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Cognitive remediation plus standard treatment versus standard treatment alone for individuals at ultra-high risk of developing psychosis: Results of the FOCUS randomised clinical trial

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ABSTRACT

Background: Individuals at ultra-high risk (UHR) for psychosis have significant cognitive deficits that can impede functional recovery. Applying cognitive remediation (CR) before the onset of frank psychosis may improve the cognitive and functional prognosis of UHR individuals, however, little is known about the feasibility and efficacy of CR for this population.
Methods: In this randomised, clinical trial 146 individuals at UHR for psychosis aged 18–40 years were randomly assigned to treatment as usual (TAU) or TAU plus cognitive remediation. The CR targeted neurocognitive and social cognitive remediation. Assessments were carried out at 6- and 12-months post baseline.
Results: A total of 73 UHR individuals were assigned to TAU and 73 assigned to TAU + cognitive remediation. Compared to the control group, cognitive remediation did not result in significant improvement on the primary outcome; the Brief Assessment of Cognition in Schizophrenia composite score at 6-month follow-up ($b = -0.125$, 95%CI: −0.23 to 0.172, $p = 0.41$). Nor did the intervention improve secondary outcomes in clinical symptoms or functioning. Exploratory analyses found emotion recognition latencies to be significantly more reduced in the intervention group at 6-months. At 12-months, the intervention group exhibited significantly better performance on two measures of executive function and visual memory.
Conclusion: The 20-session treatment protocol was not well received in the UHR group, and unsurprisingly global measures did not improve. The benefit found in isolated neuro- and social cognitive measures after even a few sessions points to a potential for cognitive malleability if people can be engaged sufficiently to practice the skills. Trial registration ClinicalTrial.gov identifier: NCT02098408.

1. Background

Cognitive deficits are prominent in individuals at ultra-high risk (UHR) for psychosis (Fusar-Poli et al., 2012) and have consistently been linked to severe functional impairments in UHR individuals and patients with established psychosis (Bolt et al., 2018; Green et al., 2000). Acknowledging the essential role of cognitive deficits in psychotic states, the improvement of cognitive deficits has become a crucial goal in the treatment of psychotic and psychotic-like disorders (Medalia and Choi, 2009). Cognitive remediation seems to be the most promising treatment targeting cognitive deficits, and it has proven to lead to cognitive and functional improvements in patients with psychosis (Wykes et al., 2011). It can be hypothesized that the effect of cognitive remediation may be even more beneficial in the putative prodromal stage of psychosis (i.e. the UHR state), with the potential of greater brain plasticity making the cognitive deficits potentially more amenable

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to treatment (Keshavan and Hogarty, 1999). In addition, cognitive remediation is a behavioural intervention that carries low risk of unwanted side effects (Klingberg et al., 2012), and the potential of substantial benefits (Wykes et al., 2011), which is of vital importance when offering interventions to young people in a putative prodromal state of psychosis.

The effectiveness of cognitive remediation on cognition and functioning is well established in patients with psychosis (Wykes et al., 2011). Contrasting the abundant evidence for the effect of cognitive remediation in psychosis, there is a dearth of studies that have evaluated the effectiveness of cognitive remediation in individuals at UHR for psychosis. The few studies conducted offer preliminary evidence for the effectiveness of cognitive remediation in the UHR state, but most studies suffer methodological limitations such as low sample sizes and high attrition rates (Glenthøj et al., 2017). Furthermore, none of the previous randomised, clinical trial has specifically targeted social cognitive deficits, which are aspects of cognitive impairments hypothesized to be proximal to patients' daily functioning (Thompson et al., 2011). Taken together, this point to the need for methodological rigorous, large scale trials evaluating the prospects of cognitive remediation as a potential non-harmful intervention that may reduce cognitive deficits, clinical symptoms, and improve the functional outcome of UHR individuals. Pursuant to this need, the current trial, the FOCUS trial (Function and Overall Cognition in the ultra-high risk State), was designed (Glenthøj et al., 2015), and is, to our knowledge, the hitherto largest trial to report on the feasibility and efficacy of neurocognitive and social cognitive remediation in the UHR state. We hypothesized that cognitive remediation would be superior to standard treatment in improving cognitive functioning, psychosocial functioning, and clinical symptoms in UHR individuals.

2. Methods

2.1. Trial design

The trial is a randomised, assessor-blinded, parallel-group, superiority clinical trial comparing treatment as usual (TAU) plus 20 weeks of intensive cognitive remediation with treatment as usual. The trial protocol has been published elsewhere (Glenthøj et al., 2015). The study was carried out at Mental Health Centre Copenhagen, Denmark. Participants were recruited from the psychiatric in-and outpatient facilities in the catchment area of Copenhagen. The sample consisted of help-seeking individuals aged 18–40 years who fulfilled one or more of the UHR criteria as assessed by the Comprehensive Assessment of At-Risk Mental State (CAARMS) (Yung et al., 2005); attenuated psychotic symptom; brief limited intermittent psychotic symptoms; and/or trait and vulnerability along with a significant drop in functioning or sustained low functioning for the past year. This age span is in keeping with previous large scale UHR trials (McGorry et al., 2017). Exclusion criteria were history of a psychotic episode of ≥one-week duration; psychiatric symptoms that were explained by a physical illness with psychotropic effect (e.g. delirium) or acute intoxication (e.g. cannabis use); a diagnosis of a serious developmental disorder (e.g., Asperger's syndrome); currently receiving methylphenidate. Psychiatric diagnoses were assessed using the Structured Clinical Interview for DSM-IV Axis I and Axis II disorders (SCID) (First et al., 1997). The SCID assessors were all certified in SCID diagnostic interviewing. Estimation of IQ was conducted using four subtests from the Wechsler Adult Intelligence Scale – Third Edition (WAIS-III) (Wechsler, 1997): Vocabulary, Similarities, Block Design, and Matrix Reasoning.

