Optimizing the prediction and treatment of functional impairments in individuals at ultra-high risk for psychosis

Doctoral dissertation

Louise Birkedal Glenthøj

Mental Health Centre Copenhagen

Faculty of Health and Medical Sciences

University of Copenhagen

The Faculty of Health and Medical Sciences at the University of Copenhagen has accepted this dissertation for public defense for the doctoral degree in medicine. Copenhagen June 17, 2021.

Ulla M. Wæver, Head of Faculty

The defense will take place
Friday 5th of November 2021 at 12pm at Henrik Dam auditoriet at Panum

Preface

This doctoral dissertation is based on studies conducted from 2016-2019 during my appointments as a clinical psychologist at Mental Health Centre Glostrup and a post.doctoral researcher at Mental Health Centre Copenhagen. The studies were a continuation of the results in my PhD which was defended January 2017.

First, I would like to thank all the participants enrolled in the FOCUS trial for their time and effort that made the research project possible.

I would like to express my gratitude to my mentor Professor Merete Nordentoft, MD, DMSc for being a continuous source of inspiration and for her support of my work. I would also like to thank all my colleagues at the Copenhagen Research Centre for Mental Health (CORE) for creating a warm and inspiring environment. Particularly, I would like to thank Carsten Hjorthøj, PhD, Lise Mariegaard, MSc, Tina Dam Kristensen, PhD, Christina Wenneberg, PhD, Kristine Krakauer, PhD, Maja Gregersen, MSc, Jens Richardt Møllegaard Jepsen, PhD, Hanne Junge Larsen, secretary, and Nikolai Albert, PhD for their truly inspiring and rewarding academic and social partnership. Additionally, I would like to thank our collaborators at Centre for Neuropsychiatric Schizophrenia Research (CNSR), especially Birgitte Fagerlund, PhD, Nikolaj Bak, PhD, and Mikkel Erlang, MSc, for their help on the project. Finally, a heartfelt thank goes to my family for their support, encouragement and not least help on practicalities that made this dissertation possible.

Funding

The FOCUS trial has been funded through The Danish Council for Independent Research; the TrygFoundation; the Mental Health Services in the Capital Region of Denmark; the research fund of the Capital Region of Denmark; the Lundbeck Foundation Center for Clinical Intervention and Neuropsychiatric Schizophrenia Research, CINS.

Content

Preface ... 3

Funding ... 3

List of publications in the dissertation ... 6

Abbreviations ... 8

Readers guide ... 9

1. General introduction ... 10

Early intervention: The putative prodromal state for psychosis ... 10

The UHR state; stressing outcomes beyond psychosis development ... 12

Aims ... 13

1.1. Study cohort ... 15

1.1.2. UHR participants ... 15

1.1.3. Healthy controls ... 16

1.1.4. Ethics ... 16

1.2. Assessments ... 17

1.2.1. Functional assessments ... 17

1.2.2. Clinical assessments ... 18

1.2.3. Cognitive assessments ... 18

1.3. Statistical analyses ... 19

2. Part 1: How should functioning be assessed in UHR states? (paper I) ... 21

2.1. Measuring functional capacity in UHR states: the High Risk Social Challenge task (HiSoC) ... 22

2.2. Discussion and conclusion on part 1 ... 23

3. Part 2: Impact of clinical and cognitive variables on functioning in UHR states (paper II-VI) ... 26

3.1. Emotion recognition and functional correlates ... 28

3.1. Cognitive basic symptoms and functioning ... 30

3.2. Negative symptoms predicting functioning ... 32

3.1. Predictors of risk remission and functional improvements ... 36

Conclusion on part 2 ... 39

4. Part 3: What is the current state of evidence on the effect of cognitive remediation to enhance functional, cognitive, and clinical outcome in the UHR state (paper VII, VIII and IX)? ... 40

4.1. Reviewing cognitive remediation trials in the UHR population ... 40

4.2. The effectiveness of comprehensive neuro- and social cognitive remediation in the UHR state: The FOCUS trial ... 42

4.3. Discussion and conclusion on part 3 ... 48

5. General methodological considerations ... 53

6. General conclusion and perspectives ... 54

6.1. Future directions ... 56

7. Summary 59
8. Danish summary (Dansk resumé) 61
References 64

List of publications in the dissertation

The publications are listed in the order following their presentation in the dissertation.

I. Glenthøj LB, Kristensen TD, Gibson CG, Jepsen JRM, and Nordentoft M. Assessing social skills in individuals at ultra-high risk for psychosis: Validation of the High Risk Social Challenge task (HiSoC). *Schizophrenia Research 2020: 215, 365-370.*

II. Glenthøj LB, Albert, N, Fagerlund B, Kristensen TD, Wenneberg C, Hjorthøj C, Nordentoft M, Jepsen JRM. Emotion recognition latency, but not accuracy, relates to real life functioning in individuals at ultra-high risk for psychosis. *Schizophrenia Research 2019: 210, 197-202.*

III. Glenthøj LB, Fagerlund B, Bak N, Hjorthøj C, Gregersen M, Kristensen TD, Wenneberg C, Krakauer K, Ventura J, Jepsen JRM, and Nordentoft M. Examining the speed of processing of facial emotion recognition in individuals at ultra-high risk for psychosis: Associations with symptoms and cognition. *Schizophrenia Research 2018; 195:562-563*

IV. Glenthøj LB, Bailey B, Kristensen TD, Wenneberg C, Hjorthøj C, and Nordentoft M. Basic symptoms influence real-life functioning and symptoms in individuals at high risk for psychosis. *Acta Psychiatrica Scandinavica 2019: 1-10.*

V. Glenthøj LB, Kristensen TD, Wenneberg C, Hjorthøj C, and Nordentoft M. Experiential negative symptoms are more predictive of real-life functional outcome than expressive negative symptoms in clinical high-risk states. *Schizophrenia Research 2020; 218; 151-156.*

VI. Glenthøj LB, Kristensen TD, Wenneberg C, Hjorthøj C, and Nordentoft M. Predictors of remission from the ultra-high risk state for psychosis. *Early Intervention in Psychiatry*, *2020; 1-9.*

VII. Glenthøj LB, Hjorthøj C, Kristensen T.D., Davidson C.A., and Nordentoft M. Cognitive remediation in individuals at ultra-high risk for psychosis: A systematic review. *Npj schizophrenia 2017, 3:20*

VIII. Glenthøj LB, Mariegaard LM, Fagerlund B, Jepsen JRM, Kristensen TD, Wenneberg C, Krakauer K, Medalia A, Roberts DL, Hjorthøj C, and Nordentoft M. 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. *Schizophrenia Research*, 2020, 224: 151-158.

IX. Glenthøj LB, Mariegaard LM, Fagerlund B, Jepsen JRM, Kristensen TD, Wenneberg C, Krakauer K, Medalia A, Roberts DL, Hjorthøj C, and Nordentoft M. Effectiveness of cognitive remediation in the ultra-high risk state for psychosis. *World Psychiatry, 2020, 19 (3) 401-402.*

None of the listed papers or results herein have previously been submitted with the aim of acquiring an academic degree.

Abbreviations

APS	Attenuated Psychotic Symptoms
AQoL	Assessment of Quality of Life
ARMS	At Risk Mental State
BACS	Brief Assessment of Cognition in Schizophrenia
BLIPS	Brief Limited Intermittent Psychotic Symptoms
BPRS	Brief Psychiatric Rating Scale
CAARMS	Comprehensive Assessment of At-Risk Mental States
CANTAB	Cambridge Neuropsychological Test Automated Battery
COGDIS	Cognitive disturbances of the basic symptoms criteria
DART	Danish Adult Reading Task
ERT	Emotion Recognition Task
ESM	Experience Sampling Method
FOCUS	Function and Overall Cognition in Ultra-high risk States
HC	Healthy Controls
HiSoC	High-Risk Social Challenge
IQ	Intelligence Quotient
NEAR	Neuropsychological Educational Approach to Cognitive Remediation
RCT	Randomized Clinical Trial
SANS	Scale for the Assessment of Negative Symptoms
SCIT	Social Cognition and Interaction Training
SCSQ	Social Cognition Screening Questionnaire
SIPS	Structured Interview for Prodromal Symptoms
SRS-A	Social Responsiveness Scale – Adult version
TASIT	The Awareness of Social Inferences Task
TAU	Treatment As Usual
ToM	Theory of Mind
UHR	Ultra-High Risk
WAIS III	Weschler Adult Intelligence Scale, 3rd version

Readers guide

The background and purpose of the dissertation is described in chapter one along with the study methods. The dissertation subsequently contains three parts that builds on the articles included in the dissertation and addresses the questions of how we can advance the assessment and prediction of UHR individuals' functional outcome by use of clinical and cognitive variables along with optimizing ways to alleviate functional deficits exemplified by a cognitive remediation intervention. Lastly, chapter five and six comprise methodological considerations, a general conclusion of the contribution of the present research and suggests future directions for the research field.

The dissertation is based on nine publications. Further information on participant characteristics, methodology, and more detailed discussion of the study findings are provided in these publications.

1. General introduction

Early intervention: The putative prodromal state for psychosis

Schizophrenia is associated with notable impairments and profound consequences for the affected individuals and the larger society[1]. The past two decades have witnessed a growing interest in understanding the early stages of psychosis. Initially, the research and clinical focus targeted first-episode psychosis (FEP) with the aim of reducing the duration of untreated psychosis as a mean to improve the patients' clinical and functional outcome[2,3]. Subsequently, the research interest grew beyond instituting early treatment of established psychosis by exploring the prospect of preventing psychosis onset; that is, intervening in the putative prodromal phase of psychosis[4]. This potential of prospectively identifying individuals at incipient psychosis serves as the foundation for primary, selected prevention, which ultimately may prevent illness progression - or improve the clinical and functional prognosis of at-risk individuals.

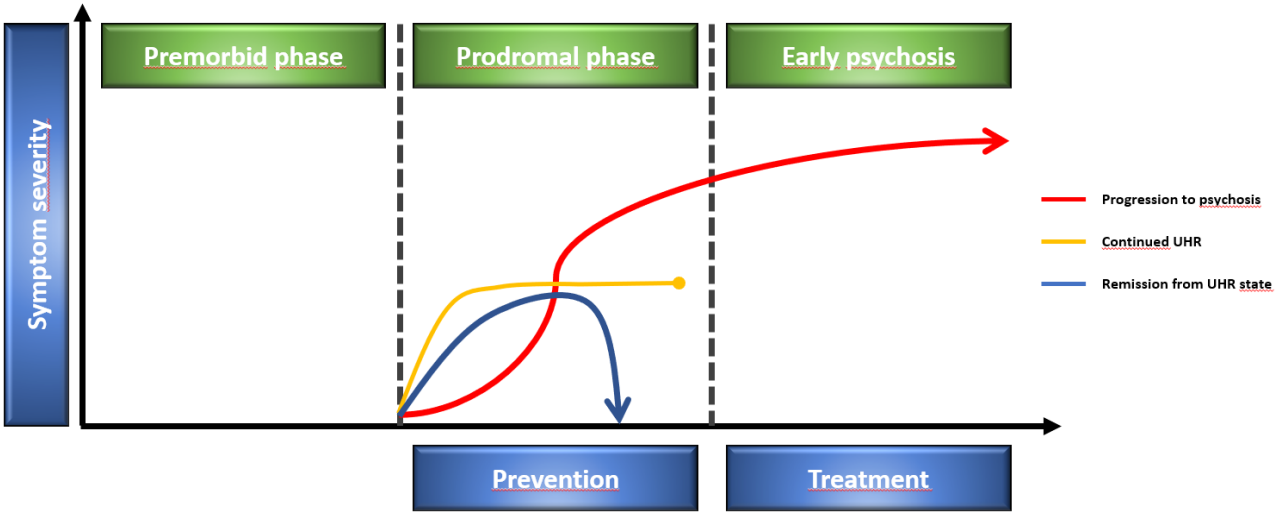

Figure 1: Outcomes of Ultra-High Risk (UHR) individuals.

The construct of the at-risk mental state (ARMS) for psychosis was established with the operationally defined Ultra-High Risk (UHR) criteria[5] that have been adapted world-wide[2]. The UHR criteria comprise three at-risk groups; the attenuated psychotic symptoms group, the brief limited intermittent psychotic symptom group, and the genetic vulnerability group[5,6]. The attenuated psychotic symptoms group is the most frequently occurring[7]. Alternate psychosis high-risk criteria exist that are based on subjectively experienced abnormalities in areas such as cognition, attention, perception, movement, or the basic sense of self, which constitute the *basic symptoms* of psychosis risk[8–10]. Psychosis prediction and prevention have traditionally been the

main outcome of interest in UHR research[11] with initial studies reporting conversion rates up to 40-50% over a one-year period[12–14] and subsequent meta-analytical findings of a 36% psychosis risk after three-years follow-up[15]. Progress in the research field has, however, been accompanied by declining conversion rates to as low as 10-15%[16,17]. The fact that the majority of identified UHR individuals do not convert to a psychotic disorder raised debate regarding a proposal to include the attenuated psychosis syndrome state in the diagnostic manual DSM-5[7], and impacted the decision of instead including it in the DSM-5 appendix as a condition needing further study[18]. The low transition rates have also prompted ethical concerns emphasizing that the UHR concept comprises the risk of labelling and potentially stigmatizing young people that will not develop psychosis, i.e. the false positive notion[19–21]. On this note, critics of the UHR paradigm have stressed that, in contrast to early intervention in somatic disorders, disease mechanisms are not fully understood in psychotic disorders, which may minimize the chance of benefitting patients[22]. The utility of the UHR paradigm has additionally been questioned with the argument that the help-seeking nature of the identified UHR individuals results in the UHR paradigm capturing a selected population that is not representative of the patients that will develop psychosis, i.e. not true prodromal patients[23]. Furthermore, the criticism emphasizes the finding that few presenting with a FEP have previously been in contact with UHR services[24–26]. Contrasting the current high-risk approach, some critics of the UHR concept advocate a prevention strategy that is based on a broader public health approach. Such an approach should aim at reducing replicated risk factors such as cannabis use, and on providing a low-stigma intervention setting to youths such as the Headspace organisation[23,25]. Debating the UHR paradigm[27,28] is indeed important as it stimulates reflection on current practice and potentially finding ways to further reduce the stigma associated with a serious mental illness. While this criticism therefore represents a valid and important perspective to the field of UHR research, it must be noted that although only a minor proportion of the identified UHR individuals will go on to develop psychosis, the UHR population presents with inarguable distressing symptoms, functional impairments, and display help-seeking behavior, which point to the utility of advancing and broadening the outcome targets for UHR identification and intervention strategies.

The UHR state; stressing outcomes beyond psychosis development

The expanding research into the UHR state has recognized that the UHR status confers a clinical risk beyond conversion to psychosis; that is the risk of poor functional outcome irrespective of psychosis development[29,30]. This has led to a spurring interest into other equally important outcomes such as the clinical and functional prognosis of UHR individuals. Functioning is a multifaceted construct comprising elements such as independent living skills (basic functions such as taking public transportation, cooking, managing money, medication adherence), social functions (being able to interact socially), vocational functioning (attaining or holding a job/education), and lastly the ability for self-care[31]. Acknowledging that UHR studies capture a heterogenous patient group with the majority not converting to psychosis over an average of three-years follow-up[15], calls for an improved understanding of the outcome of the group of non-converters. Persistence, or recurrence of comorbid, non-psychotic disorders (mainly anxiety, depressive, and substance use disorders) are found to occur in the majority of the non-converting UHR individuals[32], with further evidence of equal rates of comorbidity in individuals who convert to psychosis compared to those that do not[33]. Concerning the functional outcome of non-converting UHR individuals, studies reveal profound and persistent decrements in overall-, social- and role functioning in a significant proportion of UHR individuals compared to healthy controls – even in cases who remit from their UHR state[30,34–37]. The functional disability of UHR individuals is also reflected in the finding of long-term unemployment in almost a quarter of a large UHR sample followed-up up to 14-years after ascertainment[38]. At a meta-analytical level, evidence reveal UHR individuals to exhibit large baseline impairments in functioning and quality of life compared to healthy controls, with impairments at a level comparable to patients with established psychosis[39] (illustrated in figure 2). While recognizing that functional impairments in psychotic disorders are debilitating at the individual level, they are also costly at a societal level. The Danish Health Authority has estimated that schizophrenia is among the most expensive disorders in terms of lost workforce and costs of treatment[40]. Additionally the functional impairments in psychosis are estimated to contribute to the indirect cost of the illness at about double the direct cost of the illness[31]. The rationale for intervening in the UHR state, and potentially preventing psychosis, is therefore obvious. While the costs associated with the non-converting UHR individuals is not fully known, it can be assumed that the disability and functional impairments experienced by this group

also constitue a significant economic burden. Consequently, the need to elucidate on predictors of functional outcome in UHR states is obvious but the field is, however, characterized by a dearth of evidence on this issue. Functional outcome therefore constitutes a key strategic research focus in the next decades of research into UHR states. An increase in studies investigating the functional outcome of UHR individuals are warranted along with intervention studies that more directly aim at improving the functional prognosis of UHR individuals[41]. At a clinical level, identifying correlates to functional impairments may not only inform on which UHR individuals that are at greatest risk of a poor functional prognosis, but it may also inform intervention approaches into this population and potentially help clinicians allocate resources to those UHR individuals that are in most need. While this argues the case for functioning as a separate and important outcome in UHR research, functioning is also relevant at the level of psychosis prediction as the literature consistently link early functional impairments to psychosis development[12,39,42–44]. Hence, priority should be given to assess and treat functional impairments in UHR states as this may be pivotal to the long-term clinical and functional prognosis of psychosis converters and non-converters.

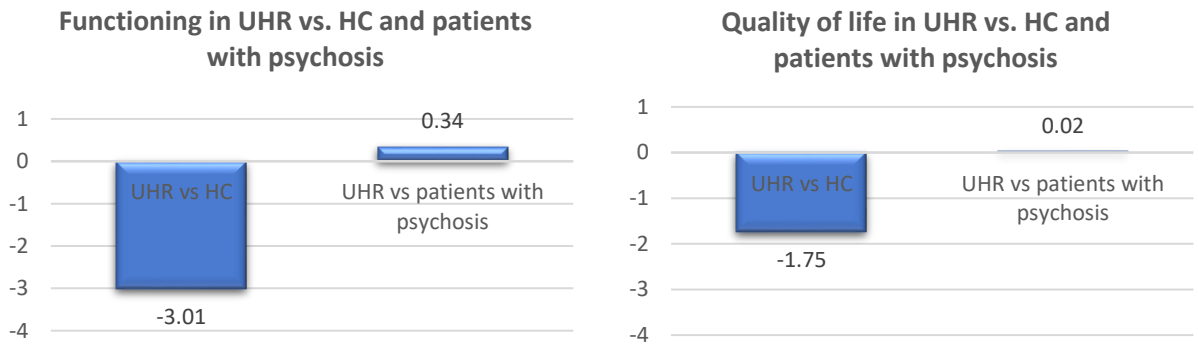

Figure 2. Effect sizes (Hedges g) for functioning and quality of life in UHR patients compared with healthy controls and patients with psychosis. Figure based on data from Fusar-Poli et al. (2015)[39].

Aims

The aims of this dissertation were to:

- Investigate and discuss optimal ways to assess functioning in the UHR state.
- Investigate the impact of specific clinical and cognitive variables on functioning in UHR individuals.
- Identify and discuss the current knowledge on the effectiveness of cognitive remediation on functioning, cognition, and symptoms in the UHR population exemplified by the results

of a comprehensive cognitive remediation trial, the FOCUS (Function and Overall Cognition in Ultra-high risk State) trial.

The dissertation is based on nine published papers: One paper addressing the assessment of functional impairments in the UHR population (paper I). Five papers addressing cognitive and clinical predictors of functioning in UHR individuals (paper II-VI), a systematic review on the efficacy of cognitive remediation in the UHR state (paper VII), and finally a trial evaluating the effectiveness of a comprehensive cognitive remediation intervention in the UHR population (paper VIII and IX).

1.1. Study cohort

1.1.2. UHR participants

The papers in this dissertation are based on data from a cohort of a total of 146 UHR individuals that were recruited as part of the randomized, clinical trial, the FOCUS trial, examining the effect of cognitive remediation in individuals at UHR for psychosis[45]. Participants were recruited from the psychiatric in- and outpatient facilities in the Copenhagen area from April 2014 to December 2017. Clinicians referred help-seeking individuals, aged 18 to 40 years, to the trial if they experienced subthreshold psychotic symptoms. This recruitment strategy is found to lead to significant psychosis risk enrichment compared to recruitment from non-clinical settings (i.e. intensive outreach campaigns in the general population and self-referrals)[46]. Upon referral, trial researchers read the individuals medical files to rule out any exclusion criteria (described below). Subsequently, participants were invited to an approximately three-hours interview using the Comprehensive Assessment of At-Risk Mental States (CAARMS)[5] to determine whether they met one or more of the UHR criteria (see table 1). In case participants met the UHR criteria, they were invited to participate in the study. Subsequently, they underwent comprehensive baseline assessments on symptoms, functioning, cognition, and MRI-scans, prior to being randomly assigned to either treatment as usual + cognitive remediation or treatment as usual. MRI-data are not included in this dissertation. Copenhagen trial unit (CTU) carried out the randomization which was centralized and computerized with concealed randomization sequence. Stratification variables were current use of antipsychotic medication (yes/no) and estimated IQ score (≤100/>100). Block size was four and eight and was unknown to the investigators and therapists. Treatment allocation was concealed until the statistical analyses of resulting data had been completed. Research assessor, that were masked to participants treatment allocation, conducted re-examination at 6-, and 12 months follow-up to elucidate on the immediate and long-term response to the cognitive remediation intervention. Prior to assessments, participants were instructed not to disclose their allocation. If an assessor was unblinded, the assessment would be conducted by another research assessor. All the assessments were conducted at a site remote from the intervention site. Figure 3 displays the study flowchart.

