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# Schizophrenia Research: Cognition

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# Social cognition in patients at ultra-high risk for psychosis: What is the relation to social skills and functioning?



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#### ARTICLE INFO

### Article history: Received 9 May 2016 Received in revised form 22 June 2016 Accepted 27 June 2016 Available online 8 July 2016

Keywords: Clinical high risk psychosis Social cognition Social skills Functioning

#### ABSTRACT

Objective: Patients at ultra-high risk (UHR) for psychosis show significant impairments in functioning. It is essential to determine which factors influence functioning, as it may have implications for intervention strategies. This study examined whether social cognitive abilities and clinical symptoms are associated with functioning and social skills.

*Methods*: The study included 65 UHR patients and 30 healthy controls. Social cognitive function, social skills, and a broad range of functioning measures were assessed.

Results: The UHR patients demonstrated significant decrements on The Awareness of Social Inferences Task total score (p = .046, d = .51), and on the CANTAB emotion recognition task total percent correct (p = .023, d = .54) displaying particular difficulties in negative affect recognition. The patients exhibited significant impairments in social skills measured with the High Risk Social Challenge (p $^{\circ}$ .001, d = 1.05). Aspects of emotion recognition were associated with role functioning and social skill performance. The level of attributional bias was associated with overall functioning, and theory of mind ability was associated with self-reported functioning, Negative symptoms were associated with all measures of functioning (p  $\leq$  .05).

Conclusion: Significant impairments in social cognition and social skills were found in UHR patients. The patients' social cognitive function was associated with overall functioning and social skills. Negative symptoms appear to play an important role for functioning. Research is needed to investigate how the relations between social cognition, social skills and functioning develop from the UHR state to the stage of manifest illness. Research into how deficits in social cognition and social skills can be ameliorated in UHR patients is warranted. © 2016 The Authors. Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

### 1. Introduction

Social cognition involves the cognitive processes of perceiving, interpreting, and processing social information (Green et al., 2008). A growing body of evidence has established that significant impairments in social cognition are present in patients with schizophrenia

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(Bora and Murray, 2014; Savla et al., 2013) and are significant determinants of functional outcome (Buck et al., 2016; Fett et al., 2011). Social cognitive impairments have also been found in patients at ultra-high risk (UHR) for psychosis (Lee et al., 2015; van Donkersgoed et al., 2015), but heterogeneous results are found regarding the domains most impaired; some studies report the largest effect sizes for deficits in attributional bias (Lee et al., 2015), while others find the largest effect sizes for theory of mind (ToM) and emotion recognition deficits (Thompson et al., 2012). Although limited in number, studies indicate that ToM deficits are associated with transition to psychosis (Kim et al., 2011; van Donkersgoed et al., 2015).

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Functioning has become an important area of research as many UHR patients exhibit pervasive impairments in functioning (Addington et al., 2011). There is an ongoing search for significant predictors of functional outcome in UHR. Studies examining the association between social cognition and functioning in UHR patients are scarce and the results inconsistent, with some studies finding positive association between ToM and functioning (Cotter et al., 2015), and affect recognition and functioning (Amminger et al., 2013), while others fail to find an association (Stanford et al., 2011). Numerous studies suggest negative symptoms to be a strong symptom predictor of social and role functioning in schizophrenia (Fulford et al., 2013; Ventura et al., 2009). Among UHR patients, negative symptoms have consistently been associated with impaired social and role functioning (Brandizzi et al., 2015; Fulford et al., 2013; Kim et al., 2011; Meyer et al., 2014) and have been found to be predictive of transition to psychosis (Demjaha et al., 2012; Valmaggia et al., 2013). A previous study has assessed the association between social cognition, clinical symptoms, and functioning in a UHR sample, and found deficits on the ToM visual jokes task to be associated with impairments in global functioning after adjusting for negative symptoms (Cotter et al., 2015). However, due to the study's rather small sample size (n = 30)these findings need to be replicated in a larger sample assessing multiple aspects of functioning as functioning is a multifaceted concept.

Social skills reflect the patients' interpersonal behavior. It can be understood as a mixture of behaviors and perceptual abilities, that includes both verbal, non-verbal, and paralinguistic communication behaviors (Liberman et al., 1986). To our knowledge there are no previous studies of social skill performance in UHR samples.