To act as reference on the Brief Assessment of Cognition in Schizophrenia (BACS) composite score, a total of 70 healthy controls were recruited from the community by advertising on a webpage, or via ads at local educational institutions. They did not meet criteria for any DSM-IV disorder and did not have a first degree relative with a psychotic disorder currently or previously. The healthy controls were matched to patients on gender, age (±2 years), ethnicity, and parental socioeconomic status. All participants provided informed consent prior to inclusion into the study.

The study protocol was approved by the Committee on Health Research Ethics of the Capital Region Denmark (H-6-2013-015) and the Danish Data Protection Agency (RHP-2014-009-02670). The trial was registered at ClinicalTrial.gov (NCT02098408). All the assessors were psychologists and medical doctors with extensive training in using the instruments. Cognitive tests were done by psychologists or psychologist students trained and supervised by senior psychologists.

2.2. Randomisation and blinding

On completion of baseline assessments, participants were randomly assigned to one of the two treatment arms. Research assessor masked to treatment allocation conducted assessments at 6-month (cessation of treatment) and 12-month post baseline. Participants were instructed not to disclose their allocation prior to assessments. In case an assessor was unblinded, the assessment would be conducted by another research assessor. The assessments were conducted at a site remote from the intervention site. Additionally, therapists conducting the intervention were restricted from disclosing any information about the participants in the intervention group to the research assessors. The randomisation was centralised and computerised with concealed randomisation sequence carried out by the Copenhagen trial unit (CTU). Randomisation was stratified by current use of antipsychotic medication (yes/no) and IQ score (≤100/>100). Block size was four and eight and was unknown to the investigators and clinicians. The randomised intervention allocation was concealed until the statistical analyses of resulting data had been completed.

2.3. Interventions

The experimental intervention was delivered at a single clinical location. The cognitive remediation was delivered by a senior psychologist, specialized in psychotherapy and a psychologist student. The experimental intervention consisted of manualized cognitive remediation comprising 2 h of group training (firstly 1 h of neurocognitive training, with subsequent 15 min of bridging session, and secondly 1 h of social cognitive training) once a week for a total of 20 weeks. That is; a total of 20 weeks of neuro- and social cognitive remediation. The groups had a maximum of 8 participants. This integrated cognitive remediation design was based on the notion that a combined neuro- and social cognitive remediation format may work synergistically to produce the desired functional gains in psychosis spectrum disorders (Eack et al., 2011). Additionally, the cognitive remediation was delivered as an adjunctive to treatment as usual as meta-analytical evidence from patients with psychosis find increased effect of cognitive remediation when provided in the context of psychiatric rehabilitation (Wykes et al., 2011). On the request of participants in the first experimental group, the group sessions were reduced from 24 to 20.

The neurocognitive remediation was done using a dosing modification of the Neuropsychological Educational Approach to Cognitive Remediation (NEAR) (Medalia and Freilich, 2008), an evidence-based remediation approach. One hour a week, participants received individual neurocognitive training on a computer followed by a group discussion (bridging) relating the cognitive exercises to real world activities. To achieve the recommended 2 h per week of neurocognitive training, participants were instructed to train at home using the web-based training programs at least 1 h per week. The therapist personalized the homework based on the participants' baseline neurocognitive profile displaying areas of deficit. Homework was monitored in the training programs and training motivation was addressed throughout the trial using cognitive-behavorial motivational techniques, sending regular text reminders and offering the home-based training to be conducted with the group therapist. Hence, if adhering to the protocol, the

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participants would do at least 40 h of neurocognitive training over the 20-weeks trial period (expecting they attended all 20 session and did the minimum amount of 1 h of home-based training). Training was conducted using exercises from ScientificBrainTrainingpro.com and Brainhq.com. The social cognitive training was done using the Social Cognition and Interaction Training (SCIT) manual (Roberts et al., 2015); a group psychotherapy and skills training. It addresses several of the key social cognitive domains; e.g. attributional biases, theory of mind, and emotion recognition. In collaboration with Dr. David Roberts, first-author of the SCIT manual, adaptations were made to the SCIT treatment to match the needs of the UHR population. In addition to the group training, the participants received 12 individual sessions designed to maximise the transfer of the effect of the cognitive training to the participants' daily lives. The individual sessions were semi-manualized, embedded in cognitive behavioural therapy and targeted individual problems and goals related to the cognitive deficits.

The therapists attended a SCIT training course conducted by SCIT expert Dr. David Roberts and were offered ad hoc Skype supervision from Dr. Roberts throughout the trial. All the therapy sessions were audiotaped, and nine randomly chosen recordings, obtained throughout the trial period, were used to rate adherence to the treatment manual by an independent rater according to the SCIT Fidelity Scale (Roberts et al., 2015).

Both the cognitive remediation group and the control group received TAU which consisted of a regular contact to health professionals in the in- and outpatient facilities in the capital region of Denmark usually involving supportive counselling, but not specific cognitive remediation.