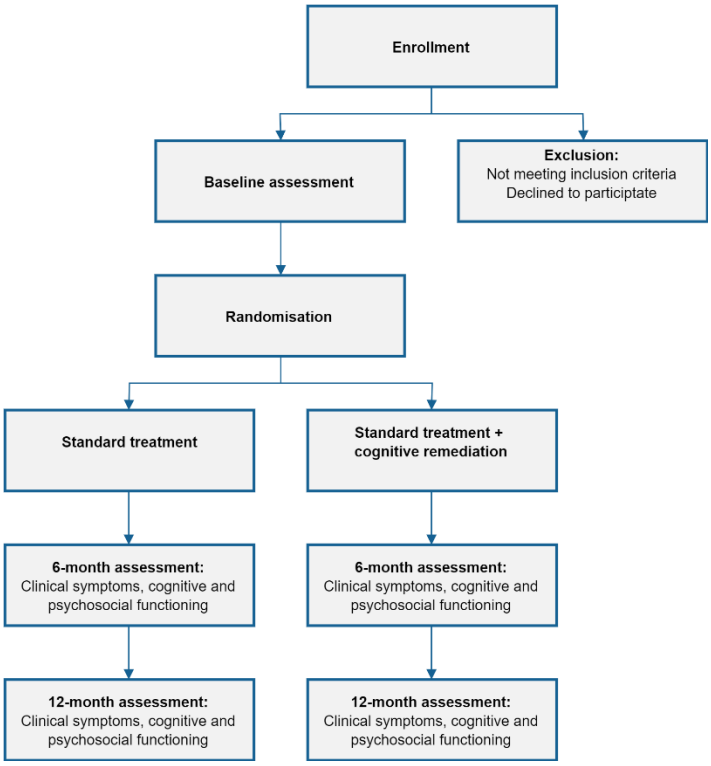

Figure 3. FOCUS trial design. Reprinted with permission from Glenthøj et al. Trials 2015; 16:25.

Participants were excluded if they: Had a history of a psychotic episode of ≥ one-week duration; Experienced psychiatric symptoms that were entirely explained by a physical illness with psychotropic effect (e.g. delirium) or acute intoxication (e.g. cannabis use); Had a diagnosis of a serious developmental disorder (e.g., Asperger's syndrome); Currently received methylphenidate.

1.1.3. Healthy controls

To act as reference on the functional and cognitive assessments, a total of 70 healthy controls were recruited from the community by advertising on a webpage designed to recruit participants to research studies, or via ads at local educational institutions. Assessment of the healthy controls ruled out any DSM-IV disorder or a first degree relative with a psychotic disorder currently or previously. The healthy controls were matched at a group level to the UHR participants on the parameters of gender, age (+/- 2 years), ethnicity, and parental socioeconomic status (i.e. low, middle, high). Paralleling the UHR individuals, the healthy controls were assessed at baseline, and at 6- and 12-months follow-up.

1.1.4. Ethics

The Danish Scientific Ethics Committee (H-6-2013-015) and the Data Protection Agency (ref.no. 2007-58-0015) approved the study protocol. The study was conducted in accordance with the

Declaration of Helsinki. All participants gave written, informed consent. The trial was registered at clinicaltrials.gov (NCT 02098408).

1.2. Assessments

The CAARMS ratings determined UHR status and hence study eligibility. The CAARMS is a semi-structured, clinical interview in which psychotic and psychotic-like symptoms are rated in terms of intensity and frequency revealing whether the participants fulfil one of the three at-risk groups (see table 1 for elaborate description of the UHR criteria). The CAARMS can be used as a dichotomous variable (fulfilling the UHR criteria or not), or as a continuous variable, displaying level of attenuated psychotic symptom by weighing the intensity of symptom scores by their frequency to form a CAARMS composite score[33,47]. The assessors of the CAARMS, and other clinical measures, were all psychologists and medical doctors, that had received training on the instrument by the creator of the CAARMS, Professor Allison Yung. In addition, a large proportion of the CAARMS ratings were based on consensus ratings by at least two researchers in the trial.

Table 1. The UHR criteria according to the CAARMS.

1. **Attenuated Psychotic Symptoms (APS) group**	Individuals with sub-threshold (intensity or frequency) positive psychotic symptoms. The symptoms must have been present during the past year.
2. **Brief Limited Intermittent Psychotic Symptoms (BLIPS) group.**	Individuals with a recent history of frank psychotic symptoms that resolved spontaneously (without antipsychotic medication) within one week. The symptoms must have been present during the past year.
3. **Vulnerability (Trait and State Risk Factor) group**	Individuals with a combination of a trait risk factor (DSM schizotypal personality disorder or a family history of psychotic disorder in a first degree relative) and a significant deterioration in functioning or sustained low functioning during the past year.

1.2.1. Functional assessments

Five functioning measures were included to capture different elements of functioning: Global, interviewer-rated functioning was assessed using the Social and Occupational Functioning Assessment Scale (SOFAS)[48] and the Personal and Social Performance Scale (PSP)[49] that assess functioning in areas such as social-, and role functioning, and self-care. These are frequently used functional measures in research on psychiatric disorders. Social and role functioning was assessed with the two separate measures; the Global functioning Social and Role Scales (GF-S and GF-R)[42] which have been designed specifically to assess functioning in the putative prodromal psychosis

state and is widely used in UHR research. A self-report measure of quality of life was obtained using the Assessment of Quality of Life (AQoL-8D)[50] which assess quality of life in the overarching dimensions of physical (tapping dimensions such as independent living and pain) and psycho-social (tapping dimensions such as happiness, relationships, and coping). The composite quality of life score was used in the analyses, but domain scores can be extracted from the instrument. The AQoL-8D has been used in another large-scale UHR trial[51]. In addition, a self-report measure of social impairments was obtained with the total score on the Social Responsiveness Scale – Adult version (SRS-A)[52]. The SRS-A has originally been validated in autism spectrum disorders, but additionally administered to subjects with non-autistic disorders[53–55]. Finally, we included the High Risk Social Challenge (HiSoC) as a functional capacity social skills measure[56] (further described in the following section and in paper I).

1.2.2. Clinical assessments

The following measures were included to assess multiple symptom aspects: attenuated psychotic symptoms using the CAARMS composite score[5]; negative symptoms using the Scale for the Assessment of Negative Symptoms (SANS)[57] extracting a total score by averaging the four domain score excluding the attention domain[58]; depressive symptoms using the total score on the Montgomery-Åsberg Depression Rating Scale (MADRS)[59]; general psychiatric symptom level using the total score on the Brief Psychiatric Rating Scale Expanded Version (BPRS)[60]; and cognitive basic symptoms using nine items forming the COGDIS criteria from the Schizophrenia Prediction/Proneness Instrument – Adult Version (SPI-A)[61]. These symptom measures are frequently used in large scale UHR studies[62].

1.2.3. Cognitive assessments

1.2.3.1. Social cognition

Three of the four proposed domains of social cognition was assessed[63]; that is, Theory of mind (ToM) by use of The Awareness of Social Inference Task (TASIT)[64]; attributional bias by use of the Social cognition screening questionnaire (SCSQ)[65]; and finally emotion recognition accuracy and latency by use of the Emotion Recognition Task from the Cambridge Neuropsychological Test Automated Battery (CANTAB ERT)[66] (please see part 2 of the dissertation on paper II and III for further description of the task). The social cognitive domain of social perception/knowledge was not assessed in the trial. The TASIT has shown good psychometric properties[67] and efficacy in assessing ToM impairments in schizophrenia spectrum disorders[68,69]. The ERT is a promising task

to examine emotion recognition deficits in clinical populations[70], and has proven initial discriminant validity in UHR individuals relative to healthy controls[71]. The SCSQ has proven initial validity in a schizophrenia sample[72].

1.2.3.2. Neurocognition

Neurocognition was indexed with the Brief Assessment of Cognition in Schizophrenia Battery (BACS)[73] which includes six subtests that index cognitive function in the domains of verbal learning and memory, speed of processing, and executive functions. These subscales can be used individually, indexing specific cognitive domains, or they can be combined to form a **neurocognitive composite score**. Additionally, nine tests from the Cambridge Neuropsychological Test Automated Battery (CANTAB) [66] were included that assess the cognitive domains of: **working memory and strategy**; **executive function/planning** and **set shifting**; **visual memory**; **processing speed**; and **visual attention**. Both the BACS and the CANTAB have proven high validity and reliability[73–75]. Additionally, current IQ was estimated using four subtests from the third version of the Danish Weschler Adult Intelligence Scale (WAIS-III) (Vocabulary and Similarities Block Design and Matrix reasoning)[76] which are known to correlate strongly with full-scale IQ[77].

A more detailed description of the study designs, participants, and assessments can be found in the papers included in the dissertation.

1.3. Statistical analyses

All study participants with available data on the relevant variables were included in the analyses. Between-group analyses were conducted by use of Chi-square tests and analyses of variance (ANOVAs). Univariate and multiple regression analyses were used on continuous outcomes to investigate associations between the relevant predictors and the functional outcome measures and also regarding analyses on variables predicting a response to the cognitive remediation intervention. Dichotomous outcome (risk remission) was analyzed using binary logistic regression. Analyses on the effect of the FOCUS intervention (paper VIII) were computed by generalized linear models 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. All analyses in paper VIII were conducted according to the intention-to-treat approach, analyzing all participants

in the groups they were assigned to by randomization. Primary efficacy analyses on the FOCUS intervention were conducted by a blinded and independent researcher.

Analyses were performed using SPSS version 22.0, 25.0, Stata/SE version 15.1. or R version 3.5[78].

2. Part 1: How should functioning be assessed in UHR states? (paper I)

The assessment of functioning in psychotic disorders poses considerable challenges as functioning is a multifaceted construct. The commonly used way to assess functioning in schizophrenia spectrum disorders is by interview/observer-based ratings or patients self-reports tapping the individual's real-world achievements. While these assessment methods provide important information on the individuals functioning, they may suffer biases which may influence their validity[31]; The subject's self-appraisal may be influenced by the individuals impaired insight affecting the accuracy of the reported level of functioning[79]. The informant-based ratings may not be appropriate for many behaviors (e.g. the person may be unemployed or without a social network) and furthermore, the informant/interview-based rating may be biased as the information is filtered through the informant's perception of the individual. Actual real-world functional achievements such as employment/educational status may, perhaps, offer the most objective, reliable, and robust functional outcome measure. Such assessments may on the other hand be influenced by a number of external circumstances; e.g. local economics/job opportunities etc.[80], and such real-world outcomes may also take longer time to occur than the common clinical trial duration[81]. Performance-based measures of functioning may mitigate the problem of biased ratings by providing an assessment of the individuals *capacity* for real-life functioning opposed the real-world behavior/achievements[82]. Functional capacity can be conceptualized as the ability to perform life skills under optimal conditions[82]. This delineation of capacity versus achievements implies that capacity is the foundation for what can be achieved in the respective functional domain. Furthermore, functional capacity can be regarded as intermediate between basic cognitive function and intricate real-world behaviors/achievements (figure 4), with additional evidence indicating that symptoms impact the deployment of functional capacity skills rather than being an underlying factor for functional capacity deficits[82,83]. In a previous publication, we tested whether this mediating effect of a functional capacity measures established in psychosis[82], would also apply for the UHR state, but failed to find functional capacity mediating the relationship between neurocognition and real-world functional outcome[84]. Significant methodological limitations may, however, have masked the finding of a true mediating effect of functional capacity.

Figure 4. Conceptualization of functional capacity as an intermediate variable between basic cognition and real-world outcomes.

An important element of UHR individuals functioning is social skills, which reflect their capacity for social interactions/social functioning[85]. There is, however, a shortage of available instruments to assess social skills performance in UHR individuals[86]. This study (paper I[87]) therefore aimed to test the utility of the functional capacity social skills measure, the High Risk Social Challenge (HiSoC) task, with established evidence in children and adolescents at *genetic* high risk for psychosis[56], in our cohort of young adults at *clinical* high risk for psychosis.

2.1. Measuring functional capacity in UHR states: the High Risk Social Challenge task (HiSoC)

At total of 102 UHR individuals and 66 healthy controls were assessed with the HiSoC task, which is a performance-based, standardized videotaped task in which the participants are instructed to do a 45-second audition in a mock competition, with a grand money prize, on being the most interesting person in the country. In scoring of the task, social skills are assessed in terms of the display of affect, odd behavior and language, social-interpersonal anxiety, and interest in the task. A higher score on the task indicate better social skills.

We established the utility of the HiSoC task in our UHR sample by evaluating the convergent and discriminant validity of the task, and found the HiSoC to be significantly, positively related to the social- and overall functional achievements measures (GF-S and SOFAS) and the social cognitive, theory of mind measure (TASIT). Furthermore, HiSoC scores were negatively correlated with the negative symptoms measure (SANS). No influence was found of age, IQ, attenuated psychotic- or depressive symptoms on the HiSoC performance. Additionally, we found the HiSoC ratings to be highly reliable with ICC in the range= 0.88 – 0.98. Secondly, we found the HiSoC task (total score and subscales scores) to discriminate between UHR individuals and healthy controls (N=66) displaying large effect sizes; that is, Cohens *d* in the range= 1.40 – 1.94. While these results provide encouraging evidence on the usefulness of the HiSoC task in UHR research, an important limitation of low task tolerability must be addressed. Thirty-nine (27%) of the total sample declined to perform the task, which leaves open the possibility of the study having a biased sample. Furthermore, the large effect sizes found between UHR individuals and healthy controls must be considered in the context of difficulties in maintaining blinding (UHR individuals or healthy controls) of the HiSoC raters due to practical circumstances. Hence, the possibility of biased ratings cannot be ruled out.

2.2. Discussion and conclusion on part 1

The HiSoC functional capacity social skills measure displayed high levels of reliability and validity in our sample of UHR individuals. Furthermore, the findings revealed the HiSoC to be sensitive to social skills deficits in our UHR sample. This stresses the utility of a functional capacity social skills measure to be used in UHR research, but the important point regarding the task tolerability must be considered. This highlights the potential of performance-based measures suffering problems such as poor motivation, low task acceptance, and uncooperativeness which may influence task performance. In accordance with the notion of functioning encompassing the two separate dimensions (capacity vs. achievement), the performance-based and interview/observer-rated ratings inform on different levels of functional difficulties. That is, whereas performance-based measures, such as the HiSoC, may convey a more objective assessment of the UHR individual's social functional capacity, there is a need to include additional measures such as observer/interview-based ratings and self-reports on functional impairments, that may capture the real-world areas of deficit and distress. While functional achievement is influenced by many external factors, a strength of functional capacity measures is their proximity to biological and genetic causation[88]. The importance of elucidating on functional capacity in UHR research is therefore obvious, but functional capacity measures rarely form part of assessment batteries in UHR studies. Our current findings on functional capacity deficits, that aligns with two previous UHR studies[85,88], stress the need for UHR research to broaden the scope of functional assessment to include functional capacity, as diminished capacity may constitute a key barrier to favorable functional outcomes. The finding of functional capacity predicting conversion to psychosis[85,88] further emphasizes that diminished functional capacity may be vital to the etiology of the established disorder. Preferably, functional capacity should test skills that are carried out in actual, real-world settings, but this is burdensome for researchers and clinicians and often offers practical, economic, and logistical challenges. Laboratory-based capacity tests such as the HiSoC act as proxy measures of these real-world skills. The expanding digital technologies, however, offer new and possibly advanced ways to conduct functional capacity assessments that closely simulates real-world settings. For example, the Virtual Reality Functional Capacity Assessment Tool (VRFCAT) which is a virtual reality, functional capacity measure, that has shown high levels of reliability, validity, and tolerability in psychotic disorders[81]. Such virtual reality-based functional

assessment instruments may have significant advantages in offering flexibility in the assessments (i.e. fine-tuning the virtual reality scenarios) and may also be appealing to the younger individuals that constitute the UHR population, and thus potentially increase task acceptability.

In conclusion, the intricacy of functioning may not be captured by one assessment procedure; the use of multiple functional assessment instruments is therefore warranted in UHR studies. Different ways of assessing functioning; i.e. observer-rated, interview-based, self-report, and functional capacity assessments have individual advantages and limitations. This study provides important results for the widespread use of the HiSoC as a social functional capacity measure in UHR research and potentially in clinical practice.

With regard to functional achievements, one of the most widely used functional assessments scales in psychiatric disorders is the Global Assessment of Functioning (GAF)[89] which is an easily administered scale. It does, however, suffer the problem of using one item to assess diverse areas of functioning[90]. Additionally, it comprises an assessment of both function and symptoms with evidence of the GAF being more strongly related to psychiatric symptoms than actual functioning[91]. The SOFAS and the PSP, which are functional scales commonly used in psychosis research and clinical practice, also suffer the problem of combining different areas of functioning (e.g. social, and role functioning) into one global score. While these scales have the advantage of providing an estimate of the individuals overall functional abilities, they may, however, not be sensitive enough to capture subtle treatment-related changes in patients with schizophrenia-spectrum disorders. Furthermore, the operationalization of functioning in these scales may also relate more to functioning in adults and miss the functional issues that arise in adolescence and early adulthood such as school settings, dating etc.[42]. The GF-Social and GF-Role are designed to detect difficulties that are more subtle than what is found in more established and chronic psychotic cases, and moreover, they are not confounded by psychiatric symptoms[37], which strengthens the utility of using the GF-Social and GF-Role in UHR research and clinical settings. By providing a more subtle and age-appropriate definition of functioning, and further by delineating functioning into the separate domains of social and role functioning, the GF-Social and GF-Role seem to offer the currently most appropriate measures of functional achievements in UHR research. Taken together, designing research studies to include multiple functional variables that encompass both functional capacity- and achievement measures will provide the most accurate

way to predict the prognosis of UHR individuals. Owing to the complexity of functional deficits, research studies should conduct a multifaceted functional profile which may inform research on advancing and personalizing targeted interventions that aim at improving the functional prognosis of UHR individuals.

3. Part 2: Impact of clinical and cognitive variables on functioning in UHR states (paper II-VI)

On the path to improving functional outcome of UHR individuals, evidence need to be established on functional predictors constituting potential treatments targets which can be found within clinical, functional, and cognitive domains. A delineation of the schizophrenia symptomatology can be made into positive (psychotic) and negative symptoms[92]. The conceptualization of positive symptoms was developed to reflect alterations in normal functions, whereas the term negative symptoms reflect a loss of function[93]. Attenuated psychotic symptoms, while traditionally capturing the focus of UHR research, show little impact on the functional outcome of UHR individuals[94–99]. Previous literature has indicated that level of negative symptoms, cognitive deficits, and poor baseline functioning are indicators of UHR individual's functional prognosis in cross-sectional and longitudinal studies[95,97–109] - over and above the effect of anxiety-, and depressive symptoms[94,96,110–114]. This influence of negative symptoms and cognition on functioning mirrors findings in patients with established psychosis[115–120] that additionally suggests the domain of social cognition possibly being more strongly related to functional outcome than neurocognition[121]. Social cognition can be defined as "the mental operations that underlie social interactions, including perceiving, interpreting, and generating responses to the intentions, dispositions, and behaviors of others" [122]. It comprises the functions of social perception and knowledge, theory of mind, attributional bias, and emotional processing[63]. Social cognition is a relatively young research field that has suffered the main problem of lacking social cognitive tests with good psychometric properties. To rectify this, the Social Cognition Psychometric Evaluation (SCOPE) initiative was established to evaluate the psychometric properties of the most widely used social cognitive tests[63]. The final test recommendations from the SCOPE expert panel underscore the problems with the available social cognitive measures, as the experts found only three out of the evaluated eight social cognitive tests to have adequate psychometric properties for them to be included in clinical trials[123]. These measures were; the Bell Lysaker Emotion Recognition Task (BLERT)[124], the Hinting task[125], and the Penn Emotion Recognition Task (ER-40)[126] covering the two social cognitive domains of mental state attribution and emotion recognition. Thus, at current no psychometrically sound tests are available to capture attributional bias and social perception, that constitute the last two of the hypothesized four aspects of social cognition. This warrants a need to refine the existing social cognitive measures or develop new measures to

capture the breadth of social cognitive deficits that may also show amenable to social cognitive treatments. Additionally, no social cognitive battery is currently recommended for use in UHR states, and, while the three SCOPE-recommended tests show promise to form part of a future social cognitive battery in more persistent psychotic cases, the psychometric properties of the tests do not seem to apply to the early stages of psychosis[127], which indicates that they neither will apply to the UHR population. Hence, progress in social cognitive assessments in UHR states constitutes a key future research area.

UHR individuals do, indeed, display significant deficits in social cognition (overall effect size= -0.45 – -0.52), which are of a magnitude intermediate to that of patients with established psychosis and healthy controls[128,129]. The importance of social cognitive deficits in UHR states is stressed by the finding of areas of social cognition (ToM and affect recognition) being predictive of psychosis development[130,131]. Social cognitive correlates to functioning are generally understudied in UHR samples, but we have previously reported on the cross-sectional influence of aspects of social cognition on overall-, social- and role functioning along with self-report social functioning in a subsample of the FOCUS cohort[71] which is comparable to previous literature[97,108,132].

Research into neurocognitive deficits in UHR states and psychotic disorders has a longer tradition, and thus a stronger evidence base, than research into social cognitive deficits. Neurocognition in psychotic disorders has been suggested to encompass seven separable dimensions of neurocognitive deficits being: Speed of Processing, Attention/Vigilance, Working Memory, Verbal Learning and Memory, Visual Learning and Memory, Reasoning and Problem Solving, and Verbal Comprehension[133], as identified by the National Institute of Mental Health (NIMH) initiated expert panel. This delineation of neurocognitive deficits into separable domains was the foundation for the development of a consensus cognitive battery, the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) consensus cognitive battery (MCCB), to be used as a standardized battery in pro-cognitive research trials in psychosis spectrum disorders[134]. The MCCB is widely used in psychosis research, but not that frequently used in UHR research[135]. The cognitive tests employed in UHR research therefore often relies on local preferences or tests available in specific languages. Neurocognitive deficits are key features of the UHR state and established psychotic disorders. UHR individuals display significant, widespread cognitive deficits of a magnitude around half a standard deviation below the norm[136,137]. The important role of

neurocognitive deficits in UHR states is reflected in the findings of greater neurocognitive deficits in those individuals that convert to psychosis[136,138] and additional evidence of diverse cognitive domains (e.g. processing speed, attention, executive functions, verbal and visual memory and learning, and working memory) being predictive of psychosis development[136–140]. Neurocognitive deficits have also been implicated in the functional outcome of UHR individuals with regard to global neurocognition[84,99,106], and the specific cognitive domains of verbal learning and memory[95,104,141], spatial working memory[105], processing speed[104,107,139,141], attention[104], and executive function[98]. In a previous paper, we suggested an interrelationship between neurocognition, negative symptoms, and functioning based on the finding of negative symptoms mediating the effect of neurocognition on functioning[84].

Given the lack of a strong evidence base on cognitive and clinical correlates to functioning, this research area in need of further studies. Additionally, there is a need to elucidate on subdomains of cognition and symptoms, as opposed to global measures that are frequently used in research in schizophrenia spectrum disorders. Identifying specific and consistent functional correlates, which likely impact different domains of real-life functional disability, will not only improve the understanding of the UHR state, but also inform the development of highly targeted treatment approaches.

