Identifying at-risk states beyond positive symptoms: a brief task assessing how neurocognitive impairments impact on misrepresentation of the social world through blunted emotional appraisal

Identificando estados de risco para além dos sintomas positivos: um teste breve que avalia o impacto de disfunções neurocognitivas sobre a interpretação errônea do mundo social resultante de avaliação emocional embotada

Mariana Galdos[1,2], Claudia J.P. Simons[1,3], Marieke Wichers[1], Aranzazu Fernandez-Rivas[2], Oscar Martinez-Azumendi[2], Tineke Lataster[1], Guillermo Amer[4], Inez Myin-Germeys[1], Miguel Angel Gonzalez-Torres[2], Jim van Os[1,5]

[1] Department of Psychiatry and Neuropsychology, South Limburg Mental Health Research and Teaching Network, EURON, Maastricht University Medical Centre , PO Box 616 (DRT 10), 6200 MD Maastricht, The Netherlands
[2] Department of Neuroscience, University of the Basque Country and Department of Psychiatry, Basurto Hospital, Bilbao, Spain
[3] GGzE, Institute of Mental Health Care Eindhoven en de Kempen, P.O. Box 909, 5600 AX Eindhoven, The Netherlands
[4] Service of Neurology, "Son Dureta" Hospital, Palma de Mallorca, Spain
[5] King's College London, King's Health Partners, Department of Psychosis Studies, Institute of Psychiatry, London, UK

Abstract

Objective: Neurocognitive impairments observed in psychotic disorder may impact on emotion recognition and theory of mind, resulting in altered understanding of the social world. Early intervention efforts would be served by further elucidation of this mechanism. **Method:** Patients with a psychotic disorder (n=30) and a reference control group (n=310) were asked to offer emotional appraisals of images of social situations (EASS task). The degree to which case-control differences in appraisals were mediated by neurocognitive alterations was analyzed. **Results:** The EASS task displayed convergent and discriminant validity. Compared to controls, patients displayed blunted emotional appraisal of social situations (B=0.52, 95% CI: 0.30, 0.74, P<0.001; adjusted for age, sex and number of years of education: B=0.44, 95% CI: 0.20, 0.68, P<0.001), a difference of 0.88 (adjusted: 0.75) standard deviation. After adjustment for neurocognitive variables, the case-control difference was reduced by nearly 75% and was non-significant (B=0.12, 95% CI: -0.14, 0.39, P=0.37). **Conclusions:** Neurocognitive impairments observed in patients with psychotic disorder may underlie misrepresentation of the social world, mediated by altered emotion recognition. A task assessing the social impact of cognitive alterations in clinical practice may be useful in detecting key alterations very early in the course of psychotic illness.

Descriptors: Psychotic disorders; Schizophrenia; Cognition; Disease prevention; Neurobehavioral manifestations

Resumo

Objetivo: *Melhoras neurocognitivas observadas no transtorno psicótico podem ter impacto no reconhecimento de emoções e na teoria da mente, resultando numa alteração na compreensão do mundo social. Esforços para uma intervenção precoce poderiam se beneficiar de uma maior elucidação deste mecanismo.* ***Método:*** *Pacientes com transtornos psicóticos (n=30) e um grupo controle de referência (n=310) foram convidados a realizar avaliações emocionais de imagens de situações sociais (teste AESS). A relação das diferenças entre casos e controles com as alterações neurocognitivas foi analisada.* ***Resultados:*** *O teste AESS apresentou validade convergente e discriminatória. Quando comparados aos controles, os pacientes apresentaram avaliação emocional embotada das situações sociais (B=0,52, 95% CI: 0,30, 0,74, P<0,001; ajustado para a idade, sexo e número de anos de educação: B=0,44, 95% CI: 0,20, 0,68, P<0001), uma diferença de 0,88 (ajustado: 0,75) desvio-padrão. Após o ajuste para as variáveis neurocognitivas, as diferenças no estudo caso-controle foram reduzidas em quase 75% e deixaram de ser significativas (B=0,12, 95% CI: -0,14, 0.39, P=0,37).* ***Conclusões:*** *Disfunções neurocognitivas observadas em pacientes com transtornos psicóticos podem ser subjacentes a uma distorção do mundo social, mediada pela alteração no reconhecimento de emoções. Um teste que avalie o impacto social de alterações cognitivas na prática clínica pode ser útil para a detecção das principais alterações nos primeiros estágios de transtornos psicóticos.*

Descritores: *Transtornos psicóticos; Esquizofrenia; Cognição; Prevenção de doenças; Manifestações neurocomportamentais*

Correspondence
Jim van Os
Department of Psychiatry and Neuropsychology, Maastricht University
P.O. BOX 616 (DRT12), 6200 MD Maastricht, The Netherlands
Tel.: (+31 43) 3875443
Fax: (+31 43) 3875444
E-mail: j.vanos@maastrichtuniversity.nl