2.4. Outcomes

The primary outcome was overall cognitive function, measured with BACS (Keefe et al., 2004) composite score at 6-months follow-up. The BACS includes six subtests assessing verbal learning and memory, speed of processing, and executive functions that can be combined to a composite score. Secondary outcomes assessed function and symptom levels at 6-months follow-up with: the Personal and Social Performance Scale (PSP) (Morosini et al., 2000); Brief Psychiatric Rating Scale Expanded Version (Ventura et al., 2000); Scale for the Assessment of Negative Symptoms (SANS) (Andreasen, 1984); the Montgomey-Åsberg Depression Rating Scale (MADRS) (Montgomery and Asberg, 1979). Exploratory outcomes were: transition to psychosis; CAARMS composite score; the Schizophrenia Prediction/Proneness Instrument – Adult Version (SPI-A) (Schultze-Lutter et al., 2012); the Young Mania Rating Scale (YMRS) (Young et al., 1978); the Cambridge Neuropsychological Test Automated Battery (CANTAB ERT) (Sahakian and Owen, 1992); The Awareness of Social Inference Test (TASIT) (McDonald et al., 2003); the Social Cognition Screening Questionnaire (SCSQ) (Roberts et al., 2011); the High-Risk Social Challenge task (HiSoC) (Gibson et al., 2010); the Social and Occupational Functioning Assessment Scale (SOFAS) (Hilsenroth et al., 2000); Social and role functioning was assessed with the Global functioning: Social and Role Scales (Cornblatt et al., 2007); the Social Responsiveness Scale, Adult version (SRS-A) (Constantino and Todd, 2005); the Assessment of Quality of Life (AQoL-8D) (Richardson et al., 2014); the Behavior Rating Inventory of Executive Functions – Adult Version (BRIEF-A) (Gioia et al., 2010); the Cambridge Neuropsychological Test Automated Battery (CANTAB) (Sahakian and Owen, 1992) comprising the tests: Motor Screening Test, Spatial Span, Spatial Working Memory, Emotion Recognition Task, Stockings of Cambridge, IED Set Shifting Test, Paired Associate Learning, 5-Choice Serial Reaction Time, and Rapid Visual Information Processing. Additionally, we used the client satisfaction questionnaire (CSQ) (Larsen et al., 1979), and lastly assessed number of participants experiencing adverse events.

2.5. Statistical analyses

We planned to enroll 126 participants. Considering a clinically relevant difference on BACS composite score at 6-months follow-up to correspond to a Cohen's d of 0.50 (e.g., assuming a between-group difference of 3.0 and a pooled SD of 6.0) (Wykes et al., 2011), we calculated that a sample size of 63 participants in each group would have 80% power to detect a net effect size of 0.5 on the BACS composite score using a two-group *t*-test with a 0.05 two-sided significance level. The comparisons between the two groups on continuous outcomes were conducted with a generalised linear model adjusted for stratification variables and baseline imbalances with missing data handled by multiple (m = 100) imputations using multivariable normal regression. Secondary analyses were conducted with linear mixed models with repeated measurements and an unstructured covariance matrix assessing the interaction term between time and intervention. Logistic regression was applied for dichotomous outcomes. All analyses were conducted according to the intention-to-treat principle, analysing all participants in the groups they were assigned to by randomisation. Inter-rater reliability was assessed using intra-class correlations for the outcome measure SANS, BPRS, MADRS, and PSP in 12 interviews. Primary efficacy analyses were conducted by a blinded and independent researcher with no contact to participants in the trial. All analyses were performed using SPSS version 25.0 and Stata/SE version 15.1.

3. Results

Between April 2014 and January 2017, 241 participants were screened for study eligibility. Of these 185 fulfilled the UHR criteria and were invited to participate in the study. Thirty-nine participants were excluded (i.e. met exclusion criteria), leaving a total of 146 UHR individuals that were assigned to either treatment as usual (TAU) or TAU + cognitive remediation (CR) (Fig. 1). Sociodemographic variables were well balanced between the groups (Table 1). Twenty-two participants (30% attrition rate) discontinued the CR intervention, including eight that did not start treatment (Fig. 1 displays causes for discontinuing intervention). The participants discontinuing treatment did not differ from the ones finalizing treatment on any demographic, symptom, cognition, or functioning variables.

Nine randomly chosen sessions were rated for fidelity to the SCIT treatment. The therapists had an average total score of 19.5 (out of a maximum of 20), corresponding to an excellent adherence to the SCIT therapy manual. Intra-class correlations for inter- rater reliability on the outcome measures of SANS, BPRS, MADRS, and PSP ranged from 0.96 to 0.99, showing excellent agreement.

The TAU+CR group received significantly less TAU (average hours = 20.20, SD = 13.18) within the 6 months intervention period compared to the TAU group (average hours = 26.21, SD = 19.95) p = 0.04. Within the 12-months period, the TAU + CR group had received an average of 41.71 (SD = 27.44) hours of TAU, and the TAU group had received an average of 49.30 (SD = 31.36) hours of TAU, p = 0.14.

Feasibility analysis examined protocol adherence, defined as completing 40 h of neurocognitive training over the 20-weeks trial period (20 sessions and 20 h of home-based training). The TAU + CR group attended an average of 10.9 (SD = 7.6) neuro-and social cognitive remediation sessions and had an average of 11.9 (SD = 16.4) hours of total neurocognitive training (including the participants not starting treatment). Two (2.7%) had protocol adherence and nine (12.3%) competed ≥20 sessions of neurocognitive training.