The studies included in the following chapter serve this purpose of describing the contribution of different domain variables within the cognitive and clinical global- and subdomains to the functional outcome of UHR individuals. The first three studies (paper II, III and IV) report cross-sectional data while the additional two studies (paper V and VI) report longitudinal data with a 12-month follow-up.

3.1. Emotion recognition and functional correlates

Deficits in emotional processing, that is facial emotion recognition, is a key feature of social cognitive deficits in UHR individuals as well as in patients with frank psychosis[128,142–145], and may be an essential determinant of functioning and transition to psychosis in UHR states[146]. While aspects of anomalies in facial emotion recognition have been investigated in patients with psychosis[147], they remain largely unexplored in UHR individuals with no previous study assessing the relationship between emotion recognition latency and functioning in UHR states. The aims of the current papers (paper II[148] and III[149]) were therefore to investigate potential differences in emotion recognition accuracy and latency in UHR individuals along with the relationship between

emotion recognition accuracy, latency and neurocognition, clinical symptoms, and functioning measures. Emotion recognition was assessed using the CANTAB ERT task which is a computerized test covering the recognition of six, basic facial emotional expressions: happiness, sadness, anger, disgust, fear, and surprise. Following a quick presentation (200 ms) of a facial expression, the participant must select between the six emotional expressions presented on the screen by pressing the touch screen (see test illustration in figure 5). The outcome of the task is total percent emotions correctly identified, along with a mean response latency (reported in ms) for all emotions correctly identified.

Figure 5. The CANTAB emotion recognition task (ERT). Adapted with permission from the CANTAB test administration guide.

The findings presented in paper II and III reveal UHR individuals (N=132) to display significant deficits in accurately identifying facial emotions along with longer processing speed of facial emotions compared to healthy controls (N=60), (Cohens *d* for total emotion recognition accuracy and latency -0.47 and -0.35, respectively). Additionally, multivariate analyses found higher emotion recognition accuracy to be associated with better sustained attention (RVP A'= b: -7.978, 95% CI:-12.748 – -3.207, p=.001) and worse attenuated psychotic symptoms (CAARMS composite= b: -0.16, 95%CI: -.032 – .000. p=.048), but not with other of the hypothesized six core neurocognitive domains[150], nor negative symptoms.

In the subsequent regression analyses, emotion recognition latency, but not accuracy, was found to be significantly, negatively associated with the overall functioning measure PSP (b:-16.20, 95%CI: -28.53 – -3.87, p=.01), SOFAS (b:-14.41, 95%CI: -27.64 – -1.17, p=.03), and GF-Social (b:-1.57, 95%CI: -2.92 – -0.22, p=.02), and a trend association with GF-Role (b:-1.30, 95%CI: -2.81 – .20, p=.09), but not with the SOFAS and the AQoL-8D. To control for the potential that emotion recognition latency simply reflected a general neurocognitive processing speed, we conducted post-hoc regression analyses with neurocognitive processing speed (BACS symbol-coding) as an additional predictor. We found ERT latency to continue to relate significantly with the PSP (b: -13.61, 95%CI: -26.18 – -1.04, p=.03). This observed relationship was maintained when controlling

for other relevant confounders; years of education and estimated IQ. To test whether this observed relationship could also be found in the healthy control population, we conducted regression analyses between emotion recognition accuracy, latency and the five functioning measures in the healthy control sample. We did not find any significant associations between these variables indicating that the influence of slower emotion recognition latencies on lower functioning form part of the disease process in UHR individuals. While deficits in emotion recognition accuracy are the most commonly investigated emotion recognition impairments in UHR[128] and psychotic disorders[63], the findings in paper II and III highlight the importance of assessing latency in emotion recognition tasks, as this processing of social cognitive information may have important influence on aspects of social functioning in UHR individuals, albeit no evidence-based relationship with role functioning. This observed relationship between longer processing speed of facial emotions and lower social functioning could be understood in a daily social context, as the fast-paced nature of social interactions may make demands on both accurate and fast emotion recognition. This mirrors previous findings from psychosis research of a significant relationship between social cognitive response time and functional outcome[86,123]. Taken together, the findings indicate the importance of targeting social cognitive processing speed (such as emotion recognition latency) in intervention trials in the UHR population that aim at enhancing social functioning.

When interpreting the findings in paper II and III an obvious limitation needs to be considered as the studies are cross-sectional which precludes any causal inferences to be made. Hence, the findings need to be replicated in longitudinal studies to reach firm conclusions. In addition, the use of the multiple functional outcome measures in paper II has the scope of capturing the abovementioned many elements of UHR individuals functioning, but also increases the risk of multiplicity with the reported relationships in the multivariate analyses between emotion recognition latency and a global functioning measure being spurious.

3.1. Cognitive basic symptoms and functioning

The CAARMS criteria were used to establish UHR status in the FOCUS trial. Two complementary approaches can, however, be used to detect UHR individuals and yield information on level of psychosis risk symptoms; the previously defined CAARMS criteria and the alternative basic symptoms criteria that identifies subjective disturbances in attention, thinking, speech, and motor action to constitute the prodromal symptoms[151]. The basic symptoms criteria can detect emerging

psychosis early in the illness course in contrast to the CAARMS criteria identifying at-risk individuals at a more pronounced illness stage[152]. Preliminary evidence combining the CAARMS and basic symptoms criteria has shown increased sensitivity and specificity in psychosis risk prediction compared to using just one criteria[153,154], although findings diverge[155]. With the scope of extending the findings of basic symptoms as a psychosis illness marker, the study (paper IV[156]) aimed to investigate whether a relationship could also be established between basic symptoms and functioning in UHR individuals.

The study included cross-sectional data from 133 of UHR individuals in the FOCUS trial that, in addition to the CAARMS, were assessed on level of cognitive basic symptoms by use of the Schizophrenia Proneness Instrument for Adults (SPI-A) COGDIS criteria that are composed of nine basic symptoms[61,157]. COGDIS criteria are depicted in table 2. SPI-A can be used as a dichotomous variable displaying psychosis risk or not, but also as a continuous variable (composite score) representing level of basic symptoms. Initially, SPI-A assessors were trained by a national expert on basic symptoms, and subsequently attended a three-day training course conducted by Dr. Frauke Schultze-Lutter, an international expert on basic symptoms.

Table 2. Basic symptom criterion "Cognitive disturbances" (COGDIS)

At least any two of the following basic symptoms with a SPI-A score of ≥3 within the last 3 months:	
Inability to divide attention	Disturbance of expressive speech
Thought interference	Unstable ideas of reference
Thought pressure	Disturbance of abstract thinking
Thought blockages	Captivation of attention by details of the visual field
Disturbance of receptive speech	

Conducting univariate regression analyses revealed cognitive basic symptoms to be highly influential on role functioning (GF-Role), self-report social functioning (SRS-A), and quality of life (AQoL-8D), and trending significant association with the overall functioning measure (SOFAS) (table 3). This finding was maintained when controlling for the effect of negative symptoms that are known to be highly influential on UHR individuals functioning[100,158]. Additionally, we found that at-risk participants meeting both the UHR + basic symptoms (COGDIS) criteria were more impaired in the domains of overall-, role functioning, and quality of life: SOFAS (p=.035, Cohen's d=.38), GF-R (p=.002, Cohen's d=.54) and AQoL-8D (p=.003, Cohen's d=.48) compared to at-risk individuals only fulfilling UHR criteria. Additionally, there was a trending significant difference between the

groups on the self-report social functioning measure SRS-A (p=.06, Cohen's d=-.35) with the UHR + COGDIS group reporting higher levels of social functioning deficits. These between-group findings were controlled for the presence of any comorbid psychiatric diagnosis, as comorbid disorders are known to impact functioning in UHR states[33], but that did not change the results.

Table 3. Univariate regression analyses demonstrating the influence of cognitive basic symptoms (composite score) on functioning in UHR individuals (N=133).

Functional outcomes	B [95% CI]	t	p	R^2
SOFAS	-.219 [-.443 – .005]	-1.94	.06	.028
GF:Social	-.017 [-.039 - .005]	-1.53	.13	.018
GF:Role	-.036 [-.061 – -.010]	-2.77	.006**	.055
AQol-8D	-.006 [-.009 – -.003]	-3.80	<.001**	.099
SRS-A	.974 [.346 – 1.602]	3.07	.003**	.071

SOFAS: Social and Occupational Functioning Scale; GF:Social: Global Functioning Social scale; GF:Role: Global Functioning Role scale; AQoL-8D: Assessment of Quality of Life; SRS-A: Social Responsiveness Scale Adult Version. Higher scores indicate better functioning except for the SRS-A where lower scores equal better self-report social functioning. Adapted version based on data from Glenthøj et al. Acta Psychiatrica Scandinavica 2019: 1-10.

The current findings indicate cognitive basic symptoms to influence different aspects of UHR individuals functioning (i.e. role functioning, self-report social functioning, and quality of life) explaining between 6-10% of the variance on these measures. Albeit needing replication, these findings do indicate that the subtle self-perceived cognitive disturbances contribute to UHR individuals' functional decrements and perceived distress, and hence may constitute an important treatment target in the UHR population. Our study design did, however, not allow for the inclusion of an at-risk group based on the basic symptoms criteria only. That constitutes a limitation to the study, as we cannot conduct comparisons on functional level in different at-risk profiles presenting with only basic symptoms, UHR symptoms, or the combination of these.

3.2. Negative symptoms predicting functioning

Negative symptoms comprise the domains of affective flattening, alogia, avolition, apathy, anhedonia, asociality, and attention[57,159]. Negative symptoms may exert a considerable influence on many aspects of the individual's daily life, as it affects the ability to engage socially, to experience motivation, affective expressivity etc. Negative symptoms are linked to profound functional decrements in UHR individuals[84,99,101,102,160], and the pivotal role of negative symptoms in at-risk states is reflected in the proposal to include negative symptoms to define and enroll UHR samples[161]. Negative symptoms are commonly defined as encompassing the two domains *experiential* and *expressive* negative symptoms[162,163]; with experiential negative symptoms

comprising anhedonia and avolition, and expressive negative symptoms comprising alogia and affect. Experiential negative symptoms are known to impact UHR individuals functioning in cross-sectional study designs[100], but evidence is scarce on the relative contribution of experiential and expressive negative symptoms to UHR individuals long-term functional outcome. In paper V[164] we investigated the predictive strength of baseline experiential and expressive negative symptoms to UHR individuals (n=146) global functioning, self-report social functioning and quality of life at 12-months follow-up (n=91) using the SANS.

Overall, the regression analyses revealed negative symptoms to influence UHR individuals 12-months functional outcome explaining 7-35% of the variance on the functional measures of overall functioning, self-report social functioning, and quality of life. In contrast to expressive negative symptoms, experiential negative symptoms impacted all the five functioning measures in the multivariate analyses (figure 6); PSP was influenced by avolition and anhedonia; GF-Role was influenced by avolition; SRS-A was influenced by anhedonia; and AQoL-8D was influenced by avolition. Alogia was the only aspect of negative symptoms impacting functioning (GF-social) in addition to anhedonia. Post-hoc analyses controlled for the effect of baseline neurocognition (using a composite score), antipsychotic mediation, and depressive symptoms and revealed only neurocognition to influence functioning on one measure (GF-Social) in addition to anhedonia and alogia. The additional robust findings of experiential negative symptoms predicting functioning was maintained. These findings support that rather than assessing negative symptoms as one factor, negative symptoms can appreciably be delineated into the two factors experiential and expressive, that associate differently with the functional outcome of UHR individuals; while expressive symptoms may have a strong relationship with social skills performance (functional capacity) (as described in paper I)[87], experiential negative symptoms may be more influential on real-life functioning and quality of life and thus represent different targets for intervention. An apparent limitation to our study is, however, the fact that measures of negative symptoms, particularly the aspect of experiential negative symptoms, and functioning have content overlap which may inflate the association between these variables. While it was not possible to remove the potentially overlapping items on the SANS subscales used in our study, previous studies have succeeded in removing the overlapping items on a global negative symptoms score and finding it to remain a significant contributor to functional impairments of UHR individuals[99]. This notion of

overlapping items on negative symptoms- and functional assessment scales underscores the utility of more recently developed negative symptom scales such as the Brief Negative Symptoms Scales (BNSS)[165] and the Clinical Assessment Interview for Negative Symptoms (CAINS)[166] in future UHR studies on negative symptoms, as these scales have been designed to reduce the item overlap with functioning measures. Furthermore, the utility of refined negative symptoms scales such as the BNSS or the CAINS in future studies is also in keeping with the serious concerns raised against the SANS and the Positive and Negative Symptoms Scale (PANSS) negative symptom scale, which are perhaps the most frequently used negative symptoms scales in psychotic disorders. Critics argue that these scales include items that are not part of the negative symptom complex (e.g. taps on cognitive abilities), and further that they suffer the shortcoming of encompassing items that are not adequately defined (e.g. the distinction between consummatory and anticipatory pleasure) or contain items that are ambiguously operationalized and hence may reflect different processes, and finally, that they predominantly rely on the observed behavior of individuals and consequently may miss assessing the core psychological processes that constitute the essential part of negative symptoms (the latter limitation especially holds for the PANSS negative symptoms scale)[167,168]. These conceptual and methodological limitations of the traditional negative symptom scales may impede on an accurate negative symptom measurement which may again hinder the potential of optimizing targeted therapeutic approaches for negative symptoms, that currently constitute a pivotal unmet treatment need.

Employing negative symptom measures in UHR states need, however, to be modified in order to make them relevant to the adolescent and young adult population. The SIPS and CAARMS negative symptom scales are some of the most widely used negative symptom measures in UHR research, but the instruments also suffer the limitation of the mentioned content overlap between negative symptoms and functioning and furthermore, is not in keeping with the advanced conceptualization of negative symptoms as they do not measure the five identified negative symptoms domains[169]. This highlights the paramount need to develop negative symptoms scales specifically for the UHR population that adhere to the progress made in the understanding of the core of negative symptoms. The Prodromal Inventory of Negative symptoms (PINS) is one such potential instrument which has proven preliminary reliability and validity in a UHR sample[170]. Additionally, adapted version of the BNSS[171] and the CAINS[172] have been developed to be used in

the UHR population with preliminary reports of satisfying psychometric properties. These second-generation negative symptom scales may currently be the most suitable instruments to use in UHR research studies and hold the potential for optimizing the understanding and treatment of negative symptoms in UHR research and the broader research in psychotic disorders. It must, however, be taken into account that the validation of these instruments in UHR samples has produced positively skewed data indicating that they may not be capturing the differences in negative symptoms at the lower end of the spectrum. Hence, there is a need for further refinement of these scales, or the development of new negative symptom scales, with extended item selection that may map the breadth of negative symptoms in UHR states along with proving robust psychometric properties. A compelling large-scale study has been initiated aimed at validating a newly developed second-generation negative symptom measure for use in the UHR population, with the specific aim of overcoming the conceptual and methodological limitations of existing measures[173].

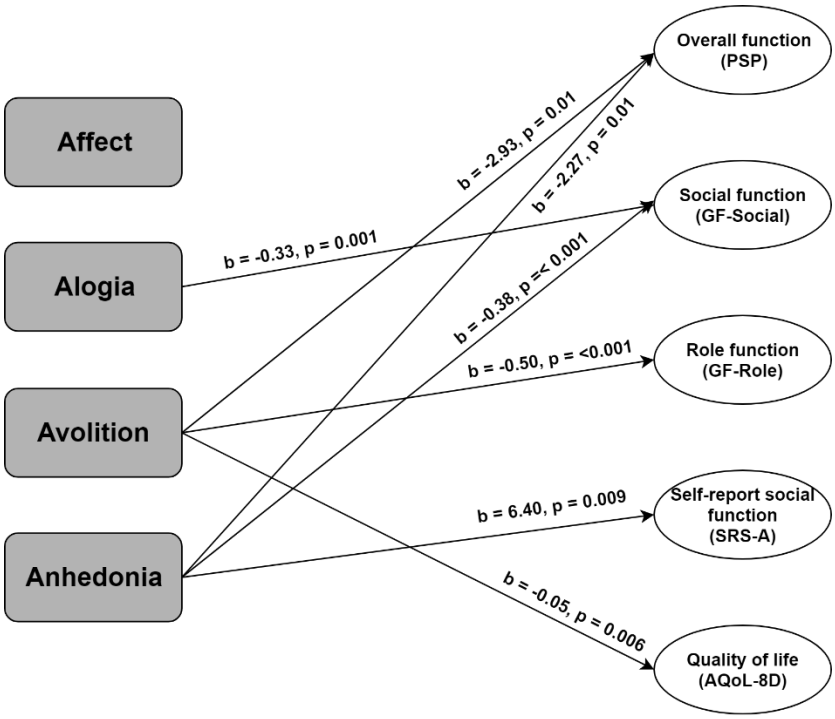

Figure 6. Illustration of multiple regression analyses with forward selection of negative symptom domains predicting overall functioning, self-report social functioning, and quality of life at 12-months follow-up.
PSP: Personal and Social Performance scale; GF:Social: Global Functioning Social scale; GF:Role: Global Functioning Role scale; SRS-A: Social Responsiveness Scale Adult Version; AQoL-8D: Assessment of Quality of Life. Higher scores indicate better functioning

except for the SRS-A where lower scores equal better self-report social functioning. Based on data from Glenthøj et al. Schizophrenia Research 2020; 218: 151-156.

3.1. Predictors of risk remission and functional improvements

An outcome of interest, in addition to the functional prognosis of UHR individuals, is their symptomatic recovery, that can be defined as remission from the ultra-high risk state (i.e. no longer fulfilling the CAARMS criteria of the psychosis UHR state). Previous data reveal 46% of UHR individuals to display full remission from their UHR status over the course of 24-months[174] and additionally, UHR remitters are found to have a better functional outcome than non-remitters at two-years follow-up[29,36,175–177]. These findings point to the importance of elucidating on what predicts a favorable clinical outcome such as remission from the UHR state, but evidence in the area is limited[35,178–180]. This study (paper VI[181]) therefore aimed to investigate the multiple, potential baseline predictors of symptoms, cognition, and functioning to remission from the psychosis UHR state at 12-months follow-up. The sample consisted of the 146 UHR individuals of which 91 were assessed at 12-months follow-up. Potential predictors of remission were symptom variables (attenuated psychotic-, negative-, and depressive symptoms), and functional variables (GF-Social, GF-Role, AQoL-8D, and the SRS-A), along with the variables of gender, antipsychotic medication (y/n), and estimated IQ. Neurocognitive measures were included capturing the established six core neurocognitive domains of verbal learning; processing speed, visual learning and memory, working memory, executive function, and sustained attention[133]. Social cognition was assessed in the area of theory of mind, attributional bias, and emotion processing (please see description in the method section and in paper III and IV for a further elaboration of the cognitive domains).

We found a 12-month remission rate of 36% in our UHR sample largely corroborating existing literature[174]. Univariate logistic regression analyses revealed that the baseline measures of social and role functioning were the only predictors of risk remission at 12-months (table 4), and role functioning remained a significant predictor in the multivariate regression analyses using the same predictor variables as the univariate analyses (OR=1.648, 95%CI: 1.105 – 2.457, p= .014). Furthermore, at 12-months follow-up, the UHR remitters showed significantly better social functioning, role functioning, and self-report social functioning (Cohens *d*= 0.83, 0.48, and 0.50, respectively) along with lower levels of depressive symptoms and, as expected, lower levels of

attenuated psychotic symptoms compared to non-remitters (Cohens *d* = 0.82 and 2.25, respectively).

The functional level of UHR individuals at ascertainment may therefore be pivotal to their clinical prognosis, which is in accordance with a previous study finding[36]. Hence, functional level could potentially be used as a baseline marker for the need for monitoring and intervention in subgroups of UHR individuals; that is, UHR individuals presenting with high baseline functioning may have a better clinical and functional trajectory than UHR individuals with low functioning at ascertainment. Limiting this study finding is the well-established notion of remission rates increasing over the longer-term of >2 years[36], and thus a longer follow-up period than the current rather short follow-up (i.e. 12-months) would be preferable to shed light on risk remission in UHR states. A further limitation that must be stressed is the fact that this was analyses secondary to the RCT, which excludes conducting power calculations to determine whether the sample had statistical power to assess remission. The findings may therefore be considered preliminary and need replication in adequately powered samples.

Table 4. Univariate logistic regression analyses of cognitive, symptoms- and functional variables predicting remission at 12-month follow-up. Adapted version from Glenthøj et al. Early Intervention in Psychiatry 2020; 1-9.

Predictors	OR	95%CI for OR	P-value
Symptoms			
Attenuated psychotic symptoms (CAARMS)	1.006	.997 – 1.035	.700
Negative symptoms (SANS)	.656	.368 – 1.168	.152
Depressive symptoms (MADRS)	.956	.897 – 1.018	.161
Functioning			
Social function (GF-Social)	**1.786**	**1.104 – 2.891**	**.018**
Role function (GF-Role)	**1.581**	**1.079 – 2.316**	**.019**
Quality of life (AQoL-8D)	8.256	.383 – 178.072	.178
Self-report social function (SRS-A)	.996	.980 – 1.012	.613
Neurocognition			
Verbal Learning (BACS List learning)	1.011	.958 – 1.066	.701
Processing speed (BACS Symbol coding)	1.029	.990 – 1.070	.143
Visual memory (CANTAB PAL)	.961	.891 – 1.033	.279
Working memory (CANTAB SWM)	.995	.956 – 1.036	.800
Executive function (CANTAB SOC)	1.091	.847 – 1.406	.499
Attention (CANTAB RVP A')	1.088	.000 – 6909.338	.985
Social cognition			
Theory of mind (TASIT	1.049	.937 – 1.175	.402
Emotion recognition accuracy (CANTAB ERT accuracy)	.978	.915 – 1.044	.499
Emotion recognition latency (CANTAB ERT latency)	-	–	-
Attributional bias (SCSQ)	1.055	.851 – 1.309	.624
Other			
Antipsychotic medication	1.024	.376 – 2.789	.963
Gender	1.032	.429 – 2.482	.944
Estimated IQ	1.034	.994 – 1.075	.098
Intervention group	1.200	.504 – 2.858	.680

Predictors that are significant at the P≤ 0.05 level are given in bold.