Introduction

Early recognition of psychosis to date has made use mainly of psychometric measures of risk indexing positive psychotic symptoms. While important, research suggests that developmental alterations resulting in social dysfunction may be closer to the core disturbance of the disorder. Thus, psychotic disorder is associated not only with neurocognitive deficits, impacting negatively on community functioning[1], but also with alterations in the processing of social information[2-5]. It has been suggested that alterations in the areas of social cognition, particularly as regards the processing of emotions, social perception, mentalization, and social knowledge may have important effects on interpersonal relationships and community functioning in schizophrenia and may serve as useful indicators of impending risk in individuals at risk of developing psychotic illness[6,7]. Indeed, a number of studies investigating this issue have shown that, in schizophrenia, alterations in social cognition affecting social competence[8] impact on social functioning[9]. Given the fact that neurocognitive abilities are relevant for the acquisition of social or living skills and for the deployment of these skills in the real world[10], it has been hypothesized that social cognition may serve as a mediating link between neurocognition and community functioning, acting sequentially on the same pathway[1,6,11]. In support of this, studies have shown that social cognition deficits may mediate at least part of the relationship between neurocognitive function and psychosocial status[12-17].

Given the clinical importance of the relationship between cognition and community functioning, and its likely mediation by social cognition, particularly very early in the course of expression of psychotic symptoms, there is a need for a task which (i) offers a direct assessment of the impact of neurocognitive impairments on the patient's ability to understand the social world; (ii) can be copied to multiple parallel versions; and (iii) is simple enough for repeated use in routine clinical practice, particularly in the area of early intervention, where it can be used to assess developing needs in the realm of daily living in individuals at risk or in a prodrome of psychotic illness, as well as effects of treatment over time. In the current study, therefore, a simple experimental task of interpreting social situations was developed and validated, followed by an analysis of the degree to which patient-control differences on this task could be explained by differences in neurocognition[18]. The use of a reference control group allows for the identification of disease-specific cognitive impairments impacting on the understanding of the social world. Given the fact that the largest effect sizes of neurocognitive deficits have been reported for attention/information processing speed, memory, and executive functioning[19-23], hypothesized mediating variables reflected these functions. In addition, IQ was included as a measure of global cognitive ability.

We hypothesized that patients, compared to controls, would have altered emotional interpretations of the social world, in the direction of a consistently blunted emotional appraisal due to impaired emotion recognition[24], and that these differences would be accounted for, at least in part, by differences in neurocognitive impairment. The task was designed in such a way that it would not be sensitive to information biases associated with positive symptoms[25], as this could arguably lead to enhanced emotion attribution rather than blunted appraisals. Given the importance of intact social cognition for successful completion of developmental tasks[26] and the conceptual focus on early intervention, a sample of adolescents and young adults who were early in the course of psychotic illness was targeted.

Method

Sample

Adolescent patients in the early course of a psychotic disorder were recruited between January 2007 and September 2008 at the Psychiatric Hospitalization Unit of the Basurto, Zaldibar and Zamudio Hospitals in Basque Country, Spain. Patients were assessed in a stable phase outside an acute episode as judged by the responsible medical officer. Controls were recruited at schools serving these areas. Inclusion criteria for both groups were: age of 16-35 years, white ethnic group, native Spanish speaker, IQ in excess of 75 according to the WAIS, and (patients) meeting criteria for DSM-IV affective or non-affective psychotic disorder. Exclusion criteria were: patients in an acute psychotic phase or intoxicated with drugs of abuse, patients with comorbid autism, and patients with organic psychosis. Most of the healthy controls (218 out of a total of 310) were one of a pair of sibs (the familial relationship in controls was required for another, genetically sensitive aspect of the study) meeting similar inclusion and exclusion criteria. They were recruited in the same catchment area as the patients, through educational institutes (vocational school, professional school, university) and staff and relatives of these. The study was approved by the local ethics committee and subjects provided written informed consent.