At baseline, the groups differed on three measures: the TAU+ CR group had significantly higher levels of depressive symptoms (MADRS), self-report social functioning deficits (SRS-A), and self-report executive functioning deficits (BRIEF). All participants completed the baseline assessments, 113 participants completed the post-treatment assessment (6-month follow-up), and 92 participants completed 12-month assessment. Participants in the TAU+ CR group

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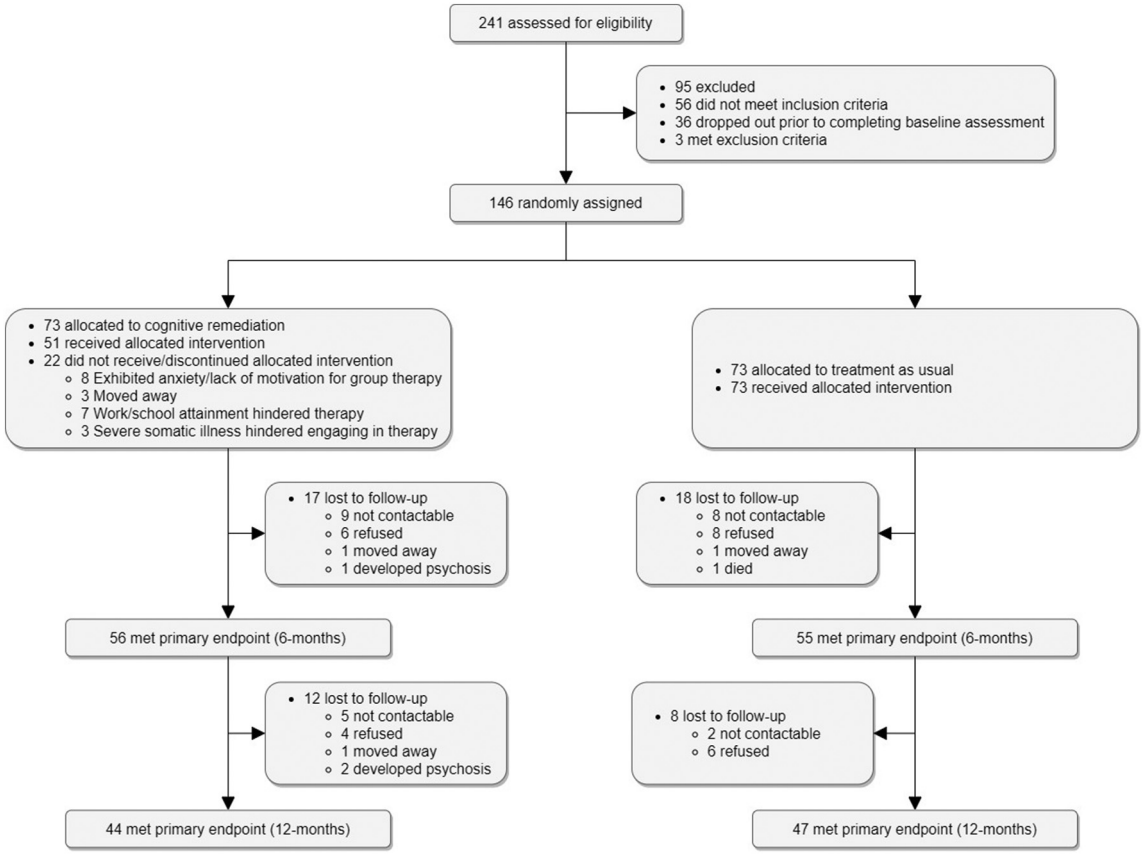

Fig. 1. Study flowchart.

attending 6-month follow-up significantly differed from those not attending 6-month assessment by being older and with more taking antipsychotic medication, but they did not differ on any other sociodemographic variables. Participants in the TAU group attending 6-month assessments did not differ from the ones not attending on any sociodemographic variable except for a significantly higher number of individuals with an anxiety disorder in the group attending follow-up. Participants in the TAU+ CR group attending 12-month follow-up differed significantly from those not attending by being older but not on any other sociodemographic variable. The participants in the TAU group attending 12-month follow-up significantly differed from the ones not attending follow-up by having significantly fewer taking antipsychotic medication and with more having an anxiety disorder. At 12-month follow-up 14 (9.5%) of the participants in the total sample had developed a psychotic disorder (Odds ratio 0.67, $p = 0.53$).

3.1. Between-group differences at treatment cessation and 12 months follow-up

As depicted in Table 2, we found no between-group difference on the primary outcome, BACS composite score, measured at cessation of treatment ($b = -0.125$, 95% CI −0.423 to 0.172, $p = 0.41$). Neither did we find any treatment effect on our secondary outcomes PSP; BPRS-E; SANS, or MADRS. On our explorative outcomes, we found a treatment effect on the Emotion Recognition Test (ERT) latency total score and ERT latency happiness; ERT latency sadness; and ERT latency fear and trending treatment effect on ERT latency surprise with the TAU + CR group demonstrating faster emotion recognition processing speed. There were no differences on the emotion recognition latency measures of anger and disgust. We did not find any treatment effect on the remaining exploratory outcomes.

At the 12-month follow-up we found no significant between-group difference on our primary, secondary or exploratory outcomes except on the CANTAB Stockings Of Cambridge (SOC) and CANTAB Paired Associate Learning (PAL) with the TAU + CR group performing superior to the TAU group on these executive functioning and visual memory measures.

The mixed models' analyses revealed significant time by group interaction in the TAU + CR exhibiting faster emotion recognition processing speed on the ERT total score and on ERT happiness, and higher emotion recognition accuracy of disgust, but lower score on the GF-role (Table 2).