Note: CAARMS: Comprehensive Assessment of At-Risk Mental States; SANS: Scale for the Assessment of Negative Symptoms; MADRS: Montgomery-Åsberg Depression Rating Scale; GF:Social: Global Functioning Social scale; GF:Role: Global Functioning Role scale; AQoL-8D: Assessment of Quality of Life; SRS-A: Social Responsiveness Scale Adult Version; BACS: Brief Assessment of Cognition in Schizophrenia: CANTAB: Cambridge Neuropsychological Test Automated Battery; PAL: Paired Associate Learning; SWM: Spatial Working Memory; SOC: Stockings of Cambridge; RVP: Rapid Visual Memory; TASIT: The Awareness of Social Inference Task; ERT: Emotion Recognition Task: SCSQ: Social Cognition Screening Questionnaire.

Conclusion on part 2

This section aimed to investigate specific cognitive and clinical baseline correlates and predictors of UHR individual's functional outcome in various domains. Impairments in overall functioning were related to both longer emotion recognition processing speed and higher levels of experiential negative symptoms. Impairments in role functioning, self-report social functioning, and quality of life were related to higher levels of basic symptoms and experiential negative symptoms. Lastly, better role functioning at baseline predicted symptomatic recovery (i.e. remission from the UHR state) at short-term follow-up. These findings imply that different areas of social cognition and clinical symptoms exert a differential influence on outcome. The cross-sectional study findings of emotion recognition latency and basic symptoms relating to functional outcome warrants, however, a need for replication in a longitudinal design in order to infer causality. Additionally, limiting the longitudinal findings is the fact that the studies were secondary to an RCT which excludes conducting power calculations to evaluate whether the sample had statistical power to investigate the predictive strength of the relevant variables on functional outcome and risk remission.

Taken together, the current findings suggest that researchers and clinicians should consider aspects of patients social cognitive functioning; that is emotion recognition processing speed, and symptom level in the domains of basic symptoms and negative symptoms along with baseline functional level at ascertainment. Assessing potential deficits in these domains will provide indications on the functional prognosis of UHR individuals and can thus form part of the treatment planning.

4. Part 3: What is the current state of evidence on the effect of cognitive remediation to enhance functional, cognitive, and clinical outcome in the UHR state (paper VII, VIII and IX)?

4.1. Reviewing cognitive remediation trials in the UHR population

Given the lead of research into established psychotic states, evidence on the effectiveness of cognitive remediation is well established in both first-episode and more chronic states of psychosis with small to medium effect sizes in both cognitive and functional outcome[182–188]. Interestingly, evidence has emerged on the beneficial effect of cognitive remediation in reducing the level of negative symptoms[189] which are known to be detrimental to the functional prognosis of patients with psychosis spectrum disorders[120], as well as being difficult to alleviate. The UHR state for psychosis offers a unique window of opportunity for the efficacy of cognitive remediation as the cognitive deficits may be more amenable to treatment at this early stage of illness with potentially greater neuroplasticity[190], than at more chronic stages. Additionally, given the fact that symptoms and deficits have been present for a shorter duration in the UHR state than established psychosis, the UHR individuals may thus have experienced shorter interruptions in their functional domains, and developed fewer defeatist beliefs and personal discouragements[191]. Early intervention may therefore offer an opportunity for more effective interventions aiming at preventing chronic functional disability and applying cognitive remediation in the UHR state may potentially be the optimal time to intervene with the aim of improving the level of cognition and the associated functional outcome. To establish the current state of evidence on the effectiveness of cognitive remediation in UHR states we conducted a systematic review (paper VII[192]) using the Cochrane risk of bias evaluations on RCTs and the Newcastle-Ottawa Scale (recommended for assessing the quality of non-randomized studies) for treatments on cognitive deficits in UHR states. Only trials in an isolated UHR sample (compared to samples of mixed UHR and FEP patients) were included. A total of six studies conducted between 2011 and 2016 were identified of which four were RCTs[193–196] and two were cohort studies[197,198]. Overall, the sample sizes were relatively low, ranging between a total of 10-128 participants. Four studies out of the five that reported a cognitive outcome found cognitive remediation to improve cognition in the domains of processing speed, attention, and verbal memory (Cohens *d* for processing speed= 0.50 – 0.84; Cohens d for attention = 0.69; and Cohens *d* for verbal memory = 0.61 - 1.23)[195–198]. Regarding functional outcome, two out of the four studies, that reported on functional outcome, found cognitive remediation to

improve aspects of functioning with treatment related benefits found in the domains of social functioning and social adjustment (Cohens *d*=3.09 and 1.04, respectively)[196,199]. Lastly, none of the five studies that reported on clinical outcomes found cognitive remediation to affect the level of clinical symptoms. None of the studies demonstrated a low risk of bias in the total domains assessed (table 5+6), but noteworthy, the risk of bias was lower in the RCTs than in the cohort studies; particularly stressing that the sample sizes in the cohort studies were small (n= 10 and 14), and the studies may therefore have been statistically underpowered to detect any treatment related benefits. Furthermore, while cohort studies can provide preliminary indications of potential treatment effects, they cannot be used to establish evidence on the effect of cognitive remediation in UHR states due to the lack of a control group. The main methodological problems in the RCTs concerned performance bias and attrition bias, with the latter ranging between 3-48%. The presence of high attrition rates is well-known in UHR studies[200], and point to the importance for clinical trials to use statistical methods to handle missing data (i.e. multiple imputations) to lower the risk of bias.

Table 5. Randomized controlled trials on the effect of cognitive remediation in the UHR population. Modified version adapted from Glenthøj et al. NPJ Schizophrenia 2017, 3-20.

Study	Selection bias	Performance bias	Detection bias	Attrition bias	Intention to treat	Reporting bias
Bechdolf et al. (2012)	Low	High	Unclear	Low	High	High
Piskulic et al. (2015)	Low	High	Low	High	Low	Low
Loewy et al. (2016)	Low	Low	Low	High	Low	Low
Choi et al. (2016)	Low	Low	Low	Low	Unclear	Low

Table 6. Cohort studies on the effect of cognitive remediation in the UHR population. A maximum of nine stars for the highest quality can be given. Modified version adapted from Glenthøj et al. NPJ Schizophrenia 2017, 3-20.

Study	Selection	Comparability	Outcome
Rauchensteiner et al. (2011)	**	**	*
Hooker et al. (2014)	**	**	***

In addition to the studies presented in the review (paper VII), an open-label, feasibility, cohort study with a small sample size (n=17) has subsequently been published[201]. It differs from the

previous cognitive remediation UHR studies by offering integrative cognitive remediation, which draws on evidence of the beneficial effect this therapy approach from patients with established psychosis[202,203]. The findings from this integrative cognitive remediation therapy, consisting of both group- and home-based cognitive training, individual coaching, and family sessions, revealed trial participants to improve significantly on a social functioning measure at treatment cessation (Cohens *d*= 1.02, p=.001)[201]. Cognitive measures were not affected indicating that the functional gains were not related to cognitive improvements.

Taken together, the field has produced few studies elucidating on the effect of cognitive remediation in UHR states, which forms a methodological limitation to the systematic review (paper VII). The level of evidence on the effect of cognitive remediation on the functional, cognitive, and clinical outcome of UHR individuals is therefore still low[204], but the trial findings propose initial evidence on the beneficial effect of cognitive remediation on aspects of cognition and functioning in UHR.

4.2. The effectiveness of comprehensive neuro- and social cognitive remediation in the UHR state: The FOCUS trial

Given the need for additional knowledge on the effect of cognitive remediation in methodological rigorous, large-scale trials, the FOCUS trial was developed, and is hitherto the largest trial to investigate the effect of cognitive remediation in the UHR population. Mitigating one of the shortcomings of previous cognitive remediation trials in UHR states, the FOCUS trial targeted both neurocognitive and social cognitive deficits. This approach is based on the assumption that neurocognitive and social cognitive remediation may work synergistically to increase the transfer of cognitive remediation gains to participants real-world functioning[202,205,206].

The FOCUS trial was a single-site, randomized, assessor-blind, clinical trial investigating the effectiveness of treatment as usual + comprehensive cognitive remediation versus treatment as usual in UHR individuals[45]. Based on previous literature in UHR and psychosis states[188,192], we hypothesized that cognitive remediation would be superior to standard treatment in improving cognition, psychosocial functioning, and clinical symptoms in UHR individuals.

The intervention in the trial consisted of comprehensive, manualized neurocognitive and social cognitive remediation along with individual sessions that aimed to maximize bridging between cognitive training benefits and real-world functioning. The intervention was initially scaled to be in

the format of 24-group sessions and 12 individual sessions. Based on the feedback from the participants in the initial experimental intervention group, that found the intervention format too long, we did, however, reduce the number of group sessions from 24 to 20. This could be done without compromising the treatment manuals. The 20 group sessions comprised two hours of training (one hour of neurocognitive training, with subsequent 15 minutes of bridging session, and one hour of social cognitive training) once a week for a total of 20 weeks. Participants were instructed to do additional home-based neurocognitive training at least one hour per week, to achieve the recommended two hours weekly of neurocognitive training[207]. The neurocognitive remediation was done according to the Neuropsychological Educational Approach to Cognitive Remediation (NEAR)[207], and the social cognitive training was done using the Social Cognition and Interaction Training (SCIT) manual[208]. Both are evidence-based treatments found to be effective in improving cognition and functioning in patients with psychosis[209–215]. See additional information on the intervention elements in table 7.

Table 7. Elements in the FOCUS intervention.

NEAR	SCIT	Individuals sessions
Emphasizes learning and motivation when doing cognitive remediation. Encompass drill-and practice training of cognitive deficits along with a manualized bridging group in each session. The neurocognition training was done using web-based exercises from ScientificBrainTrainingpro.com and Brainhq.com. Neurocognitive training was done in the group-setting and at home. **Format** Group training: 1 hour/week. Homework: minimum 1 hour/week.	Targets key social cognitive domains encompassing theory of mind, emotion recognition, attributional biases, overconfidence, and interaction skills to improve social functioning. Social cognitive training was done in the group-setting and additional weekly homework was assigned to be completed with a "practice partner". The homework was designed to enhance the effect of the elements in the group sessions. **Format** Group training: 1 hour/week. Homework: weekly.	Semi-manualized and embedded in cognitive behavioral therapy (CBT). Uses key CBT techniques to target cognitive deficits occurring in participants daily lives and reinforces participants' motivation to do cognitive remediation in the trial period. **Format** Individual, bi-weekly sessions.

A total of 146 UHR individuals were randomly assigned to treatment as usual + cognitive remediation (TAU + CR) or treatment as usual (TAU). Table 8 display selected participant baseline characteristics. The participants were re-assessed at treatment cessation (6-months follow-up) and at 12-months follow-up (see figure 7 for additional information on participant allocation and follow-up attendance). They were assessed on a multitude of cognitive, functional, and symptom measures. Detailed information on outcomes in the trial can be found in Glenthøj et al. 2015[45] and paper VIII. The primary outcome was neurocognitive global score at 6-months follow-up measured with the Brief Assessment of Cognition in Schizophrenia (BACS) battery. Secondary outcomes were levels of functioning and psychopathology assessed with Personal and social Performance Scale (PSP), Brief Psychiatric Rating Scale (BPRS), Scale for The Assessment of Negative Symptoms (SANS), and Montgomery-Åsberg Depression Rating Scale (MADRS) assessed at 6-months follow-up.

The participants in the intervention group showed an average attendance of 10.9, SD=7.6 of group sessions out of 20 and had an average of 11.9, SD=16.4 hours of neurocognitive training out of the target number of 40. Twenty-two participants discontinued the experimental intervention corresponding to a 30% attrition rate. Lastly, the intervention group received significantly less TAU (average hours= 20.2, SD=13.2) within the 6 months intervention period compared to the TAU group (average hours= 26.2, SD=20.0) p=0.04.

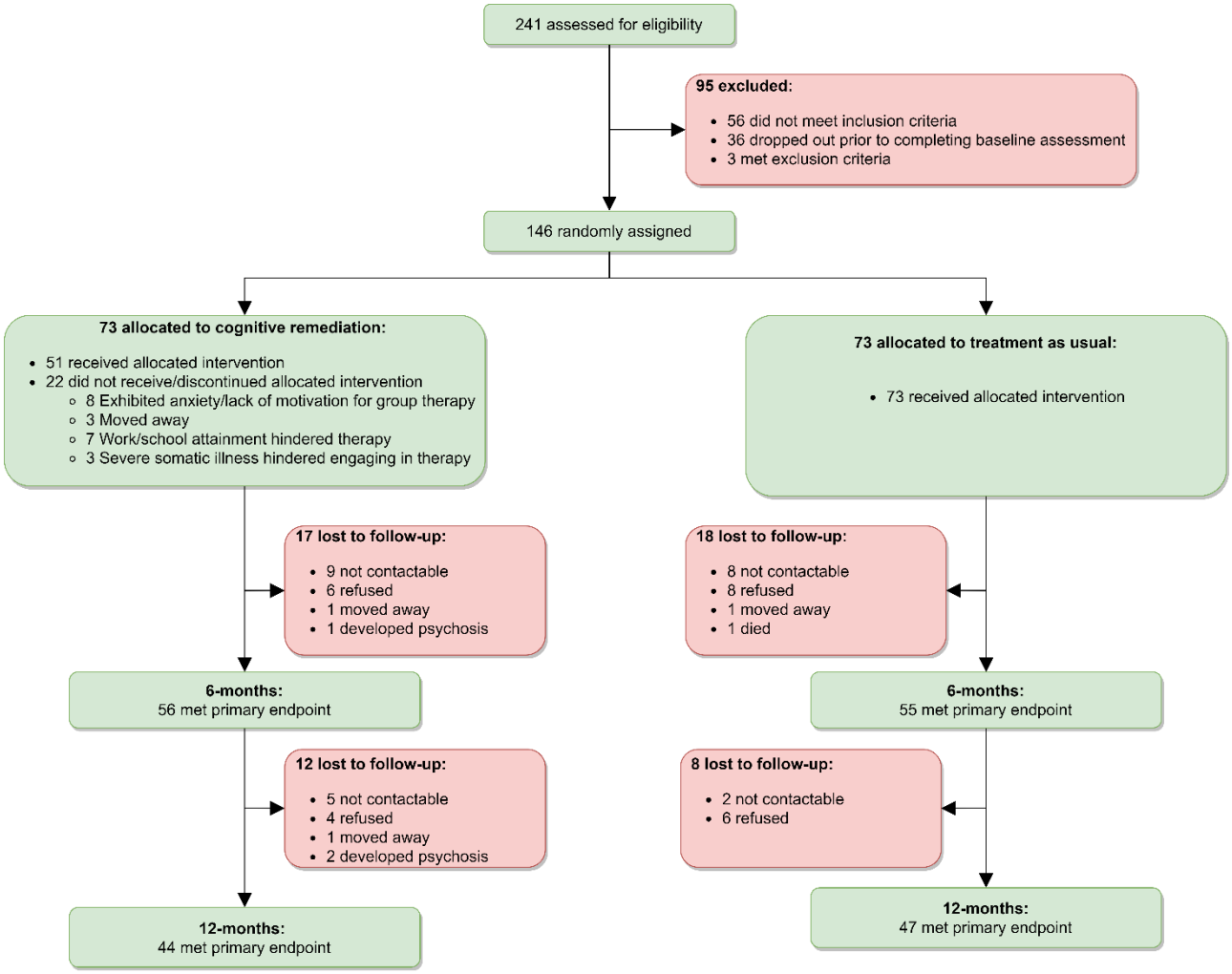

Figure 7. Study flowchart of the FOCUS trial. Based on data from Glenthøj et al. 2020, Schizophrenia Research.

Table 8. Sociodemographics and baseline levels of primary and secondary outcomes of FOCUS participants (N=146). Modified version adapted from Glenthøj et al. 2020, Schizophrenia Research, which includes a detailed description of baseline measures in the trial.

Variable	TAU + CR	TAU
	N= 73	N=73
		N (%)
Female	38 (52.06)	44 (60.27)
CAARMS status		
- APS	50 (68.49)	61 (83.56)
- 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		
- 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		
- 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)
		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)
Primary and secondary outcomes		
BACS composite score	-1.06 (1.14)	-1.26 (0.94)
PSP	56.44 (10.39)	57.15 (9.96)
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)

TAU: Treatment as usual; CR: Cognitive Remediation; 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

The FOCUS intervention did not result in any significant differences between the intervention group and the TAU group on neither the primary nor the secondary outcomes (see figure 8). Exploratory analyses did, however, reveal the intervention group to display significantly reduced processing speed of facial emotions at 6-months follow-up compared to the TAU group (beta values displays ms) on total emotion recognition latency (b=-151.98, 95%CI: -279.73 to -24.24, p=.02) and on the emotions happiness (b=-214.13, 95%CI: -344.93 to -83.33, p=.002), sadness (b=-187.07, 95%CI: -331.86 to -42.28, p=.01), and fear (b=-226.78, 95%CI: -403.41 to -50.15, p=.01). At 12-months follow-up, the between-group differences on emotion recognition latency were no longer significant. The intervention group did, however, display significantly superior performance on two exploratory outcomes of executive function (b=0.76, 95%CI: 0.10 to 1.42, p=.03) and visual

memory (b=-1.98, 95%CI: -3.67 to -0.28, p=.02). There were no adverse events reported relating to the intervention (paper VIII).

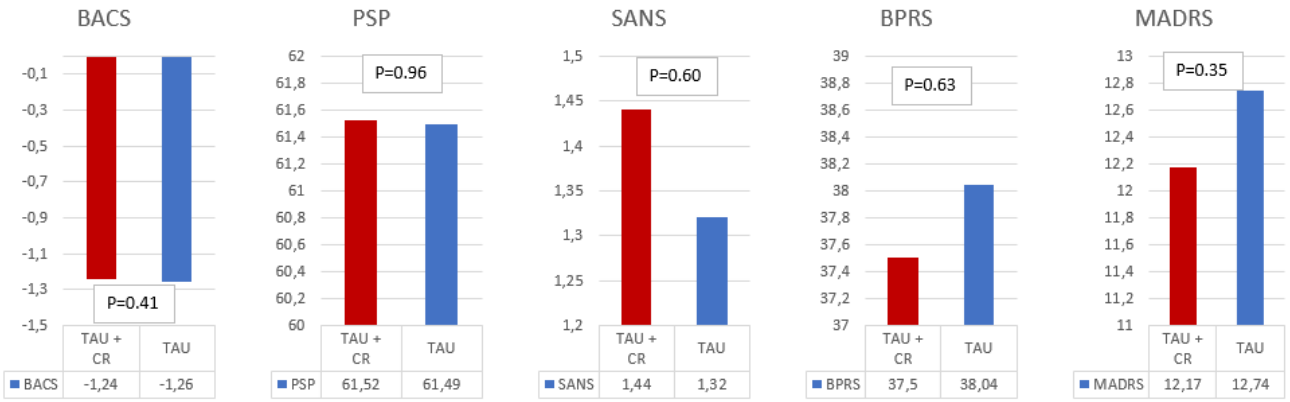

Figure 8. Primary and secondary outcomes of FOCUS participants obtained at treatment cessation (6-months). The figure displays the mean scores.
TAU: Treatment as Usual; CR: Cognitive Remediation; BACS: Brief assessment of Cognition in Schizophrenia; PSP: Personal and Social Performance Scale; SANS: Scale for the assessment of Negative Symptoms; MADRS: Montgomery-Åsberg Depression Rating Scale. Based on data from Glenthøj et al. 2020, Schizophrenia Research (accepted for publication).

Given the fact that the UHR population is characterized by substantial heterogeneity, UHR individuals may also show differences in response to a cognitive remediation intervention. To evaluate what characterizes the UHR individuals showing a response to the FOCUS intervention on exploratory outcomes, secondary linear regression analyses were conducted (paper IX[216]). These analyses elucidated on baseline cognitive, clinical, and functional predictors of a treatment response (change scores) on the exploratory outcomes of emotion recognition latency and executive function and visual memory that improved significantly more in the intervention group than the TAU group at cessation of treatment and at 12-months follow-up, respectively. A consistent pattern revealed better baseline social and role functioning leading to improved emotion recognition latency. Additionally, we found better baseline performance on emotion recognition latency scores to predict these social cognitive improvements. This finding indicates that UHR individuals with better functioning at ascertainment may be more able to benefit from a cognitive remediation intervention, but this effect was not related to their ability to engage in treatment, as we did not find number sessions attended, nor the number of training hours predicted the cognitive improvements. The data indicating that better functioning at baseline lead to cognitive remediation related improvements, suggests that the better functioning UHR individuals have a greater learning potential which contrasts some studies in patients with schizophrenia reporting that patients with lower functional levels are more able to benefit from

cognitive remediation[217]. Contrasting the findings of better baseline emotion recognition processing speed relating to more improved function on these measures, we found the 12-months improvements on executive function and visual memory were predicted by worse baseline performance on these neurocognitive measures. Furthermore, baseline functioning did not predict the neurocognitive improvements. If these findings are replicated, it indicates that there may be a need to take baseline patient characteristics into account when implementing cognitive remediation in the UHR population.

4.3. Discussion and conclusion on part 3

Acknowledging the paucity of evidence on the effectiveness of cognitive remediation in UHR states, there is an evident rationale for investigating the efficacy of cognitive remediation in a methodological large-scale trial such as the FOCUS trial. The lack of effect on the primary and secondary outcomes are surprising, particularly recognizing that the participants did show considerable cognitive, functional, and symptom decrements at baseline[71,87,149] and additionally, the experimental treatment elements have proven effective in improving function and cognition in psychosis - in both separate and combined treatment approaches[209–215,218]. The exploratory 6-months findings of improved emotion recognition processing speed and the 12-months findings of improved executive function and visual memory in the intervention group, indicate a hypothesis-generating effect of the comprehensive remediation on isolated cognitive outcomes, but due to the integrative intervention design, we cannot conclude on which treatment elements produced this effect. When evaluating the lack of expected cognitive and functional improvements, the dosage of cognitive training must be considered; the participants in the intervention group attended an average of 11 hours of group sessions (out of a total of 20) and had an average of 12 hours of neurocognitive training. Given that the intervention was designed for participants to receive a target number of 40 neurocognitive training hours, and great effort was put into addressing training motivation, the low number of training hours indicate that a comprehensive cognitive remediation format, such as the FOCUS intervention, is not feasible in an UHR population. The average of 12 hours of training are considerably less than the 20-40 hours of neurocognitive training in previous cognitive remediation trials in the UHR population[195,196] and the remediation may therefore be underdosed to drive meaningful and robust cognitive and functional improvements. The issue of low engagement in cognitive remediation interventions in

UHR populations echoes previous findings[193,195,201], and underscores a key need of the research field in designing appealing and engaging interventions for UHR individuals, as this is also key to the feasibility and scalability of cognitive remediation interventions into clinical practice. Furthermore, cognitive training programs are in competition with the availability of presumably more engaging, commercial computer games which warrants a focus on advancing the software and digital technologies used to deliver cognitive remediation. This notion is stressed by the finding that young people with psychosis appear to prefer digital platforms as the modality of delivering interventions[219], and that the use of digital technologies is generally feasible and acceptable in psychotic disorders[220]. To increase treatment engagement and adherence in the population of young UHR individuals, the potential of using mobile devices to deliver a pro functional and cognitive intervention embedded in a real-world setting is promising, and has proven preliminary feasibility in psychotic disorders[221]. Additionally, preliminary evidence indicate effectiveness of a targeted social functioning enhancing online (desktop and mobile devices) intervention that integrates strengths- and mindfulness-based elements for the UHR population[222]. Finally, delivering social cognitive training by use of a virtual reality platform has proven feasible and acceptable in a proof-of-concept study in early psychosis[223], indicating a potential of such a therapy approach to improve social functioning.