Instruments

Interviewers were Spanish psychology graduates, who had been trained extensively at Maastricht University, The Netherlands. Follow-up training sessions in order to prevent interview "drift" were conducted regularly on site. The following tasks were administered:

Emotional Appraisal of Social Situations Task (EASS): The EASS task was designed to enable quantification of differences between patients and a reference control group in their final global judgment of a social situation, allowing for a subsequent test of mediation by neurocognition. Specifically, the task was

aimed at identifying case-control differences in emotional attribution processes in 'real world settings', by asking individuals to make a judgment about the mental state of a person in a picture of a certain social situation. A sequence of 25 different pictures appeared on screen, one at a time, corresponding to different social situations, with different face-value emotional valence (positive, negative), each picture being chosen in such a way that a degree of emotion was likely to accompany the social situation depicted (Figure 1). Pictures that were neutral and did not require any degree of emotional "understanding" were avoided, as they could result in patients making an emotionally salient attribution to a neutral situation[27]. Subjects were requested to identify the feelings of one specified person in the picture on a Likert scale ranging from 1 (extreme discomfort) to 7 (wellbeing). The Likert scale options were displayed on the screen continuously through the task, thus eliminating memory requirements. Subjects were told that the task was designed to learn about how people perceive emotions. They received the following instructions: "*You will now watch a sequence of 25 pictures, which will appear on the screen one by one. These pictures represent different social situations similar to those that we can find in our common day-to-day lives. After watching each picture, you will be asked a question on how you perceive the emotional state of a specified individual appearing in the picture. You must respond on a scale from 1 (extreme discomfort) to 7 (well-being)*". A total of 25 pictures were shown in random order. The recordings were reproduced via a PC using E-prime 1.1 (Psychology Software Tools, Pittsburgh, PA). The length of the task was approximately 7 minutes. The main variable used in the analyses was the average score over the 25 pictures. Reversal in scale between items was resolved by inverting the score (i.e., 8 minus score) for the 3 EASS items where patients had lower mean scores compared to controls (items 2, 7, and 11; Figure 2).

Validation procedure: In order to test the validity of the EASS, scores were compared with four measures that on theoretical grounds should be associated with this instrument. First, we predicted convergent validity, particularly in the patient group, with a task assessing emotion recognition (the Degraded Facial Affect Recognition task)[28], predicting negative associations between emotion recognition and blunted emotional appraisal of social situations, and with tasks assessing neurocognitive impairment (see below), predicting positive associations between neurocognitive impairment and blunted emotional appraisal of social situations. Second, we predicted discriminant validity (non-correlation) with a measure of trait anxiety (neuroticism), measured with the 12-item Eysenck neuroticism scale[29] and a test of detecting affectively salient voices in neutral white noise (White Noise Task[30]). The latter task was included as it specifically assesses an affectively salient information bias associated with positive symptoms of psychosis, which was shown to be independent of neurocognitive alterations[30].

White Noise Task: The white noise task was developed as a measure to detect the tendency to spuriously attribute affective meaning to neutral stimuli[30], close to the concept of aberrant attribution of salience[27]. Subjects wore ear phones and were presented one of 3 different types of stimuli: (i) white noise only; (ii) white noise + clearly audible neutral speech; and (iii) white noise + barely audible neutral speech. Stimuli ii and iii were not separate conditions; the intermixing of white noise stimuli with audible speech was presented in order to create a higher level of expectancy, thus occasioning higher levels of

Figure 1. Example of stimuli used in the EASS task. The questions corresponding to these pictures are "*How is the child feeling?*" (left) and "*How is the man feeling?*" (right).