No adverse events were reported relating to the intervention.

4. Discussion

To our knowledge, this is hitherto the largest trial to evaluate the feasibility and efficacy of cognitive remediation in the UHR population. Feasibility challenges were evident in the low attendance rate with the TAU + CR group attending an average of 11 sessions and having an average of 12 h of neurocognitive training. Contrary to our hypothesis, we did not find this approach to cognitive remediation to improve global measures of cognition, functioning, and clinical symptoms. Exploratory analyses did suggest improvements in some specific areas of functioning: facial emotion recognition processing speed improved at treatment cessation only and executive functioning and visual memory improved at 12-month follow-up only. These relatively isolated improvements need to be considered in the context of the multiple tests of cognition that were performed.

To date, only three RCT's have tested the effect of cognitive remediation in the UHR population. Two of these previous RCT's reported cognitive remediation led to improvements in processing speed and verbal

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Table 1
Baseline characteristics for 146 ultra-high risk participants in the FOCUS trial receiving treatment as usual (TAU) + cognitive remediation (CR) or TAU.

Variable	TAU + CR N = 73	TAU N = 73
	N (%)	
Female	38 (52.06)	44 (60.27)
CAARMS status		
- APS	50 (68.49)	61 (83.56)
- BLIPS	-	-
- Trait/state	2 (2.74)	-
- APS + trait/state	18 (24.66)	12 (16.44)
- APS + BLIPS	3 (4.11)	-
Ethnicity		
- High income countries	70 (95.89)	70 (95.89)
- Low income countries	3 (4.11)	3 (4.11)
Medication[a]		
- Antipsychotics	25 (34.4)	26 (35.6)
- Antidepressant	20 (27.4)	22 (30.1)
- Mood stabilizers	1 (1.4)	6 (8.2)
- Benzodiazepines	5 (6.9)	6 (8.2)
Current DSM-IV diagnoses[b]		
- Affective disorder	33 (45.2)	48 (65.8)
- Anxiety disorder	38 52.1)	34 (46.6)
- Substance use disorder	13 (17.8)	10 (13.7)
- Somatoform disorder	1 (1.4)	3 (4.1)
- Eating disorder	4 (5.5)	2 (2.7)
- Adjustment disorder	2 (2.7)	0 (0)
- Personality disorder	29 (39.7)	29 (39.7)
- None	9 (12.3)	6 (8.2)
Drug use within last year (ASSIST)		
- Daily	4 (5.5)	2 (2.7)
- Weekly	1 (1.4)	6 (8.2)
- Monthly	7 (9.6)	4 (5.5)
- Once or twice	11 (15.1)	9 (12.3)
- Never	50 (68.5)	51 (69.9)
Variable	TAU + CR N = 73	TAU N = 73
	Mean (SD)	
Age	23.93 (4.67)	23.90 (3.79)
Years of education	14.23 (2.70)	14.79 (2.77)
Estimated IQ (WAIS III)	102.38 (12.51)	103.92 (12.11)
Clinical symptoms		
BPRS	42.70 (7.45)	40.99 (9.95)
SANS	1.58 (0.79)	1.48 (0.81)
MADRS	16.34 (6.86)	14.01 (6.68)
CAARMS composite score	30.67 (12.70)	48.89 (15.72)
YMRS	3.51 (3.46)	3.31 (4.37)
SPI-A	10.32 (7.18)	8.36 (6.44)
Functioning		
PSP	56.44 (10.39)	57.15 (9.96)
SOFAS	55.01 (11.37)	54.74 (9.43)
GF:Social	6.41 (0.96)	6.26 (1.08)
GF:Role	5.76 (1.21)	5.75 (1.10)
SRS total self-report (N = 68 & 66)	79.19 (26.49)	69.64 (28.58)
SRS total informant (N = 42 & 41)	59.21 (27.12)	51.76 (24.51)
AQoL-8D	0.43 (0.14)	0.45 (0.15)
Social cognition		
ERT total % accuracy	68.97 (8.18)	69.58 (6.20)
ERT latency total (msek)	1561 (726)	1406 (571)
TASIT	51.75 (4.65)	52.70 (4.32)
SCSQ	51.25 (7.99)	50.70 (5.51)
HiSoC (N = 48 & 54)	51.25 (7.99)	50.70 (5.51)
Neurocognition		
BACS composite score	−1.06 (1.14)	−1.26 (0.94)
CANTAB tests		
Spatial Span length	7.13 (1.33)	7.23 (1.15)
SWM strategy	27.40 (6.61)	26.92 (6.04)
SWM between err.	11.10 (10.87)	10.81 (10.46)
SWM 6 + 8 boxes	10.85 (10.57)	10.87 (10.44)
SOC problems solved in min. moves	9.81 (1.62)	10.03 (1.76)
IED Set Shifting Test total errors adj.	18.49 (15.89)	19.92 (18.66)
IED Set Shifting Test EDS errors	7.14 (8.23)	8.01 (10.10)
IED stages completed	8.75 (0.62)	8.68 (0.71)
Paired Associate Learning, total error adj.	5.97 (6.83)	8.62 (26.40)
PAL 6 + 8 boxes	5.57 (6.58)	5.12 (7.63)
RTI Simple Reaction Time	312.00 (65.68)	295.58 (47.79)
Rapid Visual Information Processing A'	0.90 (0.006)	0.89 (0.052)
BRIEF GEC, self-report (N = 68 & 64)	143.74 (22.54)	134.92 (20.52)
BRIEF GEC, informant (N = 53 & 50)	122.62 (25.01)	121.70 (21.17)