Another important finding in the FOCUS trial concerns the comprehensive intervention format as adjunctive to treatment as usual. The majority of participants in the FOCUS trial received standard treatment in the Danish early intervention facilities (termed OPUS), which offers an intensive two-years treatment with a minimum of one weekly session[224]. The design of the FOCUS intervention as an augment to standard psychiatric treatment aligns with evidence from patients with psychosis of increased effect of cognitive remediation when provided in the context of psychiatric rehabilitation[188]. Nonetheless, a shortcoming of the FOCUS trial may be that the significant scheduling burden of the entire intervention format hindered participants engaging fully in the experimental intervention resulting in the low number of training hours. Also, it must be noted that the intervention group received significantly less treatment as usual compared to the TAU group in the intervention period, and thus the effect of the FOCUS intervention on functional outcome may potentially be underestimated. Another methodological concern in the FOCUS trial is that the target number of 126 participants at 6-months follow-up was not reached due to

practical and financial circumstances. By employing intention to treat analyses we did, however, account for this by including all 146 participants, and consequently the likelihood of the null findings being type 2 errors are minimized. The lack of expected treatment related functional gains in the trial emphasize the main difficulty in improving functional outcome of UHR individuals with the available interventions (e.g. antipsychotic medication, psychological therapies (mainly CBT), and Omega-3 fatty acids), which has been established meta-analytically in relation to overall functioning[62,225] and specifically regarding social function[226]. Albeit it must be acknowledged that these interventions were not designed specifically to target psychosocial functional outcome. Considerably more research has been conducted on pro-functional intervention studies in patients with a first-episode psychosis than in UHR individuals. Evidence on treatment-related functional improvements in patients with a FEP psychosis has revealed cognitive remediation[227], and specialized integrated interventions, commonly consisting of CBT/supportive therapy, family intervention, and antipsychotics, to improve the patients functional prognosis and quality of life compared to treatment as usual[224,228–230]. The question of what the active treatment elements in the integrated interventions may be remain, however, elusive. This indicates that functional enhancing interventions in the UHR population may need to be multifaceted with cognitive remediation potentially being one of the target areas of deficit. Following the findings from the studies described in part 2 of this dissertation, negative symptoms and basic symptoms may constitute important treatment targets in addition to cognitive deficits when aiming at improving UHR individual's functional prognosis.

Due to the nature of the FOCUS trial being an RCT, the trial participants were randomly assigned to TAU or the experimental intervention with no additional selection based on their level of cognitive or functional difficulties, nor their motivation for cognitive remediation. Selecting trial participants based on their level of functional deficits has been done in an observational, pilot trial[201] finding integrative cognitive remediation to result in functional improvements in a UHR sample, albeit the finding must be seen in the context of the obvious methodological limitations caused by an uncontrolled study design. While such an approach may inflict the external validity of the trial findings, it may on the other hand reduce the potential of ceiling effects and may also increase attendance and engagement in the intervention. Hence, individualizing treatment based on patients' level of difficulties may be a viable approach in research and clinical settings targeted

at improving the functional prognosis of UHR individuals. The utility of a precision medicine approach is further stressed by the fact that the UHR paradigm captures a heterogenous population of which two-third or less may never develop a psychotic disorder. Indeed, the UHR population shows considerable baseline variability; e.g. regarding psychopharmacological medication, number of comorbid psychiatric disorders, duration of impairments etc., and this baseline variability may certainly influence treatment response. In this context of individualized treatment, it has been proposed that different trajectories may require different approaches to cognitive remediation in order improve the functional prognosis of patients with psychosis spectrum disorders[231]. This notion implies that cognitive remediation in UHR and FEP psychosis should not only be within a restorative approach (such as the FOCUS intervention), but also aim to strengthen and preserve abilities that are not yet impacted by the illness. On the other hand, early, persistent deficits that are evident at illness onset may require the involvement of more adaptive and compensatory approaches in order to translate into functional improvements[232,233]. At a meta-analytical level, compensatory cognitive interventions have proven beneficial effects on functioning in psychotic disorders with medium effect sizes at treatment cessation and a small effect size regarding symptom aspects[234]. An evidence base on the effect of compensatory cognitive interventions in UHR states therefore needs to be established.

Additional ways to personalize treatments and ensure treatment motivation may be by use of the motivational questionnaires (e.g. the MUSIC inventory[235] or Motivational Enhancement[236]). These instruments address motivational deficits that can be circumvented by facilitating motivating and engaging learning environments that thus may increase attendance and treatment outcome. Likewise, the digital technology allows for the deployment of advanced monitoring of participants motivation when conducting cognitive remediation, which may prove helpful in adjusting the level of difficulty and increase engagement[196].

Based on the equivocal FOCUS trial findings and the current state of evidence on cognitive remediation in UHR states, no strong support for the effect of cognitive remediation in the UHR population can be provided to patients and clinicians. The studies conducted to date do, however, indicate select functional and cognitive gains. Additionally, there is the potential of the existence of UHR subgroups responding to cognitive remediation interventions. That is, our secondary analyses on what characterizes UHR individuals that are likely to benefit from a cognitive

remediation intervention revealed that those with better functioning and social cognition at baseline showed more treatment related improvements on areas of social cognition, while those with greater domain specific neurocognitive impairments at baseline showed greater treatment related improvements on aspects of neurocognition. While clinical symptom levels did not influence outcome in the FOCUS trial, findings from patients with psychosis have revealed those with less severe negative symptoms at baseline to show enhanced cognitive remediation-specific cognitive improvements[237,238]. Based on the existing literature, and the FOCUS trial findings, it may be stated that cognitive remediation might enhance specific cognitive and functional domains in UHR states, and no evidence indicate it to be a harmful treatment element[239]. The evidence base on the effect of cognitive remediation in UHR states is, however, still scarce and the findings from the FOCUS trial, which is the hitherto largest trial on subject, only revealed significant effect on exploratory outcomes. More studies are thus needed to elucidate on the effect of cognitive remediation in UHR states and on which specific treatment elements that may be effective. Such future studies also need to investigate the potential of UHR subgroups showing a response to cognitive remediation interventions. Elucidating on these aspects is crucial in order to determine whether cognitive remediation should form part of the intervention offered in UHR treatment facilities.

The cognitive remediation in the FOCUS trial was a broad-based, comprehensive treatment integrating both neurocognitive and social cognitive remediation. There is, however, the potential that more targeted cognitive remediation treatments are needed that focus exclusively on isolated cognitive domains with the potential of generalizability to other cognitive domains and functioning. Two RCT's employing such an approach have been found to result in cognitive[195,196] and functional[196] improvements in the UHR population. A more focused cognitive remediation approach may also have the advantage of being less extensive than a comprehensive, integrative approach and may thus increase treatment adherence. This notion of a possibly more focused remediation approach also imply that neurocognitive and social cognitive treatment elements may need to be applied in a separate rather than integrated format, while acknowledging that this precludes any possible synergistic benefits. If future studies do, however, employ an integrated cognitive remediation program, it should be in an engaging and accessible format that can prove

appealing and feasible for the UHR population that may be in a more dynamic stage of illness than the probably more stabilized illness stages seen in more established psychotic disorders.

5. General methodological considerations

The findings in the thesis should be interpreted in the light of the following methodological considerations. Regarding population representativeness, the vast majority of UHR participants in the FOCUS trial were referred from the Danish early intervention facilities which for decades have specialized in assessing and treating patients with attenuated psychotic- and established psychotic disorders. Hence, the study sample is expected to be a representative UHR population mirroring UHR samples from other early intervention facilities such as the PACE or OASIS clinic[240,241]. This recruitment strategy represents a significantly superior psychosis risk enrichment than recruiting from non-clinical settings such as self-referrals or outreach campaigns in the general population[46]. The one-year conversion rate in the FOCUS trial was 9.5% (N=14) which presumably can be regarded as proximal to the 15.2% two-year conversion rate in the comparable OASIS sample; i.e. expecting that more FOCUS participants will convert to psychosis within a two-year period as this is the period with highest conversion risk[242]. On the other hand, the FOCUS conversion rate is somewhat lower than the approximately 15% one-year conversion rate seen in other UHR studies[16,178,179,242–244]. Hence, the possibility of our sample representing a UHR group that is more clinically and functionally stabilized due to a large proportion of them being in receipt of a comprehensive out-patient (i.e. OPUS) treatment cannot be excluded. Due to logistic and practical circumstances in the delineation between adult psychiatry and child- and adolescent psychiatry in Denmark, we enrolled an adult UHR sample aged 18-40 years. This is an older age range than most other UHR studies enrolling participants to as low as 12 years of age[240–242,245–248]. Acknowledging that the emergence of the initial prodromal psychotic symptomatology often begins in early adolescence or younger[249,250], our older study sample (mean age 24 years) could potentially have reached a functional, clinical, and cognitive plateau with the “optimal window of opportunity” being missed. In addition, it can affect the generalizability of the study findings to other UHR samples. Furthermore, it leaves open the possibility of our study sample encompassing a subgroup of individuals displaying a trait phenomenon; i.e. schizotypal personality disorder rather than the more dynamic UHR state. On the other hand, we have previously reported that individuals initially diagnosed with a schizotypal disorder show a 32% psychosis conversion rate within a medium

term follow-up[251], and thus share several similarities with the prototypical UHR individual. Furthermore, we cannot exclude that a selection bias may have occurred in our study population as the study participants were recruited to participate in a comprehensive RCT, which may result in only the better functioning and motived UHR individuals being able to participate. This possibility may thus inflict on the external validity of the study findings[252]. Our study follow-up of 12-months may be regarded as a short-term follow-up, and hence, a longer-term follow-up (i.e. ≥ 24 months) is required to shed light on the long-term functional prognosis of the UHR individuals. This is also relevant regarding the abovementioned elevated psychosis conversion risk being within the first two years[242]. Lastly, the study had a drop-out rate of 55 participants (38%) from baseline to 12-months. It may be that those UHR individuals with the highest symptom level and most adverse outcome were the ones not attending follow-up which may potentially have influenced the study findings.

6. General conclusion and perspectives

Research in psychotic disorders has witnessed a shift from the predominant focus on treating end-stage illness to intervening in the putative prodromal, or UHR state of psychosis. Prediction and prevention of psychosis has traditionally been the overarching focus of research into the UHR state. The current thesis emphasizes broadening the scope of UHR research to the equally important unfavourable trajectory of UHR individual's poor functional outcome. Functioning in psychosis spectrum disorders is not unidimensional but rather a multifaceted construct that can be more narrowly defined by delineating it into functional capacity and functional achievements. The research field has almost exclusively focused on real-world achievements and thus it is a well-established fact that UHR individuals suffer significant and persistent impairments within this functional domain. The current dissertation expands this finding by reporting decrements in UHR individual's functional capacity required to carry out specific real-world functions, and functional capacity may therefore constitute a barrier to functional achievements. Acknowledging these different levels of functional difficulties, assessments encompassing both functional achievement and functional capacity is warranted in UHR studies to gain a comprehensive understanding of the individual's level of deficits. Furthermore, assessing functional capacity may also be relevant with respect to identifying illness markers, as it has been reported to predict conversion to psychosis.

Identifying predictors of UHR individual's functional trajectory is important as it guide treatment targets. The investigated risk factors in this dissertation advances the understanding of variables involved in functional disability by highlighting a specific aspect of social cognition; that is emotion recognition latencies, experiential negative symptoms, basic symptoms, and baseline functioning to be critical to UHR individual's functional and clinical outcome. At a clinical level, this may translate into the development of a standardized assessment battery encompassing cognitive tests and comprehensive functional and clinical assessment in order to map an individual risk profile that may give indications on the functional prognosis and inform on individual treatment targets. Incorporating data from different modalities to increase the predictive strength of a poor functional outcome corresponds to the use of probabilistic multimodal models in predicting conversion to psychosis[253]. Likewise, preliminary evidence for the utility of a risk calculator for poor functional outcome has emerged[254]. Hence, the identification of individual risk factors will be a key factor in future strategies aimed at preventing functional disability in UHR populations. Improving the functional outcome of UHR individuals constitutes a major challenge and a primary future research area. The available treatments (e.g. antipsychotic medication, integrated psychological therapy, cognitive behavioral therapy) have proven very modest efficacy in providing durable functional improvements in UHR samples. As presented in this dissertation, and in the existing literature, cognitive deficits interfere with daily functioning, and hence targeting cognitive impairments in cognitive remediation approaches may be a viable way to alleviate areas of functional deficits in UHR states. The findings from the FOCUS trial do not support that comprehensive cognitive remediation affects the functional or clinical outcome of the UHR population, but an effect on select cognitive gains may be achieved. A possible explanation for the lack of robust effect on functioning and cognition may be due to low adherence and hence, delivering pro-functional interventions in UHR populations need to be in a feasible format with advancing technologies offering encouraging ways to increase therapy adherence and engagement. Additionally, the need for probably more focused (compared to broad-based) cognitive remediation interventions seems warranted. Furthermore, UHR studies need to consider the potential of selecting participants specifically for a specific treatment; that is, UHR samples could be stratified at baseline based on their level of functioning and motivation and targeted interventions could be applied accordingly. This notion implies that cognitive remediation may be

beneficial for a subgroup of UHR individuals; as our preliminary findings indicate, those with worse neurocognition at baseline may show greater benefit from neurocognitive remediation, and those with better social cognition and functioning at baseline may show greater response to a social cognitive remediation intervention. The potential of baseline characteristics predicting a cognitive remediation response needs further investigation in UHR research. Additionally, the findings presented in this dissertation of correlations between functioning and emotion recognition latency deficits, level of experiential negative symptoms, and basic symptoms point to the need for future pro-functional intervention studies in the UHR population targeting these specific areas of deficit. This also implies that pro-functional interventions in UHR need to be multifaceted encompassing different treatment targets. Overall, the findings in this dissertation indicate a potential need to adopt a precision medicine approach to improve the functional prognosis of the heterogenous UHR population.

6.1. Future directions

Gaining insight into functional impairments in psychotic disorders is a difficult endeavor. Future ways to potentially further refine functional assessments is by use of Experience Sampling Method (ESM) which allows for studying psychosis spectrum disorders in the realm of daily life. ESM is a structured data collection technique that assess patients functioning at different time-points over time which allows for capturing detailed fluctuations in functioning that may not be detected by traditional retrospective paper-based measures[255]. This may potentially provide functional assessments with better ecological validity compared with interview/observer-based ratings and patients self-reports[256]. Hence, ESM constitutes an interesting alternative to the commonly used functional assessment techniques by allowing for assessment of discrete and nuanced variations in functioning along with the impact of contextual variables. While acknowledging that this research area is in initial stages, the utility of the ESM approach has been found in relation to the areas of social functioning in UHR and psychotic disorders[257,258], and quality of life in patients with psychosis[256].

Owing to the findings in this dissertation, the question remains of how we can effectively treat functional impairments in UHR states? Negative symptoms are core features of psychosis spectrum disorders, and prominence of negative symptoms may impede on the effect of cognitive remediation and other treatment approaches, if they are not addressed in the treatment protocols. At current, no robust evidence exist on ways to alleviate negative symptoms in UHR

states[160] nor frank psychotic disorders[116] with marketed interventions. While meta-analytical evidence have indicated a small to moderate beneficial effect of cognitive remediation on negative symptoms in psychosis[189], the effect of cognitive remediation on negative symptoms needs further evidence base. In general, future research is warranted into combining treatment approaches to target negative symptoms more efficiently, or alternatively to elucidate on the effectiveness of providing an intervention to reduce negative symptoms before patients enter a treatment program. Furthermore, UHR individuals display dysfunctional coping strategies, self-efficacy, and external control beliefs[259–261], and these psychological aspects may therefore be additional important treatment targets to integrate in pro-functional interventions in order to make UHR individuals engage in, and benefit from, treatments.

Another point to be considered for future pro-functional trials in the UHR population is to adopt a staged approach according to the clinical staging models. A staged intervention approach towards functional deficits would infer that the most benign interventions were applied initially (e.g. supportive counselling, psychotherapy, cognitive remediation), and for those UHR individuals not responding to these treatments, more intensive or specific interventions, with possibly more adverse effects (e.g. pharmacological interventions), could be initiated[262]. Such an approach would also allow for a gradual enrichment of the UHR sample, such that those individuals not in remission of functional impairments at initial stages would be enriched for more persistent and profound functional disability[263]. Based on the findings in this dissertation, future studies should be established that replicate the findings of the variables of emotion recognition latency deficits, level of negative symptoms, prominently experiential negative symptoms, and basic symptoms correlates to adverse functional outcomes. If replicated, this would indicate that these cognitive and clinical symptoms domains constitute important treatment targets that, in conjunction with other significant predictors which has not being elucidated on in this dissertation, indicate areas of deficit that need to be treated in future pro-functional studies. If found effective, such interventions could form part of a staged treatment approach. Indeed, this would align with the research interest into a precision medicine approach. Additionally, another important future research area is the potential of refining the subgrouping of UHR individuals in terms of functional outcome by combining cognitive, clinical, and biological modalities. The relationship between aspects of cognition and clinical symptom to functioning have been investigated in the current

dissertation. Biological data (Magnetic Resonance Imaging (MRI)) is, however, also available from the FOCUS cohort and constitute an important future research area to explore in predicting UHR individual's functional prognosis. This notion of potentially identifying UHR subgroups is reinforced by research on the utility of establishing subgroups in psychotic disorders[264] and additionally, implies a need for multi-center studies to achieve adequate sample sizes.

Finally, the virtual reality paradigm, with the usage in psychosis spectrum disorders still being in its infancy, offers unique opportunities for assessment and treatment of functional deficits. Virtual reality enables great flexibility in designing scenarios that will elicit psychological responses that are very similar to those in the real world[265,266]. Virtual reality treatments have proven preliminary effectiveness in improving areas of functioning such as social skills deficits[267,268] and specific job-interview skills[269] in patients with psychosis, and is generally regarded as a safe and well-tolerated intervention[270]. Adding virtual reality techniques to the assessment and treatment of functional deficits in UHR states may thus be a promising research area to explore which allows for a highly targeted and personalized approach, that also corresponds to the great functional, cognitive, and symptom heterogeneity characterizing the UHR population. To gain robust functional improvements, this established heterogeneity also warrants a potential need for future pro-functional treatment trials into the UHR population to be based on needs-based selection criteria and consequently tailoring the intervention to the individual's primary health-related concerns.

Lastly, another point to be considered in future UHR research is to advance and broaden the UHR paradigm and the intervention strategies[271]. As mentioned, the UHR paradigm captures a complex patient group with a heterogenous outcome. This heterogeneity is exemplified by UHR individuals displaying cross-diagnostic trajectories[272]. Hence, as seen in the CHARMS (Clinical High At Risk Mental State) initiative, the UHR concept could be expanded to encompass a broad definition of a syndrome that, although the symptoms do not reach the threshold for a psychiatric diagnosis, causes distress and help-seeking behavior that merit an intervention[273]. Within this extended UHR paradigm, the outcome would move beyond psychosis development to any defined serious mental illness. Such an approach could therefore be considered as a future strategy to explore in high-risk studies aimed at preventing functional disability of a larger population of young adults at-risk for any serious mental illness.

7. Summary

The psychosis Ultra-High Risk (UHR) paradigm is a clinical syndrome associated with profound and persistent functional impairments. This dissertation argues the case for functional outcome to constitute an independent and equally important outcome to psychosis development in UHR studies. Recognizing the paucity of evidence on functional determinants and treatments in UHR research, the dissertation investigated how the assessment, prediction, and prevention of functional disability could be optimized in UHR states. At the level of assessment of functional impairments, the dissertation provided evidence to support the rationale for including multiple functional measures to capture the complexity and multifaceted nature of functioning in UHR individuals. In particular, the utility of a *functional capacity* measure *(i.e.* the individuals' *capacity* for real-life functioning) was emphasized as a supplement to the commonly used *functional achievements* measure *(i.e.* the individuals' real-world behavior/achievements) in UHR research. Regarding the prediction of functional impairments in UHR states, the dissertation found evidence for specific social cognitive and clinical predictors relating to functional outcome. In cross-sectional studies, we found emotion recognition processing speed to associate with overall functioning, and cognitive basic symptoms to associate with role functioning, self-report social functioning, and quality of life. In longitudinal studies, with a 12-months follow-up, we found experiential negative symptoms; that is, reduced motivation and experience of pleasure, to predict role functioning, self-report social functioning, and quality of life. Additionally, we found baseline functioning to predict symptomatic recovery defined as remission from the UHR state. These findings point towards the utility of conducting comprehensive baseline cognitive and clinical assessment of UHR individuals, which can translate into a functional risk profile that can inform researchers and clinicians of the individual's risk of a poor functional trajectory. This may aid in adjusting the need for monitoring and intervention along with the potential of allocating resources to those who are at greatest risk for a poor functional outcome.