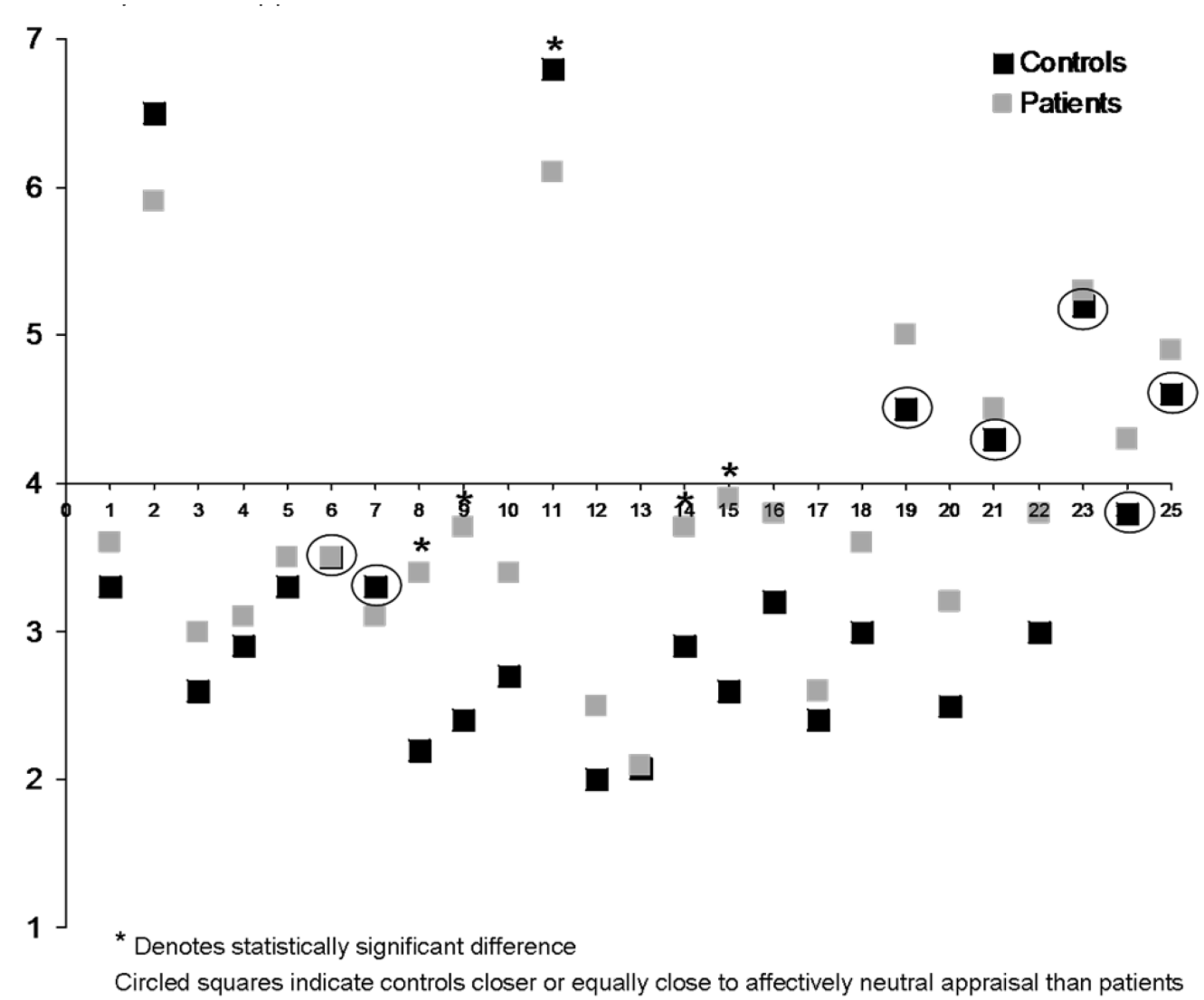

Figure 2. Case control comparison for mean EASS item scores. Line crossing Y-axis at 4 indicates affectively neutral appraisal of social situation.

top-down processing. Participants were presented 25 fragments of each in random order and asked to respond by pressing one of five buttons hereafter referred to as 1: positive speech illusion (endorsed hearing positive voice); 2: negative speech illusion (endorsed hearing negative voice); 3: neutral speech illusion (endorsed hearing neutral voice); 4: no speech heard; and 5: uncertain. The latter option was included in order to make the ratings of 1-3 more conservative. The recordings were delivered using stimulation software E-prime 1.1 (Psychology Software Tools, Pittsburgh, PA) and stimuli were reproduced in random order. The length of the task was approximately 15 minutes. The rate of hearing a voice in the white noise only condition (25 trials) was the variable of interest in the analyses, expressed as a binary variable (1=heard a voice in neutral white noise).

Degraded Facial Affect Recognition (DFAR) task: The DFAR task is a measure of facial affect recognition[28]. Photographs of four different actors, two males and two females, are used. Sixty-four trials are presented, consisting of 16 face presentations in each of four conditions: angry, happy, fearful, and neutral. The photographs of the faces were passed through a filter that reduced visual contrast by 30%. This procedure was adopted in order to increase the difficulty of the task and to enhance the contribution of perceptual expectancies and interpretation. Subjects are asked to indicate the expression of each face with button press (F1 to F4) and are asked to respond as accurately as possible. The number of correctly recognized neutral, happy, angry, and fearful faces was used in the analyses.

Wechsler Adult Intelligence Scale (WAIS): General cognitive abilities and achievement, expressed as a single IQ score, were assessed using the WAIS-III subtests similarities, arithmetic, vocabulary, block design, and object assembly[31,32].

Flanker: The flanker continuous performance test (Cogtest plc, London)[33,34] is a measure of executive control of attention. The task is to respond by pressing the right or left mouse button

depending on whether the middle element in a display of 5 lines has an arrowhead pointing to the right or left. There are three trial types. In neutral trials, the flankers are just horizontal lines without arrowheads. In congruent trials, all flankers have arrowheads pointing in the same direction as the target. In incongruent trials the flankers have arrowheads pointing in the direction opposite to that of the target. The incongruent condition involves more cognitive effort because the flankers are associated with a response that needs to be suppressed. One half of the trials of each trial type is presented with the stimuli above the fixation cross on the screen, the other half is presented below fixation, in order to prevent subjects from keeping their gaze fixed in one position. The test consists of 144 trials of neutral, congruent, and incongruent flankers, which are presented randomly. Outcome measures were the proportion of correct trials for the neutral, congruent, and incongruent conditions.