CAARMS: Comprehensive assessment of at-risk mental states; APS: Attenuated Psychotic Symptom; BLIPS: Brief Limited Intermittent Psychotic Symptom; BPRS: Brief Psychiatric Rating Scale; SANS: Scale for the Assessment of Negative Symptoms; MADRS: Montgomery-Åsberg Depression Rating Scale; YMRS: Young Mania Rating Scale; SPI-A: The Schizophrenia Prediction Instrument, Adult Version; PSP: Personal and Social Performance Scale; SOFAS: Social and Occupational Functioning Assessment Scale; GF: Global Functioning; SRS: Social Responsiveness Scale; AQoL: Assessment of Quality of Life; ERT: Emotion Recognition Task; TASIT: The Awareness of Social Inferences Task; SCSQ: the Social Cognition Screening Questionnaire; HiSoC: The High Risk Social Challenge; BACS: Brief assessment of cognition in schizophrenia; CANTAB: Cambridge Neuropsychological Test Automated Battery; ERT: Emotion Recognition Task; SSP: Spatial Span; SWM: Spatial Working Memory; SOC: Stockings of Cambridge; IED: Intra-Extra Dimensional Set Shifting; PAL: Paired Associates Learning; RTI: Reaction Time; RVP: Rapid Visual Information Processing; BRIEF: Behavior Rating Inventory of Executive Functions; GEC: Global Executive Composite.

[a] Patients would be taking one or a combination of the listed compounds.

[b] Patients fulfilling one or more of the DSM-IV diagnoses.

memory, along with improvements in self-reported social functioning in one of the trials (Choi et al., 2016; Loewy et al., 2016). Of note, these trials applied targeted, bottom-up based cognitive remediation which provides exercises at the level of early sensory processing. The current trial offered exercises at a higher level of cognitive functioning, i.e. starting at processing speed and attention, and still found some evidence of benefit to select cognitive skills. The third RCT within the UHR population only found trend level neurocognitive benefits but did result in improvements in social functioning (Piskulic et al., 2015). Additionally, a pilot study in patients with first-episode psychosis evaluated comparable treatment elements (i.e. NEAR and SCIT + compensatory cognitive training) and found the intervention to improve areas of neuro- and social cognition, but no effect on social functioning and clinical symptoms (Vidarsdottir et al., 2019). Taken together with prior literature these trial findings reflect the heterogeneity in the learning needs of this population. Even within the diagnosed schizophrenia population, the need to personalize treatment is increasingly recognized as a factor lowering effect sizes in group studies. Needs for dosing, target cognitive skills, clinician involvement and neuroplasticity enhancers are known to vary in schizophrenia populations, and can be expected to vary in the UHR population as well. Our lack of robust trial findings could potentially be explained by the dosage of neurocognitive training in this trial being too low to result in significant cognitive improvements; The average of 12 h of neurocognitive training (with the target number being 40 h) is noticeably lower than the average of 20–40 h of training in previous CR trials in UHR populations (Choi et al., 2016; Loewy et al., 2016; Piskulic et al., 2015), and recommendations stating 25–30 h of cognitive training to be necessary for cognitive benefits (Hooker et al., 2014). The low number of training hours could reflect participants low motivation, as some participants could attend the one-hour neurocognitive training session but only conducted few minutes of training - even in the presence of support and encouragements. Additionally, it may reflect the disadvantage of the extensive intervention format, along with the design of the experimental intervention as an add on to TAU, with TAU comprising participants attending weekly sessions in most cases. Hence, the total treatment format may have been too extensive for the participants to engage fully in the experimental intervention. Our trial findings stress the need to establish the optimal number of training hours necessary to produce significant cognitive, functional, and clinical gains.

Exploratorily, we found a beneficial post-treatment effect of the intervention on emotion recognition processing speed of happiness,

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Table 2
Treatment efficacy for outcomes at 6- and 12-month follow-up.