Evidence is still sparse on the relative contribution of social cognitive deficits and clinical symptoms to the functional deficits and social skills in UHR patients. If strong relationships between social cognition, symptoms and social skills and functioning are found, it could have implications for targeted treatment strategies in the UHR population.

#### 1.1. Hypotheses

We hypothesized that UHR patients would perform significantly worse on measures of social cognition and social skills than matched healthy controls (HCs). Also, we hypothesized that the UHR patients' social cognitive deficits, and their level of negative symptoms, would significantly predict their overall functioning (i.e. composite measures of occupational functioning, social functioning, and self-care), specific measures of social functioning, and their social skills.

# 2. Method

Participants were recruited as part of a randomized clinical trial examining the effect of cognitive remediation in UHR patients (Glenthøj et al., 2015). This report includes baseline data on symptomatology, functioning, social skills, and social cognition. The study was carried out at the Mental Health Centre Copenhagen, Denmark. Patients were recruited from the psychiatric in-and outpatient facilities in the catchment area of Copenhagen, between April 2014 and January 2016. The study protocol was approved by the Committee on Health Research Ethics of the Capital Region Denmark (study: H-6-2013-015).

# 2.1. Participants

The sample consisted of 65 help-seeking patients aged 18–40 years who fulfilled one or more of the UHR criteria as assessed by the Comprehensive Assessment of At-Risk Mental State (CAARMS) (Yung et al., 2005); attenuated psychotic symptom group; brief limited intermittent psychotic symptoms group; and/ or trait and vulnerability group along with a significant drop in functioning or sustained low functioning for the past year.

Exclusion criteria were (1) past history of a psychotic episode of ≥1 week duration; (2) psychiatric symptoms that were explained by a physical illness with psychotropic effect (e.g. delirium) or acute intoxication (e.g. cannabis use); (3) a diagnosis of a serious developmental disorder (e.g., Asperger's syndrome); and (4) currently receiving methylphenidate.

A total of 30 HCs were recruited from the community by advertising on a Web page designed to recruit HC to clinical trials, or via ads at local educational institutions. They did not meet criteria for any DSM-IV disorder and did not have a first degree relative with a psychotic disorder currently or previously. The HCs were matched to patients on gender and age ( $\pm 2$  years). All participants provided informed consent prior to inclusion into the study.

#### 2.2. Assessment

Diagnoses were assessed using the Structured Clinical Interview for DSM-IV Axis I and Axis II disorders (SCID) (First et al., 1997; Ventura et al., 1998). The SCID assessors were all certified in SCID diagnostic interviewing. Other psychopathological assessments were conducted using the Brief Psychiatric Rating Scale (BPRS) (Ventura et al., 2000), and the Scale for the Assessment of Negative Symptoms (SANS) (Andreasen, 1984). The SANS total score was calculated by averaging the global scores excluding the attention global score (Arndt, 1995).

Broad, interview-based ratings served as a measure of overall functioning that consisted of the Social and Occupational Functioning Assessment Scale (Hilsenroth et al., 2000) (SOFAS), Global functioning: Social and Role Scales (Cornblatt et al., 2007), and the Personal and Social Performance Scale (PSP) (Morosini et al., 2000). These measures assess functioning in areas such as occupational functioning, social functioning, and self-care. A self-report measure of overall functioning and quality of life was obtained using the Assessment of Quality of Life (AQoL-8D)(Richardson et al., 2014). The AqoL-8D was scored according to the algorithm (weighted): http://www.aqol.com.au/index.php/ scoring-algorithms. We assessed social skill performance using the High-Risk Social Challenge task (HiSoC), a performance-based behavioral measure that has been validated in patients at genetic high-risk of developing psychosis (Gibson et al., 2010). The laboratory assessment of the patients' social skills can be seen as proximal to their interpersonal behavior in real life. Finally, participants completed the Social Responsiveness Scale, Adult version (SRS-A) (Constantino, 2014; Constantino and Todd, 2005) which is a self-report measure of social impairments validated in autism spectrum disorders, and administered to subjects with non-autistic disorders (Bölte et al., 2008; Constantino et al., 2003; Joshi et al., 2016).