Rey Auditory-Verbal Learning test (RAVLT): A Spanish version of the RAVLT[35] was used to measure auditory verbal episodic memory and related executive function. The test was presented as described by Spreen & Strauss[36]. The responses were recorded on a database solution based on FileMaker Pro®, to automate recording and analysis[37]. The test consists of two learning lists of 15 words, and a third with the 30 words of the 2 learning lists and 20 distracter words. The test assesses learning, interference, and delayed free recall and recognition. Several indexes can be obtained. Outcomes used were immediate recall index (total proportional acquisition), delayed recall index (proportion correct delayed recall), and the retention index (proportion of words retained).

Continuous Performance Test (CPT): Visual sustained attention was assessed using a continuous performance test (CPT-HQ) with working memory load. The CPT-HQ is the same as the CPT known in the literature as CPT-AX[38,39]. The task for the participant is to respond to letter Q only when it is preceded by letter H. Non-target letters are letters I, J, L, T. In the CPT-HQ, 300 letters are presented in a randomized sequence, at a rate of one per second. Each letter is presented for 150 ms, after which an empty screen is presented for 850 ms. The participant responds to a target by pressing the space bar of the PC keyboard. The letters are presented on a PC-controlled video monitor as white letters on a black background at a viewing distance of 100 cm. Presentation of an HQ target-pair has a probability of 0.18 (n=28) among the 150 sequential letter-pairs. In 28 (0.18) sequential letter-pairs, letter Q is presented following another letter than H (I, L, J, or T). In another 28 (0.18) pairs, letter H is presented followed by another letter than Q (I, L, J, or T). The variable used in the analyses was the reaction time for correct detections. This measure of psychomotor processing speed during sustained attention was chosen because of its ability to differentiate between the experimental groups on account of low propensity for ceiling effects[40].

Response Shifting Task (RST): Set-shifting ability was tested using the RST, a modified version of the Competing Programs Task[41]. The RST requires switching between two response rules. Subjects are presented with the stimulus word "left" or "right" in the middle of the screen and must respond by pressing a key on either the left or right side of the keyboard. Stimuli are presented for 3000 ms, followed by feedback ("correct" or "wrong") for 1000 ms. During blocks 1 and 3 (imitation), subjects must press the key congruent with the stimulus, e.g., the left key when presented with the stimulus "left". During blocks 2 and 4 (reversal), subjects must press the key incongruent with the stimulus, e.g., the right key when presented with the stimulus "left". Each block ends (and the rule changes) after either a maximum of 20 trials or the criterion of eight consecutive correct responses is reached. Subjects must deduce the response rules from trial-by-trial feedback, without explicit instruction. The variable used in the analyses was a proportional cost index to measure performance decrement related to shifting from imitation response rule to reversal response rule: (proportion correct [imitation] – proportion correct [reversal]) / proportion correct [reversal])[42-44].

Operational Criteria Checklist for Psychotic Illness (OPCRIT): The Operational Criteria Checklist for Psychotic Illness and associated OPCRIT computer program[45] were used to establish DSM-IV diagnosis on the basis of current symptomatology, assessed with the PANSS[46], as well as lifetime psychopathology, as recorded in the case notes.

Analyses

It was calculated that a sample of 30 patients and 300 controls would yield 74% power, at conventional alpha, to detect an 0.5 standard deviation difference in the continuous score of the EASS task in the case-control comparison, and 98% power to detect a difference of 0.75 standard deviation. In order to have sample constancy in the comparison between adjusted and non-adjusted analyses, only participants with complete values for the EASS task, age, sex and all the neurocognitive variables used were included in the analyses.

First, EASS item scores were plotted for each group and inspected for distance from a score of 4 (emotionally neutral appraisal), calculating whether the number of instances that control mean scores (hypothesized higher level of emotional appraisal) showed greater distance from 4 compared to patients (hypothesized lower level of emotional appraisal), exceeding chance expectation.

Second, the individual EASS item scores as well as the EASS total score were the continuous response variables, and case-control status the binary exposure variable in multiple regression models, all adjusted for age, sex, and number of years in full time

education. As controls (consisting of sib-pairs) pertained to the same family, multilevel random regression using the XTREG routine in the STATA statistical program, version 11.0[47], was conducted in order to correct standard errors for clustering at the level of family, yielding unstandardized regression coefficients as effect size. In order to test whether case-control differences were mediated by neurocognition, the model with EASS total scores was additionally adjusted for WAIS-IQ score, Flanker proportion of correct trials for the neutral, congruent, and incongruent conditions, CPT reaction time, RST proportional cost index, and RAVLT immediate recall index, delayed recall index, and retention index.

