference (95% CI)	Effect size	NEUROCOM (n = 50) Mean (SD)	Control (n = 42) Mean (SD)	Est. mean difference (95% CI)	Effect size
Rosenberg Self-esteem	26.0 (3.4)	24.1 (3.5)	0.8 (0.5–3.2)	0.54*	25.8 (5.0)	25.4 (4.8)	0.4 (−1.80 to 2.4)	0.08
PANSS Positive Scale†	10.6 (2.1)	10.8 (2.1)	−0.2 (−1.1 to 0.6)	−0.11	9.7 (3.1)	11.1 (3.1)	−1.4 (−2.7 to −0.7)	−0.44*
PANSS Negative Scale†	13.8 (4.0)	14.0 (4.0)	−0.2 (−1.8 to 1.4)	−11	13.1 (4.5)	13.8 (4.3)	−0.8 (−2.6 to 1.1)	−17
PANSS General Psychopathology Scale†	23.5 (4.5)	25.72 (4.3)	−2.3 (−4.2 to −0.3)	−0.51*	23.5 (5.9)	24.3 (5.8)	−0.8 (−3.3 to 1.2)	−0.14

*$P < 0.05$.

†Higher scores equal higher symptoms.

Discussion

We found no significant effects of cognitive remediation on functional capacity measured by the UPSA-B scale, which is the primary outcome of the trial. Our data do not allow an interpretation of the lack of generalisation to functioning. First, our trial was designed with a 10% risk of type II error. Although this is smaller than the usual 20%, we may still have overlooked an effect. Second, the observed ceiling effect on the UPSA-B questions the usability of this scale in young, non-chronic patients. In this regard, it should be noted that the mean age of patients in the current study is approximately 50 per cent lower than the mean age of the sample used for standardization of the test (33). McGurk et al. (10) conducted moderator analyses and found larger effects of cognitive remediation on psychosocial functioning in studies that included older rather than younger patients. Third, the lack of effect on functional capacity might be caused by the OPUS treatment, which may have a generalising effect on daily living and functioning (40) in both the control and the experimental intervention groups. Furthermore, OPUS treatment is without a particular vocational context known to stabilize and further develop the effect from cognitive training in relation to real-life functioning (41).

The effects of cognitive remediation on cognition, a secondary outcome of this trial, with a Cohen's d in the range from 0.41 to 0.77 are comparable to findings in a meta-analysis by Wykes et al. (11). Post-training and follow-up effect on cognition was measured in different domains of which one reached statistical significance at post-training and three at follow-up. With such high number of outcome measures, there is a risk for significant findings occurring by chance. However, except one domain, all the changes at post-training and at follow-up were in the same direction. We have therefore presented the results without Bonferroni correction for mass significance.

Even more pronounced than in the meta-analytic by Wykes et al. (11) finding of small effects on symptoms, our trial found that cognitive remediation reduced symptoms with medium effect sizes of Cohen's d in the range from -0.51 to -0.44. Self-esteem data were not reported in the meta-analysis, but in our study, cognitive remediation improved self-esteem post-training with a medium effect size of Cohen's $d = 0.54$.

These effect sizes are particularly noticeable when taking into account that the NEUROCOM trial had high methodological rigour. The randomisation was concealed and successful (42, 43); outcome assessors were blind to the treatment allocation of patients (42, 43); the number of participants was high compared with similar studies (11); the programme fidelity was relatively high; the intervention was an add on to a service, which already have high quality (40); statistical analyses were based on the intention-to-treat principle; attrition was relatively low; and post-training attrition rate was 17.5 per cent in the control group and 15 per cent in the cognitive remediation group.

In the Wykes et al. meta-analysis (11), no improvements were found on measures of the continuous performance test or on visual learning. Likewise, our trial did not find significant improvements on the MCCB domains of attention/vigilance (which corresponds solely to the CPT-IP test) or on visual learning. In contrast to the meta-analytic finding of improvement in other cognitive domains, our study did not find effects on the MCCB domains of reasoning and problem-solving, speed of processing and social cognition. There may be several reasons for not finding any effect on these domains. Ceiling effects were found on the reasoning and problem-solving measure and the NAB mazes (0–26 points) (for the entire sample: 75th percentile at baseline: 25; 75th percentile at post-training: 25; 75th percentile at follow-up: 26). This high proportion of patients reaching the highest level of performance prevents accurate measurement of optimal performance and, thus, of potential improvements from the cognitive remediation programme. At follow-up, a trend towards improved speed of processing in favour of the intervention group was observed (Cohen's $d = 0.35$, $P = 0.10$), however, this was not significant. The lack of improvement on the MCCB domain social cognition may not be surprising, as social cognition was not specifically addressed in the cognitive remediation programme.