The social cognitive test battery consisted of The Awareness of Social Inference Test (TASIT) (McDonald et al., 2003) that assess ToM abilities by use of video clips of everyday social interactions followed by forced-choice questions, making the participant infer what the characters in the video clips are thinking, doing, feeling, and saying. The outcome used is the overall total correct answers. TASIT has proven efficacy in detecting ToM deficits in UHR patients (Green et al., 2012a; Green et al., 2012b). The Emotion Recognition Task from the Cambridge Neuropsychological Test Automated Battery (CANTAB ERT) (Strauss et al., 2006) was used to assess the recognition of six basic facial emotional expressions; happiness, sadness, anger, disgust, fear, and surprise. The task outcome is percent correct for each emotion and a total percent correct. Finally, the participants completed the Social Cognition Screening Questionnaire (SCSQ) (Roberts et al., 2011) to assess the level of attributional bias. The SCSQ has demonstrated good construct validity (Kanie et al., 2014). The SCSQ total score was computed by summing the three capacity scales and subtracting the metacognitive overconfidence score.

# 2.3. Statistical analysis

Analyses were performed using SPSS version 22.0. Raw data were checked for normality and outliers. ERT sadness, ERT disgust, TASIT, and SCSQ were negatively skewed and logarithmically transformed with log 10 after reflection. SANS was positively skewed and transformed with log 10.

A univariate general linear model was used to compare social cognitive performance in UHR patients with HC. We adjusted for age and gender as covariates.

Multiple regression analyses with forward selection were calculated to predict functional outcome and social skills based on the social cognitive variables and symptom variables. The analyses were performed for each of the five outcome measures and the social skills measure. As independent variables we used the TASIT total score, SCSQ total score, the six emotion recognition subscales, and BPRS total score, and SANS total score (a total of 10). The ERT total percent correct was not included in the multiple regression analyses as it is based on the six individual tasks.

#### 3. Results

The patients and HCs did not differ significantly on sociodemographic variables (Table 1). The patients demonstrated scores of moderate severity on the negative symptoms scale, SANS (mean 1.46, SD .69).

# 3.1. Social cognition and social skills in UHR patients relative to HC

The TASIT total score showed a significant difference between patients and HC (p = .046, Cohen's d = .51). The patients demonstrated significant decrements on a global measure of emotion recognition (ERT total percent correct) (p = .023, Cohen's d = .54), and in the ability to recognize disgust (p = .001, Cohen's d = .77), anger (p = .043, Cohen's d = .47), and fear (p = .035, Cohen's d = .49). No significant between-group difference was found on the SCSQ total score. The UHR patients demonstrated significant decrements on the performance-based measure of social skills (HiSoC) (p  $\leq$  .001) compared to HC (Table 2).

As expected, the patients demonstrated significantly lower functioning on all four measures of overall functioning (SOFAS, PSP, GF:Social, GF:Role), and on the self-reported measure of functioning (AQoL-8D), and in terms of the severity of social impairments (SRS-A) (Table 2).

# 3.2. Regression analyses

Results of the multiple regressions with forward selection are depicted in Table 3.

# 3.2.1. Overall functioning

3.2.1.1. SOFAS. The SANS entered the equation first  $(F(1,59) = 15.463, p^*.001)$  with an  $R^2$  of .208, followed by SCSQ  $(F(2,58) = 11.176, p^*.001)$  with an  $R^2$  of .278. The model indicated that a higher SOFAS is accounted for by a lower SANS and higher SCSQ.

3.2.1.2. PSP. SANS was the only variable entering the equation  $(F(1,59) = 37.982, p^{\circ}.001)$  with an  $R^2$  of .392. The model indicated that a higher PSP is accounted for by a lower SANS.

3.2.1.3. *GF:Social.* SANS was the only variable entering the equation F(1,59) = 27.927, p  $^{\circ}$  .001) with an  $R^2$  of .321. The model indicated that a higher GF:Social is accounted for by a lower SANS.

3.2.1.4. *GF:Role*. The SANS entered the equation first (F(1,59) = 20.160, p $^{\circ}$ .001) with an R $^{2}$  of .225, followed by emotion recognition of disgust (F(2,58) = 16.123, p $^{\circ}$ .001) with an R $^{2}$  of .357. The model indicated that a higher GF:Role is accounted for by a lower SANS and lower ERT disgust recognition.

## 3.2.2. Social skills

3.2.2.1. HiSoC. The emotion recognition of anger (ERT anger) entered the equation first (F(1,39) = 5.460, p = .025) with an R² of .123, followed by emotion recognition of surprise (ERT surprise) (F(2,38) = 5.492, p = .008) with an R² of .224. The model indicated that a higher HiSoC is accounted for by a higher ERT anger recognition and lower ERT surprise recognition.