Results

Sample

Patients were older than controls, more frequently male, and had spent less time in full time education (Table 1). The majority of patients and controls were from social classes 3 and 4. Diagnoses in the patients were: schizophrenia or schizophreniform disorder (n=24), affective psychosis (n=3), and psychotic disorder NOS (n=3). Mean GAF score was 43 (SD=20.3) and mean age at first treatment for psychosis was 21.0 years (SD=3.0). All patients were taking antipsychotic medication and had been receiving an antipsychotic for a mean of 4.8 years. Mean total PANSS score was 67.6 (SD=15.0; negative subscore: 19.0, SD=5.0; positive subscore: 16.3, SD=6.6; general score: 32.3, SD=7.5).

Convergent and discriminant validity of the EASS

The mean number of correctly recognized facial emotions was lower in the patients than in the controls, particularly for fearful and angry faces (Table 1; p-value adjusted for age, sex, and years of education: neutral faces: p=0.78; fearful faces: p<0.040; happy faces: p=0.23; angry faces: p<0.023). Significant negative associations were apparent between EASS scores and a number of facial emotions in the patients (happy faces: adjusted B=-0.13, p=0.038; neutral faces: adjusted B= 0.02, p=0.60; fearful faces: B=-0.11, p=0.005; angry faces: B=-0.02, p=0.73), but not in the controls (happy faces: adjusted B=0.003, p=0.89; neutral faces: adjusted B= 0.006, p=0.67; fearful faces: B=-0.007, p=0.52; angry faces: B=-0.02, p=0.058).

Patients had lower scores on all neurocognitive variables (Table 1; standardized effect sizes controlled for age, sex, and years of education: WAIS-IQ score: -0.13; Flanker neutral condition: -0.33, Flanker congruent condition: -0.38; Flanker incongruent condition: -0.33; RAVLT immediate recall index: -0.30; RAVLT delayed recall index: -0.33; RAVLT retention index: -0.22; RST-cost: 0.24; CPT-RT: 0.16; all effect sizes P<0.001, except WAIS-IQ P=0.008 and CPT-RT p=0.006). In both patient and control groups, significant correlations were apparent between the EASS and neurocognitive variables; correlations were stronger in patients, but statistical power was also lower (Table 2).

Mean neuroticism scores in the patients were higher than scores in controls (Table 1; adjusted p-value: p<0.001). Neuroticism score was associated with EASS score in neither the patients (adjusted B=0.55, p=0.31) nor the controls (adjusted B=0.18, p=0.36).

Patients more often reported hearing a voice in neutral noise as reported previously[30] (Table 1; adjusted p-value: p=0.012). Hearing a voice in white noise was associated with EASS score in neither the patients (adjusted B=-0.08, p=0.78) nor the controls (adjusted B=0.10, p=0.41).

Case-control comparison EASS task

Plotting the mean EASS scores for patients and controls (Figure 2) and inspecting the distance from 4 (the level of affectively neutral appraisal) revealed that controls displayed greater distance from neutrality than patients in 18 out of 25 comparisons (72%), well exceeding chance expectation (p=0.014). In five instances, the differences between patients and controls in mean EASS item scores were significantly different, all with controls displaying greater distance from neutral affective appraisal (Figure 2). The comparison between controls (mean: 3.06, SD=0.57) and patients (mean: 3.58, SD=0.67) revealed a difference in EASS total scores, in the direction of blunted response, at an effect size of 0.9 standard deviation. In the unadjusted analyses, the difference between patients and controls in the EASS task was significant (B=0.52, 95% CI: 0.30, 0.74, P<0.001). Adjusting for age, sex, and years of full-time education reduced the association somewhat (B=0.44, 95% CI: 0.20, 0.68, P<0.001), whereas adjustment for all the neurocognitive variables together reduced the association by nearly 75% (B=0.12, 95% CI: -0.14, 0.39, P=0.37). The effects of adjustment of the individual neurocognitive variables, expressed as percentage reduction of the 0.44 effect size adjusted for age, sex, and years of full time education, were: WAIS-IQ: 16% reduction; Flanker congruent: 45% reduction; Flanker incongruent: 32% reduction; Flanker neutral: 39% reduction; RAVLT immediate recall: 7% reduction; RAVLT delayed recall; 16% reduction; RAVLT retention: 5% reduction; RST proportional cost: 14% reduction; CPT reaction time: 2% reduction.