The current available treatments have shown modest efficacy in alleviating functional deficits in UHR states. By acknowledging that UHR individuals suffer cognitive deficits that can impede functional improvements, we conducted the hitherto largest randomized clinical trial (FOCUS trial) in the UHR population to evaluate the effectiveness of intensive cognitive remediation, as an adjunctive to treatment as usual, on functioning, cognition, and clinical symptoms. We did not find a comprehensive cognitive remediation approach to result in significant benefits in functioning,

global cognition, and symptoms. Select gains in emotion recognition processing speed, working memory, and executive function were found exploratorily which, within a hypothesis-generating perspective, points to an effect of a brief cognitive remediation approach to result in cognitive gains. The lack of robust effect of the FOCUS intervention may be attributed to low adherence and convey important information on the feasibility of a comprehensive cognitive remediation protocol in the UHR population; that is, a 20-sessions cognitive remediation treatment, as an add on to treatment as usual, is not feasible. Additionally, it is likely that UHR individuals respond selectively to a cognitive remediation intervention, and hence it may be that, rather than offering cognitive remediation to the whole UHR population, it should be offered at a subgroup level. Selecting such a subgroup could potentially be based on UHR individuals baseline characteristics indicating cognitive and functional malleability. The expanding digital technologies offer new and interesting ways to deliver cognitive remediation to an UHR population that need further exploration in terms of feasibility and functional and cognitive gains. Furthermore, if replicated, the findings in the dissertation indicate that emotion recognition processing speed, negative symptoms, especially experiential negative symptoms, and basic symptoms constitute important treatment targets in future pro-functional intervention studies in the UHR population. Lastly, when aiming at improving UHR individual's functional prognosis, the established heterogeneity of this population needs to be considered which indicates a need for a precision medicine- and possibly staged intervention approach that allow for adjusting the intervention elements and duration according to the individual's response and varying needs.

8. Danish summary (Dansk resumé)

Psykosens Ultra-Høj Risiko (UHR) paradigme er et klinisk syndrom, der er forbundet med betydelige og vedvarende nedsættelser af UHR-personers funktionsniveau. I denne afhandling argumenteres der for, at det funktionelle outcome udgør et selvstændigt, og ligeså vigtigt, outcome som udvikling af psykose i UHR forskningsstudier. Grundet den begrænsede evidens, der eksisterer omkring prædiktorer for, og behandling af, funktionsnedsættelser i UHR-tilstande, undersøgte nærværende afhandling, hvordan man kan optimere undersøgelse, prædiktion og forebyggelse af funktionsnedsættelse hos UHR-personer. I forhold til undersøgelse af funktionsnedsættelser fremhæves det i denne afhandling, at der er rationale for at inkludere multiple instrumenter til at afdække funktionsnedsættelser med det formål at indfange kompleksiteten af og de mange facetter, der er forbundet med UHR-personers funktionsniveau. Særligt blev der lagt vægt på vigtigheden og brugbarheden af, at man i UHR-forskningen anvender et mål for *funktionel kapacitet* (dvs. personens kapacitet til at kunne fungere i hverdagslivet) som et supplement til *funktionelle præstationer* (dvs. hvordan man faktisk fungerer i hverdagslivet målt på f.eks. job/uddannelse, parforhold, venskabsrelationer mv.).

I forhold til at prædiktere funktionsnedsættelser i UHR-tilstande, blev der fundet evidens for, at specifikke socialkognitive og kliniske prædiktorer er relateret til det funktionelle outcome. I tværsnitsstudier fandt vi, at emotionsprocesseringshastighed var associeret med et globalt mål for funktionsniveau, og at kognitive basissymptomer var forbundet med rollefunktion, selv-rapporteret social funktion og livskvalitet. I longitudinelle studier, der havde en 12-måneders opfølgning, fandt vi, at "oplevelsesmæssige" negative symptomer (dvs. nedsat motivation og nedsat oplevelse af glæde og nydelse) prædikterede rollefunktion, selv-rapporteret social funktion og livskvalitet. Yderligere fandt vi, at funktionsniveauet ved baseline prædikterede UHR-personernes symptommæssige recovery, hvilket blev defineret som remission fra UHR-tilstanden. Disse fund peger på anvendeligheden af at foretage en omfattende kognitiv og klinisk undersøgelse af UHR-personer ved baseline, da en sådan undersøgelse kan omsættes til en individuel risikoprofil for funktionsnedsættelser. En sådan risikoprofil kan give forskere og klinikere et fingerpeg om, hvad individets risiko er for et dårligt funktionelt outcome. Det kan medvirke til at hjælpe med at tilpasse behovet for monitorering og intervention i forhold til den enkelte UHR-person. Samtidig kan det hjælpe med at fordele de behandlingsmæssige ressourcer til de personer, som er i størst risiko for et dårligt funktionelt outcome. De nuværende, tilgængelige,

behandlinger har haft begrænset effekt i forhold til at bedre UHR-personers funktionsniveau. Da UHR-personer har kognitive vanskeligheder, der kan være en barriere i forhold til at bedre funktionsniveauet, har vi gennemført det til dato største randomiserede, kliniske forsøg (FOCUS-projektet) i en gruppe af UHR-personer. I FOCUS-projektet undersøgte vi effekten af intensiv kognitiv remediering (kognitiv træning), som et supplement til standardbehandling. Effekten af behandlingen blev undersøgt i forhold til funktionsniveau, kognitive vanskeligheder og symptomniveau. Vi fandt ikke, at et omfattende kognitivt remedieringsprogram resulterede i en signifikant forbedring af UHR-personernes funktionsniveau, deres globale kognitive niveau eller deres symptomniveau. I eksplorative analyser fandt vi, at den kognitive remediering resulterede i en forbedring af udvalgte kognitive domæner; emotionsgenkendelsesprocessering, arbejdshukommelse samt eksekutive funktioner. I et hypotese-generende perspektiv peger det i retning af, at et korterevarende kognitivt remedieringsprogram kan medføre en bedring af nogle kognitive funktioner. Vi kunne dog ikke påvise en solid effekt af FOCUS interventionen, hvilket kan skyldes, at deltagerne udviste lav behandlingsadhærens. Det bidrager med vigtig information omkring gennemførligheden af et omfattende kognitivt remedieringsprogram i en gruppe af UHR-personer. Nærmere bestemt peger det på, at et 20-sessioners kognitiv remedieringsprogram, som et supplement til standardbehandlingen, ikke er hensigtsmæssigt at tilbyde UHR-personer. Yderligere er det muligt, at UHR-personer har forskelligt respons på kognitive remedieringsinterventioner, og derfor kan det potentielt være mere hensigtsmæssigt, at man tilbyder kognitiv remediering til UHR subgrupper, fremfor at tilbyde det til hele UHR-populationen. Identifikationen af sådan en subgruppe kunne basere sig på UHR-personernes baseline karakteristika, der kan indikere potentiale for kognitiv og funktionsmæssig ændring.
De hastigt udviklende digitale teknologier indebærer muligheden for at udvikle nye og interessante måder at tilbyde kognitiv remediering på til UHR-personer. Sådanne nye måder bør undersøges nærmere i forhold til deres gennemførlighed og deres effekt på UHR-personernes funktionelle og kognitive udbytte. I denne afhandling fandt vi, at emotionsgenkendelseshastighed, negative symptomer (særligt de aspekter, der vedrører motivation og nydelse) samt basissymptomer influerede på UHR-personernes funktionsnedsættelser. Hvis disse fund repliceres, peger det på, at disse domæner udgør vigtige behandlingsområder i fremtidige interventionsstudier rettet mod UHR-personer. I forsøget på at forbedre UHR-personers

funktionelle prognose, er man nødt til at forholde sig til den betydelige heterogenitet, der er i denne patientgruppe. Det indikerer, at der kan være et behov for at tilbyde en målrettet og muligvis stadieinddelt intervention, der giver mulighed for, at man tilpasser elementerne i interventionen og dens varighed i henhold til det individuelle respons.

References

1 Rössler W, Joachim Salize H, Van Os J, Riecher-Rössler A. Size of burden of schizophrenia and psychotic disorders. *Eur Neuropsychopharmacol* 2005; **15**: 399–409.

2 McGorry PD. Early intervention in psychosis: Obvious, effective, overdue. *J Nerv Ment Dis* 2015; **203**: 310–8.

3 Birchwood M, McGorry P, Jackson H. Early intervention in schizophrenia [editorial]. *Br J Psychiatry* 1997; **170**: 2–5.

4 Phillips LJ, Leicester SB, O'Dwyer LE, *et al.* The PACE Clinic: identification and management of young people at 'ultra' high risk of psychosis. *J Psychiatr Pract* 2002; **8**: 255–69.

5 Yung AR, Yuen HP, McGorry PD, *et al.* Mapping the onset of psychosis: the Comprehensive Assessment of At-Risk Mental States. *Aust N Z J Psychiatry* 2005; **39**: 964–71.

6 Miller TJ, McGlashan TH, Woods SW, *et al.* Symptom assessment in schizophrenic prodromal states. *Psychiatr Q* 1999; **70**: 273–87.

7 Woods SW, Walsh BC, Saksa JR, McGlashan TH. The case for including Attenuated Psychotic Symptoms Syndrome in DSM-5 as a psychosis risk syndrome. *Schizophr Res* 2010; **123**: 199–207.

8 Nelson B, Yung AR. The Phenomenological Critique and Self-disturbance : Implications for Ultra-High Risk ('" Prodrome "') Research. 2008; **34**: 381–92.

9 Klosterkotter J, Hellmich M, Steinmeyer EM, Schultze-Lutter F. Diagnosing schizophrenia in the prodromal phase. *Arch Gen Psychiatry* 2001; **58**: 158–64.

10 Parnas J, Handest P, Jansson L, Saebye D. Anomalous subjective experience among first-admitted schizophrenia spectrum patients: empirical investigation. *Psychopathology* 2005; **38**: 259–67.

11 Fusar-Poli P, Borgwardt S, Bechdolf A, *et al.* The Psychosis High-Risk State. *JAMA Psychiatry* 2013; **70**: 107.

12 Yung AR, Phillips LJ, Yuen HP, *et al.* Psychosis prediction: 12-Month follow up of a high-risk ('prodromal') group. *Schizophr Res* 2003; **60**: 21–32.

13 Miller TJ, Ph D, Mcglashan TH, *et al.* Prospective Diagnosis of the Initial Prodrome for Schizophrenia Based on the Structured Interview for Prodromal Syndromes : Preliminary Evidence of Interrater Reliability and Predictive Validity. 1999; **19**: 863–5.

14 Larsen T. The transition from premorbid period to psychosis: how can it be described? *Acta Psychiatr Scand* 2002; **160**: 10–1.

15 Fusar-Poli P, Bonoldi I, Yung AR, *et al.* Predicting Psychosis. *Arch Gen Psychiatry* 2012; **69**: 220–9.

16 Yung A, Yuen HP, Berger G, *et al.* Declining Transition Rate in Ultra High Risk (Prodromal) Services: Dilution or Reduction of Risk? *Schizophr Bull* 2007; **33**: 673–81.

17 Haroun N, Dunn L, Haroun A, Cadenhead KS. Risk and protection in prodromal schizophrenia: Ethical implications for clinical practice and future research. *Schizophr Bull* 2006; **32**: 166–78.

18 Tsuang MT, Van Os J, Tandon R, *et al.* Attenuated psychosis syndrome in DSM-5. *Schizophr Res* 2013; **150**: 31–5.

19 Thompson A, Marwaha S, Broome MR. At-risk mental state for psychosis: identification and current treatment approaches. *BJPscyh Adv* 2016; **22**: 186–93.

20 Yang LH, Link BG, Ben-David S, *et al.* Stigma related to labels and symptoms in individuals at

clinical high-risk for psychosis. *Schizophr Res* 2015; **168**: 9–15.
21 Corcoran C, Malaspina D, Hercher L. Prodromal interventions for schizophrenia vulnerability: The risks of being 'at risk'. *Schizophr Res* 2005; **73**: 173–84.
22 Malhi GS, Bell E, Hamilton A, Morris G. Early intervention for risk syndromes: What are the real risks? *Schizophr Res* 2020. DOI:10.1016/j.schres.2020.04.006.
23 Ajnakina O, David AS, Murray RM. 'At risk mental state' clinics for psychosis - An idea whose time has come - And gone! *Psychol Med* 2019; **49**: 529–34.
24 Ajnakina O, Morgan C, Gayer-Anderson C, *et al.* Only a small proportion of patients with first episode psychosis come via prodromal services: A retrospective survey of a large UK mental health programme. *BMC Psychiatry* 2017; **17**: 1–9.
25 Os J Van, Guloksuz S. A critique of the 'ultra-high risk' and 'transition' paradigm. *World Psychiatry* 2017; **16**: 200–6.
26 Guloksuz S, Van Os J. Need for evidence-based early intervention programmes: A public health perspective. *Evid Based Ment Health* 2018; **21**: 128–30.
27 Woods SW, Bearden CE, Sabb FW, *et al.* Counterpoint. Early intervention for psychosis risk syndromes: Minimizing risk and maximizing benefit. *Schizophr Res* 2020. DOI:10.1016/j.schres.2020.04.020.
28 Nieman DH, McGorry PD. Detection and treatment of at-risk mental state for developing a first psychosis: Making up the balance. *The Lancet Psychiatry* 2015; **2**: 825–34.
29 Addington J, Stowkowy J, Liu L, *et al.* Clinical and functional characteristics of youth at clinical high-risk for psychosis who do not transition to psychosis. *Psychol Med* 2018. DOI:10.1017/S0033291718002258.
30 Addington J, Cornblatt BA, Cadenhead KS, *et al.* At clinical high risk for psychosis: outcome for nonconverters. *Am J Psychiatry* 2011; **168**: 800–5.
31 Harvey PD, Velligan DI, Bellack AS. Performance-based measures of functional skills: Usefulness in clinical treatment studies. *Schizophr Bull* 2007; **33**: 1138–48.
32 Lin A, Wood SJ, Nelson B, Beavan A, McGorry P, Yung AR. Outcomes of nontransitioned cases in a sample at ultra-high risk for psychosis. *Am J Psychiatry* 2015; **172**: 249–58.
33 Lim J, Rekhi G, Rapisarda A, *et al.* Impact of psychiatric comorbidity in individuals at Ultra High Risk of psychosis — Findings from the Longitudinal Youth at Risk Study (LYRIKS). *Schizophr Res* 2015; **164**: 8–14.
34 Addington J, Penn D, Woods SW, Addington D, Perkins DO. Social functioning in individuals at clinical high risk for psychosis. *Schizophr Res* 2008; **99**: 119–24.
35 De Wit S, Schothorst PF, Oranje B, Ziermans TB, Durston S, Kahn RS. Adolescents at ultra-high risk for psychosis: Long-term outcome of individuals who recover from their at-risk state. *Eur Neuropsychopharmacol* 2014; **24**: 865–73.
36 Beck K, Andreou C, Studerus E, *et al.* Clinical and functional long-term outcome of patients at clinical high risk (CHR) for psychosis without transition to psychosis: A systematic review. *Schizophr Res* 2019; **210**: 39–47.
37 Carrión RE, Auther AM, McLaughlin D, *et al.* The Global Functioning: Social and Role Scales-Further Validation in a Large Sample of Adolescents and Young Adults at Clinical High Risk for Psychosis. *Schizophr Bull* 2019; **45**: 763–72.
38 Cotter J, Lin A, Drake RJ, *et al.* Long-term employment among people at ultra-high risk for psychosis. *Schizophr Res* 2017; **184**: 26–31.
39 Fusar-Poli P, Rocchetti M, Sardella A, *et al.* Disorder, not just state of risk: meta-analysis of

functioning and quality of life in people at high risk of psychosis. *Br J Psychiatry* 2015; **207**: 198–206.
40 Sundhedsstyrelsen. Sundhedsstyrelsen SIfF.[Sygdomsbyrden i Danmark], Burden of Disease in Denmark. Copenhagen, 2015.
41 Schmidt SJ, Hurlemann R, Schultz J, *et al.* Multimodal prevention of first psychotic episode through N-acetyl- <scp>l</scp> -cysteine and integrated preventive psychological intervention in individuals clinically at high risk for psychosis: Protocol of a randomized, placebo-controlled, parallel-gro. *Early Interv Psychiatry* 2019; : 1–12.
42 Cornblatt BA, Auther AM, Niendam T, *et al.* Preliminary Findings for Two New Measures of Social and Role Functioning in the Prodromal Phase of Schizophrenia. *Schizophr Bull* 2007; **33**: 688–702.
43 Mason O, Startup M, Halpin S, Schall U, Conrad A, Carr V. State and trait predictors of transition to first episode psychosis among individuals with at risk mental states. *Schizophr Res* 2004; **71**: 227–37.
44 Velthorst E, Nieman DH, Linszen D, *et al.* Disability in people clinically at high risk of psychosis. *Br J Psychiatry* 2010; **197**: 278–84.
45 Glenthøj LB, Fagerlund B, Randers L, *et al.* The FOCUS trial: cognitive remediation plus standard treatment versus standard treatment for patients at ultra-high risk for psychosis: study protocol for a randomised controlled trial. *Trials* 2015; **16**: 25.
46 Fusar-Poli P, Schultze-Lutter F, Cappucciati M, *et al.* The Dark Side of the Moon: Meta-analytical Impact of Recruitment Strategies on Risk Enrichment in the Clinical High Risk State for Psychosis. *Schizophr Bull* 2015; **42**: sbv162-.
47 Morrison AP, French P, Stewart SLK, *et al.* Early detection and intervention evaluation for people at risk of psychosis: multisite randomised controlled trial. *Br Med J* 2012; **344**: e2233–e2233.
48 Hilsenroth MJ, Ackerman SJ, Blagys MD, *et al.* Reliability and validity of DSM-IV Axis V. *Am J Psychiatry* 2000; **157**: 1858–63.
49 Nasrallah H, Morosini P, Gagnon DD. Reliability, validity and ability to detect change of the Personal and Social Performance scale in patients with stable schizophrenia. *Psychiatry Res* 2008; **161**: 213–24.
50 Richardson J, Iezzi A, Khan M a, Maxwell A. Validity and reliability of the Assessment of Quality of Life (AQoL)-8D multi-attribute utility instrument. *Patient* 2014; **7**: 85–96.
51 Markulev C, Mcgorry PD, Nelson B, *et al.* NEURAPRO-E study protocol: A multicentre randomized controlled trial of omega-3 fatty acids and cognitive-behavioural case management for patients at ultra high risk of schizophrenia and other psychotic disorders. *Early Interv Psychiatry* 2015. DOI:10.1111/eip.12260.
52 Constantino J. Social Responsiveness Scale Adult research version (SRS-A). Danish Version HOGREFE Psykologisk Forlag A/S, Virum, Denmark, 2014.
53 Constantino JN, Davis SA, Todd RD, *et al.* Validation of a brief quantitative measure of autistic traits: comparison of the social responsiveness scale with the autism diagnostic interview-revised. *J Autism Dev Disord* 2003; **33**: 427–33.
54 Joshi G, Wozniak J, Faraone S V, *et al.* A Prospective Open-Label Trial of Memantine Hydrochloride for the Treatment of Social Deficits in Intellectually Capable Adults With Autism Spectrum Disorder. *J Clin Psychopharmacol* 2016; **36**. DOI:10.1097/JCP.0000000000000499.

55 Bölte S, Poustka F, Constantino JN. Assessing autistic traits: cross-cultural validation of the social responsiveness scale (SRS). *Autism Res* 2008; **1**: 354–63.
56 Gibson CM, Penn DL, Prinstein MJ, Perkins DO, Belger A. Social skill and social cognition in adolescents at genetic risk for psychosis. *Schizophr Res* 2010; **122**: 179–84.
57 Andreasen NC. Scale for the assessment of negative symptoms. Iowa City, Iowa: Dept. of Psychiatry, College of Medicine, the University of Iowa, 1984.
58 Arndt S. A Longitudinal Study of Symptom Dimensions in Schizophrenia. *Arch Gen Psychiatry* 1995; **52**: 352.
59 Montgomery S a., Asberg M. A new depression scale designed to be sensitive to change. *Br J Psychiatry* 1979; **134**: 382–9.
60 Ventura J, Nuechterlein KH, Subotnik KL, Gutkind D, Gilbert E a. Symptom dimensions in recent-onset schizophrenia and mania: A principal components analysis of the 24-item Brief Psychiatric Rating Scale. *Psychiatry Res* 2000; **97**: 129–35.
61 Schultze-Lutter F, Ruhrmann S, Fusar-Poli P, Bechdolf A, G. Schimmelmann B, Klosterkotter J. Basic Symptoms and the Prediction of First-Episode Psychosis. *Curr Pharm Des* 2012; **18**: 351–7.
62 McGorry PD, Nelson B, Markulev C, *et al.* Effect of ω-3 Polyunsaturated Fatty Acids in Young People at Ultrahigh Risk for Psychotic Disorders. *JAMA Psychiatry* 2017; **74**: 19.
63 Pinkham AE, Penn DL, Green MF, Buck B, Healey K, Harvey PD. The social cognition psychometric evaluation study: results of the expert survey and RAND panel. *Schizophr Bull* 2014; **40**: 813–23.
64 McDonald S, Flanagan S, Rollins J, Kinch J. TASIT: A new clinical tool for assessing social perception after traumatic brain injury. *J Head Trauma Rehabil* 2003; **18**: 219–38.
65 Roberts, D. L., Fiszdon, J., & Tek C. Initial validity of the Social Cognition Screening Questionnaire (SCSQ). *Schizophr Bull* 2011; **37**, **supp1,**.
66 Sahakian BJ, Owen a M. Computerized assessment in neuropsychiatry using CANTAB: discussion paper. *R Soc Med* 1992; **85**: 399–402.
67 McDonald S, Bornhofen C, Shum D, Long E, Saunders C, Neulinger K. Reliability and validity of The Awareness of Social Inference Test (TASIT): A clinical test of social perception. *Disabil Rehabil* 2006; **28**: 1529–42.
68 Green MF, Bearden CE, Cannon TD, *et al.* Social cognition in schizophrenia, part 1: Performance across phase of illness. *Schizophr Bull* 2012; **38**: 854–64.
69 Bliksted V, Fagerlund B, Weed E, Frith C, Videbech P. Social cognition and neurocognitive deficits in first-episode schizophrenia. *Schizophr Res* 2014. DOI:10.1016/j.schres.2014.01.010.
70 Bland AR, Roiser JP, Mehta MA, *et al.* EMOTICOM: A neuropsychological test battery to evaluate emotion, motivation, impulsivity, and social cognition. *Front Behav Neurosci* 2016; **10**: 25.
71 Glenthøj L, Fagerlund B, Hjorthøj C, *et al.* Social cognition in patients at ultra-high risk for psychosis: What is the relation to social skills and functioning? *Schizophr Res Cogn* 2016; **5**: 21–7.
72 Kanie A, Hagiya K, Ashida S, *et al.* A new instrument for measuring multiple domains of social cognition: Construct validity of the Social Cognition Screening Questionnaire (Japanese version). *Psychiatry Clin Neurosci* 2014; : 1–11.
73 Keefe RSE, Goldberg TE, Harvey PD, Gold JM, Poe MP, Coughenour L. The Brief Assessment