**Table 1**Group comparison on sociodemographic variables between UHR patients and healthy controls.

Variable	UHR patients ( $N = 65$ )		Healthy controls $(N = 30)$		
	N	%	N	%	
Female	36	55.4	17	56.7	
Male	29	44.6	13	43.3	
Ethnicity					
High income countries	60	92	27	90	
Low income countries	5	8	3	10	
CAARMS prodromal status					
APS	57	87.7	-	-	
BLIPS	0	0	-	-	
Trait/state	1	1.5	-	-	
APS + trait/state	5	7.7	-	-	
APS + BLIPS	2	3.1	=	_	
Medication <sup>a</sup>					
Antipsychotic	32	49	=	_	
Antidepressant	22	34	-	-	
Mood stabilizers	5	8	-	-	
Benzodiazepines	10	15	-	-	
	Mean	SD	Mean	SD	
Age	24.59	4.17	24.20	4.11	
Years of education	15.69	2.66	15.45	2.34	
SANS average of four global scores	1.46	.69	-	-	
BPRS total	40.15	8.34	- -	_ _	

APS: attenuated psychotic symptoms; BLIPS: brief limited intermittent psychotic symptoms; SANS: the Scale for the Assessment of Negative Symptoms; BPRS: the Brief Psychiatric Rating Scale.

<sup>&</sup>lt;sup>a</sup> Patients would be taking one or a combination of the listed compounds.

**Table 2**Group comparison of social cognition, social skills, self-reported social functioning impairments, and symptoms between UHR patients and healthy controls.

Social cognitive task	UHR patients		Healthy controls		p	Cohen's d		
	Mean	SD	N	Mean	SD	N		
TASIT total <sup>a</sup>	53.08	4.53	62	55.13	3.52	30	.046*	.51
CANTAB ERT total percent correct	69.38	6.75	61	72.87	6.24	30	.023*	.54
ERT happy	81.84	9.25	61	82.33	11.45	30	.956	.05
ERT sad <sup>a</sup>	82.60	13.67	61	83.78	10.60	30	.867	.10
ERT angry	57.46	9.40	61	61.44	7.25	30	.043*	.47
ERT disgust <sup>a</sup>	68.70	13.80	61	78.56	11.77	30	.001**	.77
ERT fear	46.07	21.28	61	55.67	18.13	30	.035*	.49
ERT surprise	80.10	7.28	61	77.44	9.13	30	.118	.32
SCSQ total <sup>a</sup>	20.19	1.81	63	20.54	1.43	28	.458	.21
HiSoC total	55.17	5.91	42	62.48	7.89	27	<.001**	1.05
SRS-A total	73.89	27.81	45	26.04	15.95	28	<.001**	2.11
SOFAS	56.25	10.02	65	88.83	4.09	30	<.001**	4.26
PSP	56.42	9.08	64	87.63	5.56	30	<.001**	4.15
GF:Role	5.72	1.13	65	8.75	.54	30	<.001**	3.42
GF:Social	6.39	1.04	65	8.73	.45	30	<.001**	2.92
AQoL-8D	.44	.14	62	.89	.08	30	<.001*	3.95

The table displays the raw scores.

Note: TASIT: The Awareness of Social Inferences Task; SCSQ: the Social Cognition Screening Questionnaire; CANTAB ERT: Cambridge Neuropsychological Test Automated Battery, Emotion Recognition Task; HiSoC: The High Risk Social Challenge; SRS-A: Social Responsiveness Scale Adult Version; SOFAS: Social and Occupational Functioning Assessment Scale; PSP: Personal and Social Performance scale; GF:Role: Global Functioning Role scale; GF:Social: Global Functioning Social scale; AQoL-8D: Assessment of Quality of Life. Comparisons were done using a general linear model adjusted for age and gender. With the exception of the SRS-A higher scores on the tasks indicate better performance or higher level of functioning.

3.2.3. Self-reported measures of social functioning and quality of life

3.2.3.1. AQoL-8D. The SANS entered the equation first (F(1,57) = 7.077, p = .010) with an R² of .110, followed by BPRS (F(2,56) = 5.735, p  $^\circ$ .005) with an R² of .170, and finally ERT sadness (F(3,55) = 5.493, p = .002) with an R² of .231. The model indicated that a higher AQoL-8D is accounted for by a lower SANS, BPRS, and ERT sadness recognition.