Discussion

Findings

The aim of this study was to pilot a test for early recognition of core deficits associated with psychotic disorder in the realm of social cognition, with a view for more elaborate subsequent testing in samples of individuals at ultra-high risk. Sizeable

Table 1. Demographics and cognitive variables in patients and controls

	Patients (n=30) (n or SD)	**Controls (n=310)** (n or SD)
Males	67% (20)	49% (152)
Age	25.3 (4.5)	20.9 (3.6)
Years of full-time education	12.2 (1.8)	13.9 (2.8)
EASS score	3.06 (0.57)	3.58 (0.67)
WAIS-IQ	96.2 (16.2)	106.3 (14.4)
Flanker congruent	0.85 (0.17)	0.96 (0.06)
Flanker incongruent	0.78 (0.17)	0.90 (0.10)
Flanker neutral	0.88 (0.14)	0.96 (0.06)
RAVLT immediate recall index	0.63 (0.16)	0.75 (0.10)
RAVLT delayed recall index	0.60 (0.24)	0.81 (0.15)
RAVLT retention index	0.05 (0.01)	0.06 (0.01)
RST proportional cost index	0.28 (0.45)	0.09 (0.11)
CPT reaction time	476 .5 (107.3)	436.6 (86.4)
DFAR* correctly recognized faces:		
Happiness	13.8 (2.1)	14.6 (1.4)
Anger	9.9 (2.4)	10.6 (3.1)
Fear	7.8 (3.3)	9.1 (2.8)
Neutral	11.0 (3.3)	12.4 (2.5)
Neuroticism score	0.43 (0.26)	0.20 (0.17)
Hearing voice in white noise	9 (30%)	27 (9%)

EASS: Emotional Appraisals of Social Situations task; WAIS: Wechsler Adult Intelligence Scale; RAVLT: Rey Auditory-Verbal Learning Test; RST: Response Shifting Task; CPT: Continuous Performance Test; DFAR: Degraded Facial Affect Recognition task.

Table 2. Correlations between EASS and neurocognitive variables in patients and controls

Neurocognitive variable	Patients (n=30) Pearson r (*p*)	Controls (n=310) Pearson r (*p*)	Patients and controls (n=340) Pearson r (*p*)
WAIS-IQ	-0.47 (0.009)	-0.23 (<0.001)	-0.29 (<0.001)
Flanker congruent	-0.60 (<0.001)	-0.17 (0.004)	-0.32 (<0.001)
Flanker incongruent	-0.41 (0.02)	-0.15 (0.008)	-0.25 (<0.001)
Flanker neutral	-0.61 (<0.001)	-0.16 (0.006)	-0.30 (<0.001)
RAVLT immediate recall index	0.05 (0.81)	-0.05 (0.39)	-0.11 (0.08)
RAVLT delayed recall index	0.04 (0.85)	-0.11 (0.05)	-0.17 (0.02)
RAVLT retention index	-0.02 (0.92)	-0.06 (0.31)	-0.11 (0.04)
RST proportional cost index	0.25 (0.19)	0.12 (0.04)	0.11 (0.05)
CPT reaction time	0.24 (0.20)	0.11 (0.06)	0.05 (0.38)

differences in assessment of social situations between patients and controls were associated with blunting of emotional appraisals in the patients, and reducible to the neurocognitive impairments associated with psychotic disorder. The EASS task used displayed convergent and discriminant validity. Patients displayed blunted emotional appraisals of social situations, suggesting they were less likely to pick up subtle emotional cues embedded in displays of social interactions. The results are in agreement with evidence that patients with psychotic disorder have impairments in emotion recognition[24] and display alterations in the ability to attribute mental states to oneself and others, that in part are reducible to underlying neurocognitive impairments[11,48,49]. Although the study did not assess real world behavioral responses, it is likely that differences in appraisal of social situations will contribute to differences in response. Thus, to the degree that this is the case, similar mediation by neurocognitive impairment may be invoked.

Neurocognitive impairments mediate social cognition

There is evidence that cognitive deficits in psychotic disorder are largely generalized across performance domains[50] and that the degree to which social cognition is mediated by neurocognition similarly involves broad aspects of neurocognition[17]. In the current study, some neurocognitive tasks, particularly the Flanker task, displayed stronger evidence for mediation of EASS performance, although considerable extra mediation was apparent when all tasks were entered together in the model, suggesting a broad, non-specific contribution as well. The reason the Flanker task was a strong mediator is related to the fact that the EASS task depends on mentalizing capacity, which in turn requires monitoring of behavior and inhibition of irrelevant cues. Therefore, tasks measuring inhibition of interfering information are expected to mediate performance on mentalizing tasks.

The mediating effect of neurocognitive variables was strong and specific to the task of emotional attribution to social situations (such as the EASS task), as case-control differences on other, salience-related tasks (such as the White Noise task) were shown to be not in any degree reducible to measures of neurocognitive deficit in a related investigation[51]. The results are clinically relevant, as they suggest the degree to which neurocognitive impairments early in the course of psychotic illness can be improved by cognitive remediation[52]. Alterations in emotional appraisal of social situations may improve accordingly, although recent work suggests that the cognitive gains induced by CRT may not generalize readily to effects in the social world[53].