		6-Month follow-up			12-Month follow-up			Mixed models
	Measurement instrument	Between group difference	95% CI	p	Between group difference	95% CI	p	p-Value time * group interaction
Primary outcome								
Global neurocognition	BACS composite	−0.125	−0.423 to 0.172	0.41	0.061	−0.218 to 0.340	0.67	0.38
Secondary outcomes								
Overall functioning	PSP	−0.091	−3.538 to 3.357	0.96	−1.88	−5.711 to 1.950	0.33	0.36
General symptoms	BPRS	−0.716	−3.674 to 2.242	0.63	2.180	−0.962 to 5.320	0.17	0.25
Negative symptoms	SANS	0.070	−0.195 to 0.336	0.60	0.022	−0.477 to 0.520	0.93	0.23
Depressive symptoms	MADRS	−1.288	−4.019 to 1.443	0.35	0.488	−2.936 to 3.833	0.79	0.33
Exploratory outcomes								
Attenuated psychotic symptoms	CAARMS composite	2.903	−3.164 to 8.970	0.34	3.416	−3.216 to 10.048	0.31	0.73
Manic symptoms	YMRS	−0.047	−0.979 to 0.885	0.92	1.623	−0.128 to 3.375	0.07	0.12
Basic symptoms	SPI-A	−1.265	−3.249 to 0.720	0.21	−1.510	−4.856 to 1.836	0.37	0.91
Overall functioning	SOFAS	−1.015	−4.557 to 2.528	0.57	−0.878	−5.004 to 3.247	0.67	0.87
Role functioning	GF-social	0.232	−0.182 to 0.646	0.27	−0.307	−0.704 to 0.089	0.13	0.43
Social functioning	GF-role	−0.078	−0.469 to 0.313	0.69	0.152	−0.358 to 0.661	0.56	0.01
Social functioning – self report	SRS-A self-report	0.735	−6.721 to 8.191	0.85	1.554	−7.730 to 10.837	0.74	0.92
Social functioning -informant	SRS-A informant	−5.763	−18.721 to 7.195	0.37	1.963	−12.749 to 16.674	0.79	0.17
Quality of life	AQoL-8D	0.006	−0.049 to 0.060	0.83	0.045	−0.025 to 0.115	0.20	0.69
Theory of mind	TASIT	0.839	−0.448 to 2.127	0.20	−0.081	−1.502 to 1.340	0.91	0.22
Social cognition composite	SCSQ, total	−0.772	−1.572 to 0.027	0.06	−0.184	−1.000 to 0.632	0.65	0.42
Theory of mind	SCSQ ToM	−0.280	−0.643 to 0.084	0.13	−0.410	−0.872 to 0.057	0.09	0.50
Schematic inferences	SCSQ schematic inf.	−0.278	−0.619 to 0.062	0.11	0.030	−0.324 to 0.382	0.87	0.29
Metacognitive overconfidence	SCSQ metacognitive overconfidence	0.066	−0.220 to 0.352	0.65	−0.133	−0.478 to 0.213	0.45	0.41
Hostility bias	SCSQ hostility bias	0.048	−0.231 to 0.326	0.73	−0.016	−0.312 to 0.279	0.91	0.50
Social skills	HiSoC	−0.548	−3.679 to 2.583	0.73	0.322	−2.202 to 2.846	0.80	1.00
Facial emotion recognition latency	ERT latency total	−151.98	−279.727 to −24.235	0.020*	−32.311	−189.892 to 125.270	0.69	0.03*
	ERT latency happiness	−214.13	−344.927 to −83.329	0.002**	40.875	−112.981 to 194.731	0.53	0.001**
	ERT latency sadness	−187.07	−331.864 to −42.280	0.012**	−83.034	306.047 to 139.978	0.46	0.14
	ERT latency anger	−70.174	−227.840 to 87.493	0.38	30.406	−247.472 to 308.284	0.83	0.59
	ERT latency disgust	−39.409	−220.085 to 141.268	0.67	−16.231	−237.472 to 205.140	0.89	0.62
	ERT latency fear	−226.78	−403.414 to −50.151	0.012**	−98.403	−292.661 to 95.856	0.32	0.11
	ERT latency surprise	−114.75	−248.633 to 19.143	0.09	−15.557	−196.131 to 165.018	0.86	0.14
Facial emotion recognition accuracy	ERT accuracy total	−0.642	−3.172 to 1.889	0.62	2.492	−6.581 to 11.565	0.59	0.49
	ERT accuracy happiness	−0.788	−4.422 to 2.847	0.67	0.956	−1.199 to 3.111	0.38	0.37
	ERT accuracy sadness	0.687	−3.603 to 4.977	0.75	0.219	−1.842 to 2.280	0.83	0.91
	ERT accuracy anger	0.100	−3.882 to 4.083	0.96	0.315	−1.341 to 1.968	0.71	0.89
	ERT accuracy disgust	−4.566	−10.512 to 1.381	0.13	0.572	−1.769 to 2.913	0.63	0.04*
	ERT accuracy fear	0.590	−5.518 to 6.700	0.85	1.060	−1.313 to 3.434	0.38	0.48
	ERT accuracy surprise	−0.018	−3.506 to 3.469	0.99	−0.425	−2.071 to 1.221	0.61	0.93
Working memory capacity	CANTAB SSP span length	0.250	−0.221 to 0.720	0.30	0.025	−0.542 to 0.592	0.93	0.56
Working memory and strategy use	CANTAB SWM strategy	−1.197	−2.992 to 0.598	0.19	−0.222	−2.258 to 1.815	0.83	0.53
Working memory and strategy use	CANTAB SWM between errors	−3.110	−6.375 to 0.154	0.06	−2.666	−7.354 to 2.023	0.26	0.40
Working memory and strategy use	CANTAB SWM between errors 6 + 8 boxes	−0.2939	−6.152 to 0.275	0.07	−3.714	−7.705 to 0.277	0.07	0.95
Spatial planning	CANTAB SOC problems solved in min. moves	0.483	−0.115 to 1.081	0.11	0.759	0.095 to 1.422	0.03*	0.39
Rule acquisition and attentional set shifting	CANTAB IED total errors adj.	−1.211	−12.853 to 10.432	0.84	−2.010	−7.064 to 3.045	0.43	0.72
Rule acquisition and attentional set shifting	CANTAB IED EDS errors	−0.038	−2.272 to 2.196	0.97	−1.628	−4.336 to 1.081	0.24	0.55
Rule acquisition and attentional set shifting	IED stages completed	0.218	0.265 to 0.701	0.37	0.152	−0.057 to 0.361	0.15	0.77
Visual memory	CANTAB PAL total errors adj.	−0.227	−2.486 to 2.034	0.84	−1.357	−3.734 to 1.020	0.26	0.91
Visual memory	CANTAB PAL total errors 6 + 8 boxes	−1.192	−4.253 to 1.869	0.44	−1.975	−3.674 to −0.277	0.02*	0.65
Speed of response	CANTAB RTI simple reaction time	−3.636	−17.537 to 10.265	0.61	9.802	−13.240 to 32.843	0.40	0.24
Speed of response	CANTAB RTI 5-choice reaction time	−0.651	−20.305 to 19.002	0.95	11.699	−13.243 to 36.642	0.35	0.77
Visual sustained attention	CANTAB RVP A'	−0.006	−0.020 to 0.009	0.45	0.007	−0.007 to 0.021	0.31	0.28
Executive functions in daily life: general executive functions	BRIEF GEC, self-report	0.017	−6.763 to 6.797	1.00	0.438	−9.628 to 10.504	0.93	0.31
Executive functions in daily life: general executive functions	BRIEF GEC, informant	−1.622	−12.366 to 9.123	0.76	8.000	−6.477 to 22.471	0.27	0.73
Satisfaction with treatment	CSQ	0.089	−1.573 to 1.751	0.92	–	–	–	–