The significant long-term effects on working memory and verbal learning may be related to the fact that these functions and the preceding training of different attention and executive functions, both known to underpin memory functions (44), were enhanced by the practical and compensatory elements of the cognitive remediation programme. The effects of the cognitive remediation programme tend to be larger at follow-up than at post-training. Compared with other medical and psychological effect studies, this is a little surprising; nevertheless, it replicates a similar finding in the meta-analysis by McGurk et al. (10). One explanation might be a kind of response latency determined by the fact that participants practiced the cognitive remediation strategies for daily functioning, thereby enhancing the effect.

In regard to the outcomes psychopathology and self-esteem, an immediate post-training effect of cognitive remediation comparable to our study was also documented by Medalia et al. (45) and Wykes et al. (13). However, the effect of the cognitive remediation programme on general psychopathology disappeared at follow-up. General psychopathology is a rather heterogeneous measure with many items related to self-esteem (including anxiety, depression and feelings of guilt), and like the general psychopathology, self-esteem improved significantly at post-training, but the effect is lost at follow-up. This is also found by Wykes et al. (13), who conclude that gains made in self-esteem disappeared following the withdrawal of the intervention. This probably implies that the effect on self-esteem and general psychopathology can only be maintained if the treatment period is prolonged or entail booster sessions. Future research must investigate these non-specific effects of cognitive remediation.

At follow-up, we found positive symptoms to be significantly reduced and it could be considered that cognitive remediation might enhance to some extent the purpose of the OPUS treatment, namely to lower and eliminate psychotic symptoms, perhaps by making the participants better able to focus on and remember taking medicine. Our data on medical compliance partially support this, and associations between cognitive functioning and medical compliance have been documented by Heinrichs et al. and Pijnenborg et al. (8, 46). Furthermore, it is possible that cognitive remediation enhances the effects of the psychological elements in OPUS, for example by strengthening the ability to cope with delusions and hallucinations. Thus, it can be considered whether integrating cognitive remediation in an intervention programme targeting psychosis has an analogue effect to the integrating of cognitive remediation in rehabilitation programmes, namely enhancing the primary targets.

With respect to changes in symptomatology, it should be noted that changes are small in both the groups and patients in both the groups have been close to symptom free from inclusion to follow-up. With this in mind, the changes may be due to mere chance. More research on this topic is needed.

In regard to adherence and implicating the clinical use of the programme, our data indicate a relatively high degree of motivation. On the other hand, only 17 patients (28.3%) completed the programme within the scheduled 16 weeks, which suggests that a more individualised approach is needed so that as many patients as possible participate in the treatment. A fixed programme approach is not appropriate for many patients. Another consequence of the fixed programme approach is that some patients may have received treatment for more or less intact cognitive functions. This might be a waste of resources, yet it might also have a motivational effect on some patients with low self-esteem to discover that they actually can manage some cognitive exercises. Possibly, some degree of levelling the effects of redundant training and reinforcing the necessary training was achieved by the optional and individually adapted module four of the programme.

The study was integrated in a usual treatment setting. Realistic conditions like these increase the external validity of the results; however, they might also have contributed some limitations as they potentially can increase and decrease effects of the intervention, and some method drift of the practical and compensatory strategies cannot be excluded, as both the cognitive remediation group and the control group received their treatment in the same clinics. However, it is not likely that any computer exercises were used in the control group treatment. A number of other methodological limitations should also be noted: The ceiling effect noticed on two measurements may have hindered accurate measurement of optimal performance. The measurement of functional capacity is in particularly critical. Testing and rating procedures were carried out by trained and experienced staff, but no interrater reliability measurements were performed, creating a risk of experimenter bias. With regard to the study design, an extended follow-up period, and optimally a repeating follow-up, would have substantiated the results and further elucidated the observed prolonged effects.

For the further development of NEUROCOM intervention and continued research, it will be relevant to test it both outside of an EIS context and in a work rehabilitation context.

In accordance with other cognitive remediation programmes, the NEUROCOM treatment demonstrates some immediate and long-term effects on cognitive functioning, symptoms and self-esteem. No effects on functional capacity appear that are comparable to those found in cognitive remediation programmes combined with rehabilitation programmes; however, the NEUROCOM treatment seems to enhance the aim of the OPUS treatment to lower and eliminate psychotic symptoms. Of course these findings have to be challenged by future research.

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Declaration of interest

None.

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