of Cognition in Schizophrenia: Reliability, sensitivity, and comparison with a standard neurocognitive battery. *Schizophr Res* 2004; **68**: 283–97.
74 Levaux M-N, Potvin S, Sepehry AA, Sablier J, Mendrek A, Stip E. Computerized assessment of cognition in schizophrenia: promises and pitfalls of CANTAB. *Eur Psychiatry* 2007; **22**: 104–15.
75 Lowe C, Rabbitt P. Test/re-test reliability of the CANTAB and ISPOCD neuropsychological batteries: Theoretical and practical issues. *Neuropsychologia* 1998; **36**: 915–23.
76 Wechsler D. WAIS-III administration and scoring manual. San Antonio TX: The Psychological Corporation, 1997.
77 Axelrod BN. Validity of the Wechsler abbreviated scale of intelligence and other very short forms of estimating intellectual functioning. *Assessment* 2002; **9**: 17–23.
78 R Core Team. R: A Language and Environment for Statistical Computing. Vienna, Austria: R Foundation for Statistical Computing; 2018. R Foundation for Statistical Computing. R Found. Stat. Comput. Vienna, Austria. 2018. DOI:ISBN 3-900051-07-0.
79 Gould F, McGuire LS, Durand D, *et al.* Self-Assessment in Schizophrenia: Accuracy of Evaluation of Cognition and Everyday Functioning. *Neuropsychology* 2015; **29**: No Pagination Specified.
80 Rosenheck R, Leslie D, Keefe R, *et al.* Barriers to employment for people with schizophrenia. *Am J Psychiatry* 2006; **163**: 411–7.
81 Keefe RSE, Davis VG, Atkins AS, *et al.* Validation of a Computerized test of Functional Capacity. *Schizophr Res* 2016; **175**: 90–6.
82 Bowie CR, Reichenberg A, Patterson TL, Heaton RK, Harvey PD. Determinants of real-world functional performance in schizophrenia subjects: Correlations with cognition, functional capacity, and symptoms. *Am J Psychiatry* 2006; **163**: 418–25.
83 Strassnig MT, Raykov T, O'Gorman C, *et al.* Determinants of different aspects of everyday outcome in schizophrenia: The roles of negative symptoms, cognition, and functional capacity. *Schizophr Res* 2015; **165**: 76–82.
84 Glenthøj L, Jepsen JRM, Hjorthøj C, *et al.* Negative symptoms mediate the relationship between neurocognition and function in individuals at ultrahigh risk for psychosis. *Acta Psychiatr Scand* 2016; **135**: 1–9.
85 Pinkham AE, Penn DL, Perkins DO, Graham KA, Siegel M. Emotion perception and social skill over the course of psychosis: A comparison of individuals 'at-risk' for psychosis and individuals with early and chronic schizophrenia spectrum illness. *Cogn Neuropsychiatry* 2007; **12**: 198–212.
86 Pinkham AE, Penn DL. Neurocognitive and social cognitive predictors of interpersonal skill in schizophrenia. - PubMed - NCBI. Psychiatry Res. 2006; **143**: 167–78.
87 Glenthøj LB, Kristensen TD, Gibson CM, Jepsen JRM, Nordentoft M. Assessing social skills in individuals at ultra-high risk for psychosis: Validation of the High Risk Social Challenge task (HiSoC). *Schizophr Res* 2019; **215**: 365–70.
88 Mclaughlin D, Carrión RE, Auther AM, *et al.* Functional Capacity Assessed by the Map Task in Individuals at Clinical High-Risk for Psychosis. 2016; : 1–9.
89 Endicott J, Spitzer RL, Fleiss JL, Cohen J. The global assessment scale. A procedure for measuring overall severity of psychiatric disturbance. *Arch Gen Psychiatry* 1976; **33**: 766–71.
90 Greenberg GA, Rosenheck RA. Using the GAF as a national mental health outcome measure in the Department of Veterans Affairs. *Psychiatr Serv* 2005; **56**: 420–6.

91 Roy-Byrne P, Dagadakis C, Unutzer J, Ries R. Evidence for limited validity of the revised global assessment of functioning scale. *Psychiatr Serv* 1996; **47**: 864–6.
92 Crow TJ. Molecular pathology of schizophrenia: more than one disease process? *Br Med J* 1980; **280**: 66–8.
93 Andreasen NC. Positive vs. negative schizophrenia: a critical evaluation. *Schizophr Bull* 1985; **11**: 380–9.
94 Cotter J, Drake RJ, Bucci S, Firth J, Edge D, Yung AR. What drives poor functioning in the at-risk mental state? A systematic review. *Schizophr Res* 2014; **159**: 267–77.
95 Niendam TA, Bearden CE, Johnson JK, *et al.* Neurocognitive performance and functional disability in the psychosis prodrome. *Schizophr Res* 2006; **84**: 100–11.
96 Corcoran CM, Kimhy D, Parrilla-Escobar MA, *et al.* The relationship of social function to depressive and negative symptoms in individuals at clinical high risk for psychosis. *Psychol Med* 2011; **41**: 251–61.
97 Barbato M, Liu L, Penn DL, *et al.* Social cognition as a mediator between neurocognition and functional outcome in individuals at clinical high risk for psychosis. *Schizophr Res* 2013; **150**: 542–6.
98 Ali E, Jahshan C, Cadenhead KS. Disorganized Symptoms and Executive Functioning Predict Impaired Social Functioning in Subjects at Risk for Psychosis. *J Neuropsychiatry Clin Neurosci* 2011; **23**: 457–60.
99 Meyer EC, Carrión RE, Cornblatt B a., *et al.* The relationship of neurocognition and negative symptoms to social and role functioning over time in individuals at clinical high risk in the first phase of the North American Prodrome Longitudinal Study. *Schizophr Bull* 2014; **40**: 1452–61.
100 Schlosser DA, Campellone TR, Biagianti B, *et al.* Modeling the role of negative symptoms in determining social functioning in individuals at clinical high risk of psychosis. *Schizophr Res* 2015; **169**: 204–8.
101 Demjaha A, Valmaggia L, Stahl D, Byrne M, McGuire P. Disorganization/Cognitive and Negative Symptom Dimensions in the At-Risk Mental State Predict Subsequent Transition to Psychosis. *Schizophr Bull* 2012; **38**: 351–9.
102 Fulford D, Niendam TA, Floyd EG, *et al.* Symptom dimensions and functional impairment in early psychosis: more to the story than just negative symptoms. *Schizophr Res* 2013; **147**: 125–31.
103 Bartholomeusz CF, Allott K. Neurocognitive and social cognitive approaches for improving functional outcome in early psychosis: theoretical considerations and current state of evidence. *Schizophr Res Treatment* 2012; **2012**: 815315.
104 Lin A, Wood SJ, Nelson B, *et al.* Neurocognitive predictors of functional outcome two to 13years after identification as ultra-high risk for psychosis. *Schizophr Res* 2011; **132**: 1–7.
105 Goghari VM, Brett C, Tabraham P, *et al.* Spatial working memory ability in individuals at ultra high risk for psychosis. *J Psychiatr Res* 2014; **50**: 100–5.
106 Carrión RE, Goldberg TE, McLaughlin D, Auther AM, Correll CU, Cornblatt BA. Impact of neurocognition on social and role functioning in individuals at clinical high risk for psychosis. *Am J Psychiatry* 2011; **168**: 806–13.
107 Carrión RE, McLaughlin D, Goldberg TE, *et al.* Prediction of functional outcome in individuals at clinical high risk for psychosis. *JAMA psychiatry* 2013; **70**: 1133.
108 Cotter J, Bartholomeusz C, Papas A, *et al.* Examining the association between social

cognition and functioning in individuals at ultra-high risk for psychosis. *Aust New Zeal J Psychiatry* 2015. DOI:10.1177/0004867415622691.
109 Stanford AD, Messinger J, Malaspina D, Corcoran CM. Theory of Mind in patients at clinical high risk for psychosis. *Schizophr Res* 2011; **131**: 11–7.
110 Chudleigh C, Naismith SL, Blaszczynski A, Hermens DF, Hodge MAR, Hickie IB. How does social functioning in the early stages of psychosis relate to depression and social anxiety? *Early Interv Psychiatry* 2011; **5**: 224–32.
111 Shim GS, Kang DH, Choi JS, *et al.* Prospective outcome of early intervention for individuals at ultra-high-risk for psychosis. *Early Interv Psychiatry* 2008; **2**: 277–84.
112 Hur J, Shin N, Jang J, *et al.* Clinical and neurocognitive profiles of subjects at high risk for psychosis with and without obsessive-compulsive symptoms. *Aust N Z J Psychiatry* 2012; **46**: 161–9.
113 Niendam TA, Berzak J, Cannon TD, Bearden CE. Obsessive compulsive symptoms in the psychosis prodrome: Correlates of clinical and functional outcome. *Schizophr Res* 2009; **108**: 170–5.
114 Kim KR, Song YY, Park JY, *et al.* The relationship between psychosocial functioning and resilience and negative symptoms in individuals at ultra-high risk for psychosis. *Aust N Z J Psychiatry* 2013; **47**: 762–71.
115 Harvey PD, Green MF, Keefe RSE, Velligan DI. Cognitive functioning in schizophrenia: a consensus statement on its role in the definition and evaluation of effective treatments for the illness. *J Clin Psychiatry* 2004; **65**: 361–72.
116 Fusar-Poli P, Papanastasiou E, Stahl D, *et al.* Treatments of Negative Symptoms in Schizophrenia: Meta-Analysis of 168 Randomized Placebo-Controlled Trials. *Schizophr Bull* 2015; **41**: 892–9.
117 Green MF. What are the functional consequences of neurocognitive deficits in schizophrenia? *Am J Psychiatry* 1996; **153**: 321–30.
118 Green MF, Kern RS, Braff DL, Mintz J. Neurocognitive deficits and functional outcome in schizophrenia: are we measuring the 'right stuff'? *Schizophr Bull* 2000; **26**: 119–36.
119 Addington J, Addington D. Neurocognitive and social functioning in schizophrenia: a 2.5 year follow-up study. *Schizophr Res* 2000; **44**: 47–56.
120 Ventura J, Subotnik KL, Gitlin MJ, *et al.* Negative symptoms and functioning during the first year after a recent onset of schizophrenia and 8 years later. *Schizophr Res* 2015; **161**: 407–13.
121 Fett A-KJKJ, Viechtbauer W, Dominguez M-G de G, Penn DL, van Os J, Krabbendam L. The relationship between neurocognition and social cognition with functional outcomes in schizophrenia: a meta-analysis. *Neurosci Biobehav Rev* 2011; **35**: 573–88.
122 Green MF, Penn DL, Bentall R, *et al.* Social Cognition in Schizophrenia: An NIMH Workshop on Definitions, Assessment, and Research Opportunities. *Schizophr Bull* 2008; **34**: 1211–20.
123 Pinkham AE, Harvey PD, Penn DL. Social Cognition Psychometric Evaluation: Results of the Final Validation Study. *Schizophr Bull* 2018; **44**: 737–48.
124 Bryson G, Bell M, Lysaker P. Affect recognition in schizophrenia: A function of global impairment or a specific cognitive deficit. *Psychiatry Res* 1997; **71**: 105–13.
125 Corcoran R, Mercer G, Frith CD. Schizophrenia, symptomatology and social inference: investigating 'theory of mind' in people with schizophrenia. *Schizophr Res* 1995; **17**: 5–13.
126 Gur RC, Sara R, Hagendoorn M, *et al.* A method for obtaining 3-dimensional facial

expressions and its standardization for use in neurocognitive studies. *J Neurosci Methods* 2002; **115**: 137–43.
127 Ludwig KA, Pinkham AE, Harvey PD, Kelsven S, Penn DL. Social cognition psychometric evaluation (SCOPE) in people with early psychosis: A preliminary study. *Schizophr Res* 2017; **190**: 136–43.
128 van Donkersgoed RJM, Wunderink L, Nieboer R, Aleman A, Pijnenborg GHM. Social Cognition in Individuals at Ultra-High Risk for Psychosis: A Meta-Analysis. *PLoS One* 2015; **10**: e0141075.
129 Lee TY, Hong S Bin, Shin NY, Kwon JS. Social cognitive functioning in prodromal psychosis: A meta-analysis. *Schizophr Res* 2015; **164**: 28–34.
130 Kim HS, Shin NY, Jang JH, *et al.* Social cognition and neurocognition as predictors of conversion to psychosis in individuals at ultra-high risk. *Schizophr Res* 2011; **130**: 170–5.
131 Corcoran CM, Keilp JG, Kayser J, *et al.* Emotion recognition deficits as predictors of transition in individuals at clinical high risk for schizophrenia: a neurodevelopmental perspective. *Psychol Med* 2015; **45**: 2959–73.
132 Amminger GP, Allott K, Schlögelhofer M, *et al.* Affect recognition and functioning in putatively prodromal individuals. *Schizophr Res* 2013; **147**: 404–5.
133 Nuechterlein KH, Barch DM, Gold JM, Goldberg TE, Green MF, Heaton RK. Identification of separable cognitive factors in schizophrenia. *Schizophr Res* 2004; **72**: 29–39.
134 Nuechterlein KH, Green MF, Kern RS, *et al.* The MATRICS consensus cognitive battery, part 1: Test selection, reliability, and validity. *Am J Psychiatry* 2008; **165**: 203–13.
135 Zheng W, Zhang QE, Cai D Bin, *et al.* Neurocognitive dysfunction in subjects at clinical high risk for psychosis: A meta-analysis. *J Psychiatr Res* 2018; **103**: 38–45.
136 Fusar-Poli P, Deste G, Smieskova R, *et al.* Cognitive Functioning in Prodromal Psychosis. *Arch Gen Psychiatry* 2012; **69**: 562–71.
137 Giuliano AJ, Li H, Mesholam-Gately RI, Sorenson SM, Woodberry KA, Seidman LJ. Neurocognition in the psychosis risk syndrome: a quantitative and qualitative review. *Curr Pharm Des* 2012; **18**: 399–415.
138 Hauser M, Zhang J-P, Sheridan EM, *et al.* Neuropsychological Test Performance to Enhance Identification of Subjects at Clinical High Risk for Psychosis and to Be Most Promising for Predictive Algorithms for Conversion to Psychosis: A Meta-Analysis. *J Clin Psychiatry* 2017; **78**: e28–40.
139 Bolt LK, Amminger GP, Farhall J, *et al.* Neurocognition as a predictor of transition to psychotic disorder and functional outcomes in ultra-high risk participants: Findings from the NEURAPRO randomized clinical trial. *Schizophr Res* 2018; published online Dec 14. DOI:10.1016/j.schres.2018.12.013.
140 Carrión RE, Ph D, Cornblatt BA, *et al.* Prediction of Psychosis: External validation of the NAPLS2 Psychosis Risk Calculator with the EDIPPP project. *Am J Psychiatry* 2016; **173**: 989–96.
141 Niendam TA, Bearden CE, Zinberg J, Johnson JK, O'Brien M, Cannon TD. The course of neurocognition and social functioning in individuals at ultra high risk for psychosis. *Schizophr Bull* 2007; **33**: 772–81.
142 Young S, Bang M, Ran K, *et al.* Impaired facial emotion recognition in individuals at ultra-high risk for psychosis and with fi rst-episode schizophrenia , and their associations with neurocognitive de fi cits and self-reported schizotypy. *Schizophr Res* 2015; **165**: 60–5.

143 Allott K, Rice S, Bartholomeusz CF, *et al.* Emotion recognition in unaffected first-degree relatives of individuals with first-episode schizophrenia. *Schizophr Res* 2015; **161**: 322–8.
144 Comparelli A, Corigliano V, De Carolis A, *et al.* Emotion recognition impairment is present early and is stable throughout the course of schizophrenia. *Schizophr Res* 2013; **143**: 65–9.
145 Thompson AD, Bartholomeusz C, Yung AR. Social cognition deficits and the 'ultra high risk' for psychosis population: A review of literature. *Early Interv Psychiatry* 2011; **5**: 192–202.
146 Allott K, Schäfer MR, Thompson A, *et al.* Emotion recognition as a predictor of transition to a psychotic disorder in ultra-high risk participants. *Schizophr Res* 2014; **153**: 25–31.
147 Ventura J, Wood RC, Jimenez AM, Hellemann GS. Neurocognition and symptoms identify links between facial recognition and emotion processing in schizophrenia: meta-analytic findings. *Schizophr Res* 2013; **151**: 78–84.
148 Glenthøj LB, Fagerlund B, Bak N, *et al.* Examining speed of processing of facial emotion recognition in individuals at ultra-high risk for psychosis: Associations with symptoms and cognition. *Schizophr Res* 2017; published online Oct 25. DOI:10.1016/j.schres.2017.10.032.
149 Glenthøj LB, Albert N, Fagerlund B, *et al.* Emotion recognition latency, but not accuracy, relates to real life functioning in individuals at ultra-high risk for psychosis. *Schizophr Res* 2019; **210**: 197–202.
150 Kern RS, Green MF, Nuechterlein KH, Deng BH. NIMH-MATRICS survey on assessment of neurocognition in schizophrenia. *Schizophr Res* 2004; **72**: 11–9.
151 Klosterkötter J, Schultze-Lutter F, Gross G, Huber G, Steinmeyer EM. Early self-experienced neuropsychological deficits and subsequent schizophrenic diseases: an 8-year average follow-up prospective study. *Acta Psychiatr Scand* 1997; **95**: 396–404.
152 Schultze-Lutter F, Michel C, Schmidt SJJ, *et al.* EPA guidance on the early detection of clinical high risk states of psychoses. *Eur Psychiatry* 2015; **30**: 405–16.
153 Ruhrmann S, Schultze-Lutter F, Salokangas RKR, *et al.* Prediction of psychosis in adolescents and young adults at high risk: results from the prospective European prediction of psychosis study. *Arch Gen Psychiatry* 2010; **67**: 241–51.
154 Schultze-Lutter F, Klosterkötter J, Ruhrmann S. Improving the clinical prediction of psychosis by combining ultra-high risk criteria and cognitive basic symptoms. *Schizophr Res* 2014; **154**: 100–6.
155 Youn S, Phillips LJ, Amminger GP, *et al.* Basic symptoms in young people at ultra-high risk of psychosis: Association with clinical characteristics and outcomes. *Schizophr Res* 2019. DOI:10.1016/j.schres.2019.11.047.
156 Glenthøj LB, Bailey B, Kristensen TD, Wenneberg C, Hjorthøj C, Nordentoft M. Basic symptoms influence real-life functioning and symptoms in individuals at high risk for psychosis. *Acta Psychiatr Scand* 2019; published online Oct 16. DOI:10.1111/acps.13117.
157 Schultze-Lutter, F., Klosterkötter, J., Picker, H., Steinmeyer, E.-M., & Ruhrmann S. Predicting first-episode psychosis by basic symptom criteria. *J Treat Eval* 2007; **4**: 11–22.
158 Piskulic D, Addington J, Cadenhead KS, *et al.* Negative symptoms in individuals at clinical high risk of psychosis. *Psychiatry Res* 2012; **196**: 220–4.
159 Andreasen NC, Arndt S, Alliger R, Miller D, Flaum M. Symptoms of schizophrenia. Methods, meanings, and mechanisms. *Arch Gen Psychiatry* 1995; **52**: 341–51.
160 Devoe DJ, Peterson A, Addington J. Negative Symptom Interventions in Youth at Risk of Psychosis : A Systematic Review and Network Meta-analysis. 2018; : 1–17.
161 Fusar-Poli P, Borgwardt S. Integrating the negative psychotic symptoms in the high risk

criteria for the prediction of psychosis. *Med Hypotheses* 2007; **69**: 959–60.
162 Blanchard JJ, Cohen AS. The structure of negative symptoms within schizophrenia: Implications for assessment. *Schizophr Bull* 2006; **32**: 238–45.
163 Foussias G, Remington G. Negative symptoms in schizophrenia: Avolition and occam's razor. *Schizophr Bull* 2010; **36**: 359–69.
164 Glenthøj LB, Kristensen TD, Wenneberg C, Hjorthøj C, Nordentoft M. Experiential negative symptoms are more predictive of real-life functional outcome than expressive negative symptoms in clinical high-risk states. *Schizophr Res* 2020; **218**: 151–6.
165 Kirkpatrick B, Strauss GP, Nguyen L, *et al.* The brief negative symptom scale: Psychometric properties. *Schizophr Bull* 2011; **37**: 300–5.
166 Kring AM, Gur RE, Blanchard JJ, Horan WP, Reise SP. The Clinical Assessment Interview for Negative Symptoms (CAINS): final development and validation. *Am J Psychiatry* 2013; **170**: 165–72.
167 Blanchard JJ, Kring AM, Horan WP, Gur R. Toward the next generation of negative symptom assessments: The collaboration to advance negative symptom assessment in schizophrenia. *Schizophr Bull* 2011; **37**: 291–9.
168 Marder SR, Galderisi S. The current conceptualization of negative symptoms in schizophrenia. *World Psychiatry* 2017; **16**: 14–24.
169 Kirkpatrick, B, Fenton, WS, Carpenter, WT, Marder S. The NIMH-MATRICS consensus statement on negative symptoms. *Schizophr Bull* 2006; **32**: 214–9.
170 Pelletier-Baldelli A, Strauss GP, Visser KH, Mittal VA. Initial development and preliminary psychometric properties of the Prodromal Inventory of Negative Symptoms (PINS). *Schizophr Res* 2017; **189**: 43–9.
171 Strauss GP, Chapman HC. Preliminary psychometric properties of the brief Negative Symptom Scale in youth at Clinical High-Risk for psychosis. *Schizophr Res* 2018; **193**: 435–7.
172 Gur RCRE, March M, Calkins ME, *et al.* Negative symptoms in youths with psychosis spectrum features: Complementary scales in relation to neurocognitive performance and function. *Schizophr Res* 2015; **166**: 322–7.
173 Strauss GP, Pelletier-Baldelli A, Visser KF, Walker EF, Mittal VA. A review of negative symptom assessment strategies in youth at clinical high-risk for psychosis. *Schizophr Res* 2020. DOI:10.1016/j.schres.2020.04.019.
174 Simon AE, Borgwardt S, Riecher-Rössler A, Velthorst E, de Haan L, Fusar-Poli P. Moving beyond transition outcomes: Meta-analysis of remission rates in individuals at high clinical risk for psychosis. *Psychiatry Res* 2013; **209**: 266–72.
175 Armando M, Pontillo M, Crescenzo F De, *et al.* Twelve-month psychosis-predictive value of the ultra-high risk criteria in children and adolescents. *Schizophr Res* 2019; **169**: 186–92.
176 Cropley VL, Lin A, Nelson B, *et al.* Baseline grey matter volume of non-transitioned 'ultra high risk' for psychosis individuals with and without attenuated psychotic symptoms at long-term follow-up. *Schizophr Res* 2016; **173**: 152–8.
177 Schlosser D a., Jacobson S, Chen Q, *et al.* Recovery from an at-risk state: Clinical and functional outcomes of putatively prodromal youth who do not develop psychosis. *Schizophr Bull* 2012; **38**: 1225–33.
178 Ziermans TB, Schothorst PF, Sprong M, van Engeland H. Transition and remission in adolescents at ultra-high risk for psychosis. *Schizophr Res* 2011; **126**: 58–64.
179 Simon AE, Umbricht D. High remission rates from an initial ultra-high risk state for