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sadness, fear, and total emotion recognition latency, but not regarding emotion recognition accuracy. As the significant effect on emotion recognition latency was lost at follow-up and was not associated with robust social cognitive gains, the results while suggesting malleability in this domain leave open the question of how transfer to accuracy and other facets of social cognition occurs.

Our study had an intervention attrition rate in the moderate range (30%), which is higher than many CR studies in established psychotic disorders (Wykes et al., 2011), but lower than what has previously been reported in two of the three CR trials in UHR populations (Loewy et al., 2016; Piskulic et al., 2015). This emphasizes the critical need for designing appealing interventions for UHR individuals who might be more socially and vocationally active leaving them less time to engage in treatment.

The lack of expected treatment effect on functional outcome underscores the difficulty of improving functioning in UHR states (Devoe et al., 2019) along with the potential of longer follow-up needed for functional improvements to become manifest (Fisher et al., 2010). Additionally, meta-analytical evidence find smaller effect sizes for functioning and symptoms in early psychosis samples compared to chronic schizophrenia (Revell et al., 2015). Finally, considerable clinical and cognitive heterogeneity exist in UHR samples, which is also reflected in the multitude of comorbid disorders in our sample. This baseline variability may result in variable treatment response. Consequently, a highly personalized and possible more focused approach may be needed to target cognitive and functional rehabilitation needs for UHR individuals.

Strengths of the trial include the sample size, the randomised, assessor-blinded, clinical design, and the inclusion of a multitude of cognitive and clinical outcomes, and the high inter-rater reliability. Limiting the trial is the low number of neurocognitive training hours. Additionally, we did not reach the prespecified target number of 126 participants at 6-months follow-up. The intention to treat analyses does, however, include all 146 participants indicating that the null findings are likely not type 2 errors. Furthermore, we based our sample size calculation on a meta-analysis of patients with established psychosis (Wykes et al., 2011). We acknowledge that there is a risk that this is too optimistic a target effect size for a trial in a UHR-population. However, we do not consider this to have an influence on our conclusions as the null findings we present do not appear to be caused by a lack of statistical power.

5. Conclusion

In conclusion, our study did not find cognitive remediation to improve global cognition, functioning, or symptoms in UHR individuals, but exploratorily found select gains in specific cognitive domains. Our equivocal trial findings point to the need for investigating the effect of more individualised and possibly more focused cognitive remediation along with the intensity and dosage of cognitive remediation needed to more broadly benefit cognition as well as functioning and symptoms. Furthermore, our findings suggest that a comprehensive, integrated cognitive remediation format may not be feasible in a UHR population, which indicate a need to the separate application of neurocognitive and social cognitive treatment elements.

CRediT authorship contribution statement

MN, LBG, and BF designed the FOCUS trial. LBG, TDK, CW, and KK conducted the assessments, supervised by MN, BF, and JRMJ. LM conducted the intervention in the trial supervised by DR and AM. LBG and CH undertook the statistical analysis. LBG wrote the draft of the manuscript. All authors contributed to and have approved the final manuscript.

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Declaration of competing interest

None.

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Notes to Table 2:

BACS: Brief Assessment of Cognition in Schizophrenia; PSP: Personal and Social Performance Scale; BPRS: Brief Psychiatric Rating Scale; SANS: Scale for the Assessment of Negative Symptoms; MADRS: Montgomery-Åsberg Depression Rating Scale; CAARMS: Comprehensive Assessment of At-Risk Mental States; YMRS: Young Mania Rating Scale; SPI-A: The Schizophrenia Prediction Instrument, Adult Version; SOFAS: Social and Occupational Functioning Assessment Scale; GF:Social: Global Functioning Social scale; GF; Role: Global Functioning Role scale; SRS-A: Social Responsiveness Scale Adult Version; AQoL-8D: Assessment of Quality of Life; TASIT: The Awareness of Social Inferences Task; SCSQ: the Social Cognition Screening Questionnaire; HiSoC: The High Risk Social Challenge; CANTAB: Cambridge Neuropsychological Test Automated Battery; ERT: Emotion Recognition Task; SSP: Spatial Span; SWM: Spatial Working Memory; SOC: Stockings of Cambridge; IED: Intra-Extra Dimensional Set Shifting; PAL: Paired Associates Learning; RTI: Reaction Time; RVP: Rapid Visual Information Processing; BRIEF: Behavior Rating Inventory of Executive Functions; GEC: Global Executive Composite; CSQ: Client Satisfaction Questionnaire.

*$p \leq 0.05$.

**$p \leq 0.01$.

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