3.2.3.2. SRS-A. The TASIT entered the equation first (F(1,42) = 8.185, p = .007) with an  $R^2$  of .143, followed by SANS (F(2,41) = 8.819, p = .001) with an  $R^2$  of .301. The model indicated that a lower score on

the SRS-A (reflecting higher self-reported social functioning) is accounted for by lower SANS and higher TASIT.

#### 4. Discussion

We found support for our hypothesis of significant impairments in social cognition in UHR patients relative to HC. The UHR group scored significantly worse on the ToM measure (TASIT), and the global measure of emotion recognition (ERT total percent correct), but not on the measure of attributional bias (SCSQ). Our findings are compatible with a recent meta-analysis, which also found significant decrements in both ToM and emotion perception in UHR (van Donkersgoed et al., 2015). On the ERT we also found significant

**Table 3**Stepwise forward multiple regression of social cognitive variables and clinical symptoms predicting overall functioning, social skills, and self-report social functioning and quality of life.

Outcome	Predictors	B [min-max]	t	p	$R^2$
SOFAS					.278
	SANS	-5.436 [ $-7.790$ to $-3.083$ ]	-4.625	·.001**	
	SCSQ <sup>a</sup>	$-2.779 \left[ -5.116 \text{ to }442 \right]$	-2.380	.021*	
PSP					
	SANS	-5.764 [ $-7.636$ to $-3.893$ ]	-6.163	·.001**	.392
GFS					.321
	SANS	594[819  to 369]	-5.285	·.001**	
GFR					.357
	SANS	552[794  to 311]	-4.583	·.001**	
	ERT disgust <sup>a</sup>	.369 [.126–.612]	3.043	.004**	
AQoL-8D	-				.231
	SANS	038 [ $037$ to $002$ ]	-2.139	.037*	
	BPRS	039[074  to 003]	-2.176	.034*	
	ERT sad <sup>a</sup>	.034 [.001067]	2.080	.042*	
SRS-A					.301
	TASIT <sup>a</sup>	12.001 [4.473-19.529]	3.220	.003*	
	SANS	9.973 [2.885-17.060]	2.842	.007*	
HiSoC					.224
	ERT angry	2.438 [.560-4.317]	2.628	.012*	
	ERT surprise	-2.047 [ $-3.907$ to $188$ ]	-2.229	.032*	

<sup>&</sup>lt;sup>a</sup> These variables were transformed after reflection (i.e. positive B-values actually reflect a negative relation).

<sup>&</sup>lt;sup>a</sup> These variables were transformed to account for skewness.

<sup>\*</sup> p ≤ .05.

<sup>\*\*</sup> p ≤ .01.

<sup>\*</sup> p ≤ .05.

<sup>\*\*</sup> p ≤ .01.

differences in the recognition of the emotions disgust, anger, and fear. This suggests that the UHR patients may have a selective impairment with greater difficulty in recognizing aspects of negative facial affect, which is similar to findings from patients with schizophrenia (Marwick and Hall, 2008).

The negative findings on the SCSQ are in line with some studies reporting inconsistent findings in the domain of attributional bias (Kurtz and Richardson, 2012; van Donkersgoed et al., 2015). Less than satisfying psychometric properties of available measures of attributional bias may be a possible contributor to this finding (Pinkham et al., 2014). Another possible explanation may be that attributional bias may only occur in the subset of patients with psychotic symptoms involving delusions, as theories suggest that externalizing attributional bias may serve a key role as a defense against low self-esteem in paranoid psychosis (Bentall et al., 2001).

Our findings on the HiSoC indicate that there is clear evidence of significant impairments in social skills in UHR patients. To our knowledge, this is the first study to report social skills impairments in an UHR sample. This suggests that the patients do have substantial difficulties in face-to-face interactions and behavior, and emphasizes the importance of targeting these difficulties in interventions such as behavioral social skills training. The highly significant SRS-A differences between HC and UHR indicate that the patients subjectively experience substantial problems with social functioning. The finding also underscores the utility of the SRS-A as an instrument to detect social deficits in a UHR population.