psychosis. *Schizophr Res* 2010; **116**: 168–72.
180 Armando M, Pontillo M, De Crescenzo F, *et al.* Twelve-month psychosis-predictive value of the ultra-high risk criteria in children and adolescents. *Schizophr Res* 2015; **169**: 186–92.
181 Glenthøj LB, Hjorthøj C, Kristensen TD, Nordentoft M, Wenneberg C. Predictors of remission from the ultra-high risk state for psychosis. *Early Interv Psychiatry* 2020; : 1–9.
182 Mcgurk S., Twamley E., Sitzer D., Mchugo G., Mueser K. Analysis of Cognitive Remediation in Schizophrenia. *Am J Psychiatry* 2007; **164**: 1791–802.
183 Krabbendam L, Aleman A. Cognitive rehabilitation in schizophrenia: A quantitative analysis of controlled studies. *Psychopharmacology (Berl)* 2003; **169**: 376–82.
184 Kurtz MM, Moberg PJ, Gur RC, Gur RE. Approaches to cognitive remediation of neuropsychological deficits in schizophrenia: A review and meta-analysis. *Neuropsychol Rev* 2001; **11**: 197–210.
185 Twamley EW, Jeste D V, Bellack AS. A review of cognitive training in schizophrenia. *Schizophr Bull* 2003; **29**: 359–82.
186 Grynszpan O, Perbal S, Pelissolo a, *et al.* Efficacy and specificity of computer-assisted cognitive remediation in schizophrenia: a meta-analytical study. *Psychol Med* 2011; **41**: 163–73.
187 Pilling S, Bebbington P, Kuipers E, *et al.* Psychological treatments in schizophrenia: II. Meta-analyses of randomized controlled trials of social skills training and cognitive remediation. *Psychol Med* 2002; **32**: 783–91.
188 Wykes T, Huddy V, Cellard C, McGurk SR, Czobor P. A meta-analysis of cognitive remediation for schizophrenia: Methodology and effect sizes. *Am J Psychiatry* 2011; **168**: 472–85.
189 Cella M, Preti A, Edwards C, Dow T, Wykes T. Cognitive remediation for negative symptoms of schizophrenia: A network meta-analysis. *Clin Psychol Rev* 2016; **52**: 43–51.
190 Keshavan MS, Hogarty GE. Brain maturational processes and delayed onset in schizophrenia. *Dev Psychopathol* 1999; **11**: 525–43.
191 Nuechterlein KH, Ventura J, Subotnik KL, Hayata JN, Medalia A, Bell MD. Developing a Cognitive Training Strategy for First-Episode Schizophrenia: Integrating Bottom-Up and Top-Down Approaches. *Am J Psychiatr Rehabil* 2014; **17**: 225–53.
192 Glenthøj LB, Hjorthøj C, Kristensen TD, Davidson CA, Nordentoft M. The effect of cognitive remediation in individuals at ultra-high risk for psychosis: a systematic review. *npj Schizophr* 2017; **3**: 20.
193 Piskulic D, Barbato M, Liu L, Addington J. Pilot study of cognitive remediation therapy on cognition in young people at clinical high risk of psychosis. *Psychiatry Res* 2015; **225**: 93–8.
194 Bechdolf A, Wagner M, Ruhrmann S, *et al.* Preventing progression to first-episode psychosis in early initial prodromal states. *Br J Psychiatry* 2012; **200**: 22–9.
195 Loewy R, Fisher M, Schlosser DA, *et al.* Intensive Auditory Cognitive Training Improves Verbal Memory in Adolescents and Young Adults at Clinical High Risk for Psychosis. *Schizophr Bull* 2016; **42 Suppl 1**: sbw009.
196 Choi J, Corcoran CM, Fiszdon JM, *et al.* Pupillometer-Based Neurofeedback Cognitive Training to Improve Processing Speed and Social Functioning in Individuals at Clinical High Risk for Psychosis. *Psychiatr Rehabil J* 2016; published online Aug. DOI:10.1037/prj0000217.
197 Rauchensteiner S, Kawohl W, Ozgurdal S, *et al.* Test-performance after cognitive training in persons at risk mental state of schizophrenia and patients with schizophrenia. *Psychiatry Res* 2011; **185**: 334–9.

198 Hooker CI, Carol EE, Eisenstein TJ, *et al.* A pilot study of cognitive training in clinical high risk for psychosis: Initial evidence of cognitive benefit. *Schizophr Res* 2014; **157**: 314–6.
199 Piskulic D, Barbato M, Liu L. Effects of cognitive remediation on cognition in young people at clinical high risk of psychosis. Schizophr. Res. 2014; **153**: S218.
200 Farris MS, Devoe DJ, Addington J. Attrition rates in trials for adolescents and young adults at clinical high-risk for psychosis: A systematic review and meta-analysis. *Early Interv Psychiatry* 2019; : eip.12864.
201 Friedman-Yakoobian M, Parrish EM, Thomas A, *et al.* An integrated neurocognitive and social-cognitive treatment for youth at clinical high risk for psychosis: Cognition for Learning and for Understanding Everyday Social Situations (CLUES). *Schizophr Res* 2019; **208**: 55–9.
202 Eack SM, Hogarty GE, Cooley SJ, *et al.* Cognitive Enhancement Therapy for Early Course Schizophrenia: Effects of a Two-Year Randomized Controlled Trial. *Psychiatr Serv* 2009; **60**: 1468–1476.
203 Roder V, Mueller DR, Schmidt SJ. Effectiveness of integrated psychological therapy (IPT) for schizophrenia patients: A research update. *Schizophr Bull* 2011; **37**. DOI:10.1093/schbul/sbr072.
204 Bošnjak D, Kekin I, Hew J, Kuzman MR. Early interventions for prodromal stage of psychosis. *Cochrane Database Syst Rev* 2016; **2019**. DOI:10.1002/14651858.cd012236.
205 Horan WP, Roberts DL. Integrating social cognitive training. In: Medalia A, Bowie CR, eds. Cognitive Remediation to Improve Functional Outcomes. Oxford University Press, 2016: 194–212.
206 Eack SM, Pogue-Geile MF, Greenwald DP, Hogarty SS, Keshavan MS. Mechanisms of functional improvement in a 2-year trial of cognitive enhancement therapy for early schizophrenia. *Psychol Med* 2011; **41**: 1253–61.
207 Medalia A, Freilich B. The Neuropsychological Educational Approach to Cognitive Remediation (NEAR) Model: Practice Principles and Outcome Studies. *Am J Psychiatr Rehabil* 2008; **11**: 123–43.
208 Roberts DL, David P, Combs DR. Social Cognition and Interaction Training (SCIT): Group Psychotherapy for Schizophrenia and Other Psychotic Disorders, Clinician Guide. Oxford University Press, 2015.
209 Medalia A, Revheim N, Casey M. The remediation of problem-solving skills in schizophrenia. *Schizophr Bull* 2001; **27**: 259–67.
210 Medalia A, Revheim N, Casey M. Remediation of problem-solving skills in schizophrenia: Evidence of a persistent effect. *Schizophr Res* 2002; **57**: 165–71.
211 Hodge MAR, Siciliano D, Withey P, *et al.* A randomized controlled trial of cognitive remediation in schizophrenia. *Schizophr Bull* 2010; **36**: 419–27.
212 Ikezawa S, Mogami T, Hayami Y, *et al.* The pilot study of a Neuropsychological Educational Approach to Cognitive Remediation for patients with schizophrenia in Japan. *Psychiatry Res* 2012; **195**: 107–10.
213 Combs DR, Adams SD, Penn DL, Roberts D, Tiegreen J, Stem P. Social Cognition and Interaction Training (SCIT) for inpatients with schizophrenia spectrum disorders: Preliminary findings. *Schizophr Res* 2007; **91**: 112–6.
214 Roberts DL, Combs DR, Willoughby M, *et al.* A randomized, controlled trial of Social Cognition and Interaction Training (SCIT) for outpatients with schizophrenia spectrum disorders. *Br J Clin Psychol* 2014; **53**: 281–98.

215 Wang Y, Roberts DL, Xu B, Cao R, Yan M, Jiang Q. Social cognition and interaction training for patients with stable schizophrenia in Chinese community settings. *Psychiatry Res* 2013; **210**: 751–5.
216 Glenthøj LB, Mariegaard LS, Fagerlund B, *et al.* Effectiveness of cognitive remediation in the ultra-high risk state for psychosis. *World Psychiatry* 2020; **In press**. DOI:10.1002/wps.20760.
217 Twamley EW, Burton CZ, Vella L. Compensatory cognitive training for psychosis: Who benefits? who stays in treatment? *Schizophr Bull* 2011; **37**: 55–62.
218 Vidarsdottir OG, Roberts DL, Twamley EW, Gudmundsdottir B, Sigurdsson E, Magnusdottir BB. Integrative cognitive remediation for early psychosis: Results from a randomized controlled trial. *Psychiatry Res* 2019; **273**: 690–8.
219 Lal S, Dell'Elce J, Tucci N, Fuhrer R, Tamblyn R, Malla A. Preferences of Young Adults With First-Episode Psychosis for Receiving Specialized Mental Health Services Using Technology: A Survey Study. *JMIR Ment Heal* 2015; **2**: e18.
220 Thompson A, Gleeson J, Alvarez-Jimenez M. Should we be using digital technologies in the treatment of psychotic disorders? *Aust N Z J Psychiatry* 2018; **52**: 225–6.
221 Biagianti B, Schlosser D, Nahum M, Woolley J, Vinogradov S. Creating Live Interactions to Mitigate Barriers (CLIMB): A Mobile Intervention to Improve Social Functioning in People With Chronic Psychotic Disorders. *JMIR Ment Heal* 2016; **3**: e52.
222 Alvarez-Jimenez M, Gleeson JF, Bendall S, *et al.* Enhancing social functioning in young people at Ultra High Risk (UHR) for psychosis: A pilot study of a novel strengths and mindfulness-based online social therapy. *Schizophr Res* 2018; **202**: 369–77.
223 Thompson A, Elahi F, Realpe A, *et al.* A Feasibility and Acceptability Trial of Social Cognitive Therapy in Early Psychosis Delivered Through a Virtual World: The VEEP Study. *Front Psychiatry* 2020; **11**: 1–10.
224 Petersen L, Jeppesen P, Thorup A, *et al.* A randomised multicentre trial of integrated versus standard treatment for patients with a first episode of psychotic illness. *BMJ* 2005; **331**: 602.
225 van der Gaag M, Smit F, Bechdolf A, *et al.* Preventing a first episode of psychosis: Meta-analysis of randomized controlled prevention trials of 12month and longer-term follow-ups. *Schizophr Res* 2013; **149**: 56–62.
226 Devoe DJ, Farris MS, Townes P, Addington J. Interventions and social functioning in youth at risk of psychosis: A systematic review and meta-analysis. *Early Interv Psychiatry* 2019; **13**: 169–80.
227 Revell ER, Neill JC, Harte M, Khan Z, Drake RJ. A systematic review and meta-analysis of cognitive remediation in early schizophrenia. *Schizophr Res* 2015; **168**: 213–22.
228 Ruggeri M, Bonetto C, Lasalvia A, *et al.* Feasibility and Effectiveness of a Multi-Element Psychosocial Intervention for First- Episode Psychosis : Results From the Cluster-Randomized Controlled GET UP PIANO Trial in a Catchment Area of 10 Million Inhabitants. 2015; **41**: 1192–203.
229 Kane JM, Robinson DG, Schooler NR, *et al.* Comprehensive Versus Usual Community Care for First-Episode Psychosis : 2-Year Outcomes From the NIMH RAISE Early Treatment Program. 2016. DOI:10.1176/appi.ajp.2015.15050632.
230 Chung W, Wing V, Kwong Y, *et al.* Prediction of functional remission in fi rst-episode psychosis : 12-month follow-up of the randomized-controlled trial on extended early intervention in Hong Kong. *Schizophr Res* 2019; **173**: 79–83.

231 Pantelis C, Wannan CMJ, Bartholomeusz CF, Allott K. Cognitive intervention in early psychosis - preserving abilities versus remediating deficits. Curr. Opin. Behav. Sci. 2015; **4**: 63–72.
232 Velligan DI, Tai S, Roberts DL, *et al.* A randomized controlled trial comparing cognitive behavior therapy, cognitive adaptation training, their combination and treatment as usual in chronic schizophrenia. *Schizophr Bull* 2015; **41**: 597–603.
233 Allott KA, Killackey E, Sun P, Brewer WJ, Velligan DI. Improving vocational outcomes in first-episode psychosis by addressing cognitive impairments using Cognitive Adaptation Training. *Work* 2017; **56**: 581–9.
234 Allott K, Bryce S, Parrish EM, *et al.* OUP accepted manuscript. *Schizophr Bull* 2019; : 1–15.
235 Hansen MC, Jones BD, Eack SM, *et al.* Validation of the MUSIC Model of Motivation Inventory for use with cognitive training for schizophrenia spectrum disorders: A multinational study. *Schizophr Res* 2019; **206**: 142–8.
236 Fiszdon JM, Kurtz MM, Choi J, Bell MD, Martino S. Motivational Interviewing to Increase Cognitive Rehabilitation Adherence in Schizophrenia. *Schizophr Bull* 2015; **42**: 327–34.
237 Fiszdon JM, Kurtz MM, Parente L, Choi J. What variables predict cognitive remediation associated improvement in individuals with psychosis? *Schizophr Res Cogn* 2019; : 100148.
238 Lindenmayer JP, Ozog VA, Khan A, Ljuri I, Fregenti S, McGurk SR. Predictors of response to cognitive remediation in service recipients with severe mental illness. *Psychiatr Rehabil J* 2017; **40**: 61–9.
239 Klingberg S, Herrlich J, Wiedemann G, *et al.* Adverse Effects of Cognitive Behavioral Therapy and Cognitive Remediation in Schizophrenia. *J Nerv Ment Dis* 2012; **200**: 569–76.
240 Yung AR, McGorry PD, Francey SM, *et al.* PACE: a specialised service for young people at risk of psychotic disorders. *Med J Aust* 2007; **187**: 43–6.
241 Fusar-Poli P, Byrne M, Badger S, Valmaggia LR, McGuire PK. Outreach and support in South London (OASIS), 2001-2011: Ten years of early diagnosis and treatment for young individuals at high clinical risk for psychosis. *Eur Psychiatry* 2013; **28**: 315–26.
242 Nelson B, Yuen HP, Wood SJ, *et al.* Long-term Follow-up of a Group at Ultra High Risk ('Prodromal') for Psychosis. *JAMA Psychiatry* 2013; **70**: 793.
243 Hartmann JA, Yuen HP, McGorry PD, *et al.* Declining transition rates to psychotic disorder in 'ultra-high risk' clients: Investigation of a dilution effect. *Schizophr Res* 2016; **170**: 130–6.
244 Yung AR, Phillips LJ, Nelson B, *et al.* Randomized controlled trial of interventions for young people at ultra high risk for psychosis: 6-Month analysis. *J Clin Psychiatry* 2011; **72**: 430–40.
245 Addington J, Cadenhead KS, Cornblatt BA, *et al.* North American Prodrome Longitudinal Study (NAPLS 2): overview and recruitment. *Schizophr Res* 2012; **142**: 77–82.
246 Ising HK, Kraan TC, Rietdijk J, *et al.* Four-Year Follow-up of Cognitive Behavioral Therapy in Persons at Ultra-High Risk for Developing Psychosis: The Dutch Early Detection Intervention Evaluation (EDIE-NL) Trial. *Schizophr Bull* 2016; **42**: 1243–52.
247 Lee J, Rekhi G, Mitter N, *et al.* The Longitudinal Youth at Risk Study (LYRIKS) - An Asian UHR perspective. *Schizophr Res* 2013; **151**: 279–83.
248 Pelizza L, Poletti M, Azzali S, *et al.* Anhedonia in adolescents at ultra-high risk (UHR) of psychosis: findings from a 1-year longitudinal study. *Eur Arch Psychiatry Clin Neurosci* 2019. DOI:10.1007/s00406-019-01018-9.
249 Poulton R, Caspi A, Moffitt TE, Cannon M, Murray R, Harrington H. Children's self-reported psychotic symptoms and adult schizophreniform disorder: a 15-year longitudinal study. *Arch*

Gen Psychiatry 2000; **57**: 1053–8.
250 Schimmelmann BG, Walger P, Schultze-Lutter F. The significance of at-risk symptoms for psychosis in children and adolescents. *Can J Psychiatry* 2013; **58**: 32–40.
251 Albert N, Glenthøj LBL, Melau M, Jensen H, Hjorthøj C, Nordentoft M. Course of illness in a sample of patients diagnosed with a schizotypal disorder and treated in a specialized early intervention setting. Findings from the 3.5year follow-up of the OPUS II study. *Schizophr Res* 2016; **182**. DOI:10.1016/j.schres.2016.10.013.
252 Rothwell PM. Factors That Can Affect the External Validity of Randomised Controlled Trials. *PLOS Hub Clin Trials* 2006; **1**: e9.
253 Clark SR, Baune BT, Schubert KO, *et al.* Prediction of transition from ultra-high risk to first-episode psychosis using a probabilistic model combining history, clinical assessment and fatty-acid biomarkers. *Transl Psychiatry* 2016; **6**: 1–8.
254 Zhang T, Yang S, Xu L, *et al.* Poor functional recovery is better predicted than conversion in studies of outcomes of clinical high risk of psychosis: insight from SHARP. *Psychol Med* 2019; : 1–7.
255 Oorschot M, Kwapil T, Delespaul P, Myin-Germeys I. Momentary Assessment Research in Psychosis. *Psychol Assess* 2009; **21**: 498–505.
256 Leendertse P, Myin-Germeys I, Lataster T, *et al.* Subjective quality of life in psychosis: Evidence for an association with real world functioning? *Psychiatry Res* 2018; **261**: 116–23.
257 Schneider M, Reininghaus U, Van Nierop M, *et al.* Does the Social Functioning Scale reflect real-life social functioning? An experience sampling study in patients with a non-affective psychotic disorder and healthy control individuals. *Psychol Med* 2017; **47**: 2777–86.
258 Santesteban-Echarri O, Tang J, Shakeel MK, Fernandes J, Addington J. A mobile-based app to monitor social functioning among youth at-risk for psychosis: Single-arm feasibility and acceptability study. *Gen Hosp Psychiatry* 2020; **6**: 1–16.
259 Schmidt SJ, Grunert VM, Schimmelmann BG, Schultze-Lutter F, Michel C. Differences in coping, self-efficacy, and external control beliefs between patients at-risk for psychosis and patients with first-episode psychosis. *Psychiatry Res* 2014; **219**: 95–102.
260 Thompson A, Papas A, Bartholomeusz C, Nelson B, Yung A. Externalized attributional bias in the Ultra High Risk (UHR) for psychosis population. *Psychiatry Res* 2013; **206**: 200–5.
261 Jalbrzikowski M, Sugar CA, Zinberg J, Bachman P, Cannon TD, Bearden CE. Coping styles of individuals at clinical high risk for developing psychosis. *Early Interv Psychiatry* 2014; **8**: 68–76.
262 Mcgorry PD. Early Clinical Phenotypes, Clinical Staging, and Strategic Biomarker Research_ Building Blocks for Personalized Psychiatry. *Biol Psychiatry* 2013; **74**: 394–5.
263 Nelson B, Amminger GP, Yuen HP, *et al.* Staged Treatment in Early Psychosis: A sequential multiple assignment randomised trial of interventions for ultra high risk of psychosis patients. *Early Interv Psychiatry* 2018; **12**: 292–306.
264 Dwyer DB, Kalman JL, Budde M, *et al.* An Investigation of Psychosis Subgroups With Prognostic Validation and Exploration of Genetic Underpinnings: The PsyCourse Study. *JAMA psychiatry* 2020; : 1–11.
265 Veling W, Moritz S, Van Der Gaag M. Brave new worlds - Review and update on virtual reality assessment and treatment in psychosis. *Schizophr Bull* 2014; **40**: 1194–7.
266 Bell IH, Nicholas J, Alvarez-Jimenez M, Thompson A, Valmaggia L. Virtual reality as a clinical tool in mental health research and practice. *Dialogues Clin Neurosci* 2020; **22**: 169–77.

267 Rus-Calafell M, Gutiérrez-Maldonado J, Ribas-Sabaté J. A virtual reality-integrated program for improving social skills in patients with schizophrenia: A pilot study. *J Behav Ther Exp Psychiatry* 2014; **45**: 81–9.
268 Park KM, Ku J, Choi SH, *et al.* A virtual reality application in role-plays of social skills training for schizophrenia: A randomized, controlled trial. *Psychiatry Res* 2011; **189**: 166–72.
269 Smith MJ, Fleming MF, Wright MA, *et al.* Virtual reality job interview training and 6-month employment outcomes for individuals with schizophrenia seeking employment. *Schizophr Res* 2015; **166**: 86–91.
270 Rus-Calafell M, Garety P, Sason E, Craig TJK, Valmaggia LR. Virtual reality in the assessment and treatment of psychosis: a systematic review of its utility, acceptability and effectiveness. *Psychol Med* 2018; **48**: 362–91.
271 Fusar-Poli P, Yung AR, McGorry P, Van Os J. Lessons learned from the psychosis high-risk state: Towards a general staging model of prodromal intervention. *Psychol Med* 2014; **44**: 17–24.
272 McGorry PD, Hartmann JA, Spooner R, Nelson B. Beyond the 'at risk mental state' concept: transitioning to transdiagnostic psychiatry. *World Psychiatry* 2018; **17**: 133–42.
273 Hartmann JA, Nelson B, Spooner R, *et al.* Broad clinical high-risk mental state (CHARMS): Methodology of a cohort study validating criteria for pluripotent risk. *Early Interv Psychiatry* 2019; **13**: 379–86.