In the regression analyses we found support for our hypothesis that the UHR patients' social cognitive performance and level of negative symptoms would significantly predict their functioning and social skills. The level of negative symptoms (SANS) was the most important predictor for outcome as it was included in all six outcome measures. Including social cognitive variables improved the regression models significantly and hereby more of the variance was explained. None of the social cognitive variables entered more than one model indicating that the different aspects of social cognition have differential effect on outcome. Unexpectedly, PSP and GF:Social seem to depend on negative symptoms alone and were not found to be related to social cognition. We expected these scales to be related to social cognition as they are designed to measure social outcome (Cornblatt et al., 2007; Morosini et al., 2000). However, the finding of SANS being the only variable to influence GF: Social in UHR patients parallels findings from a previous study (Cotter et al., 2015). The finding of ERT disgust and ERT sadness being negatively correlated with role functioning and quality of life was unexpected. Speculating, it may be that difficulties in recognizing these negative emotions reflect social perceptual difficulties that may be linked to impaired insight affecting the patients' accuracy in reporting their level of functioning (Gould et al., 2015).

Aspects of emotion recognition (anger and surprise) were the only variables included in the model for the social skills outcome measure. The emotion recognition of surprise was, however, negatively correlated with social skills which is counterintuitive, and may be a spurious finding. Our findings on social skills conflict with a study of patients with schizophrenia, that found the ability to understand social cues, and the level of negative symptoms to influence social skills to a higher degree than emotion recognition (Kalin et al., 2015). This study also found negative symptoms to account for most of the variance in the overall functional outcome measures, which is compatible to our findings, and findings from a previous UHR cohort (Cotter et al., 2015). The UHR patients' level of negative symptoms was in the same range as in patients with first episode psychosis (Thorup et al., 2005). The strong association between negative symptoms and functioning stresses the importance of focusing on negative symptoms in UHR patients, and not only mild or brief psychotic symptoms. A two-factor structure for negative symptoms

(experiential vs. expressive symptoms) has been introduced in schizophrenia spectrum disorders (Blanchard and Cohen, 2006). Experiential negative symptoms (avolition, anhedonia) have been shown to be more strongly associated with functioning than expressive symptoms (alogia, affective flattening) in UHR patients (Schlosser et al., 2015) and in patients with schizophrenia (Green et al., 2012a; Green et al., 2012b). Also, anhedonia has been found to be a predictor of transition to psychosis in UHR (Velthorst et al., 2009). This indicates that difficulties in experiencing pleasure and diminished motivation may be key targets for intervention. When evaluating our strong findings on negative symptoms it is important to address the content overlap between specific negative symptom items and the measures of social functioning (e.g. in assessing work function and interpersonal relationships) (Schlosser et al., 2015; Ventura et al., 2015). This overlap may be expected to inflate the association between these domains. This warrants further research into the measurement of negative symptoms and how they overlap with functioning. Our results emphasize the need for continued research into the relationship between social cognition and social skills in UHR patients and their impact on long term functioning.

We found social cognitive function and negative symptoms to play an important role in both observer-rated and self-reported functioning in UHR patients. Our findings stress the importance of future research into targeted treatments aiming at alleviating social cognitive impairments and negative symptoms in UHR. Cognitive remediation holds promise an effective intervention targeting cognitive deficits in schizophrenia spectrum disorders (Wykes et al., 2011), but it has also proven effective in reducing the level of negative symptoms in patients with schizophrenia (Cella et al., 2016; Eack et al., 2013). The effect of social cognitive remediation in UHR is yet unknown, but ongoing research (Glenthøj et al., 2015) will provide insight into its effect on social cognition, negative symptoms, and functioning in UHR.

# 4.1. Study limitations

A limitation of this study is that social cognitive function was assessed using only three social cognition measures. Also, it is possible that conducting more detailed analyses of the social cognitive task variables used in the study may reveal more specific impairments. Further, a large proportion of the patients may not be truly at risk for a psychosis, and therefore an association between social cognition and functioning may be not be expected in these false positives.

#### **Contributors**

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

# Role of funding source

This work was supported by Mental Health Services in the Capital Region of Denmark; the research fund of the Capital Region of Denmark; TrygFonden (grant number ID 108119); The Danish Council for Independent Research (grant number DFF-4004-00314); and the Lundbeck Foundation Center for Clinical Intervention and Neuropsychiatric Schizophrenia Research, CINS (grant number R155-2013-16337).

# Acknowledgements

The authors would like to thank Lise Mariegaard and Kristian Andersen for their valued help with the project.

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