The EASS requires skills in several domains, including the domain of mentalization and emotion recognition, and

application of these to a daily life scene. It can therefore not be considered as a test of social cognition per se; it was designed to test the degree to which cognitive alterations associated with schizophrenia impact on a person's understanding of the social world. Strengths of the current study include minimal dependence of the EASS on memory and attention, contrary to, for example, the hinting task[54], allowing for the separation of task-dependent neuropsychological abilities and neurocognitive mediation of observed case-control differences. A further strength was the use of a "real world" approach in assessing case-control differences in cognition using images of daily life social scenes. Limitations are the relatively small sample size, the lack of a behavioral outcome reflecting actual social functioning, and the fact that this was the first time the EASS was used, requiring further replication. Further development of the EASS and its application to samples at ultra-high risk of psychotic disorder may be useful, as it represents a direct way of assessing the (proxy) impact of cognitive alterations in patients rather than the alterations per se, thus complementing the repertoire of instruments used to provide care tailored to specific needs in individual patients and risk of transition in individuals at ultra-high risk of psychotic disorder.

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Disclosures

Writing group member	Employment	Research grant[1]	Other research grant or medical continuous education[2]	Speaker's honoraria	Ownership interest	Consultant/ Advisory board	Other[3]
Galdos M	Maastricht University Medical Center, The Netherlands/Basurto Hospital, Spain	-	-	-	-	-	-
Simons CJP	Maastricht University Medical Center, The Netherlands/ Institute of Mental Health Care Eindhoven en de Kempen, The Netherlands	-	-	-	-	-	-
Wichers M	Maastricht University Medical Center, The Netherlands	-	-	-	-	-	-
Fernandez-Rivas A	Basurto Hospital, Spain	-	-	-	-	-	-
Martinez-Azumendi O	Basurto Hospital, Spain	-	-	-	-	-	-
Lataster T	Maastricht University Medical Center, The Netherlands	-	-	-	-	-	-
Amer G	Son Dureta Hospital, Spain	-	-	-	-	-	-
Myin-Germeys I	Maastricht University Medical Center, The Netherlands	-	-	-	-	-	-
Gonzalez-Torres MA	Basurto Hospital, Spain	-	-	-	-	-	-
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** Modest*
*** Significant*
**** Significant: Amounts given to the author's institution or to a colleague for research in which the author has participation, not directly to the author.*

References

1. 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(1):119-36.

2. Green MF, Leitman DI. Social cognition in schizophrenia. *Schizophr Bull*. 2008;34(4):670-2.

3. Marwick K, Hall J. Social cognition in schizophrenia: a review of face processing. *Br Med Bull.* 2008;88(1):43-58.

4. Penn DL, Sanna LJ, Roberts DL. Social cognition in schizophrenia: an overview. *Schizophr Bull.* 2008;34(3):408-11.

5. Bora E, Yucel M, Pantelis C. Theory of mind impairment in schizophrenia: meta-analysis. *Schizophr Res.* 2009;109(1):1-9.

6. Vauth R, Rusch N, Wirtz M, Corrigan PW. Does social cognition influence the relation between neurocognitive deficits and vocational functioning in schizophrenia? *Psychiatry Res.* 2004;128(2):155-65.

7. Pinkham AE, Penn DL. Neurocognitive and social cognitive predictors of interpersonal skill in schizophrenia. *Psychiatry Res*. 2006;143(2-3):167-78.

8. Bowie CR, Depp C, McGrath JA, Wolyniec P, Mausbach BT, Thornquist MH, Luke J, Patterson TL, Harvey PD, Pulver AE. Prediction of real-world functional disability in chronic mental disorders: A comparison of schizophrenia and bipolar disorder. *Am J Psychiatry.* 2010;167(9):1116-24..

9. Couture SM, Penn DL, Roberts DL. The functional significance of social cognition in schizophrenia: a review. *Schizophr Bull.* 2006;32 Suppl 1:S44-63.

10. Bowie CR, Harvey PD. Communication abnormalities predict functional outcomes in chronic schizophrenia: differential associations with social and adaptive functions. *Schizophr Res.* 2008;103(1-3):240-7.

11. van Hooren S, Versmissen D, Janssen I, Myin-Germeys I, a Campo J, Mengelers R, Van OS J, Krabbendam L. Social cognition and neurocognition as independent domains in psychosis. *Schizophr Res.* 2008;103(1-3):257-65.

12. Addington J, Saeedi H, Addington D. Facial affect recognition: a mediator between cognitive and social functioning in psychosis? *Schizophr Res.* 2006;85(1-3):142-50.

13. Brekke J, Kay DD, Lee KS, Green MF. Biosocial pathways to functional outcome in schizophrenia. *Schizophr Res.* 2005;80(2-3):213-25.

14. Sergi MJ, Rassovsky Y, Nuechterlein KH, Green MF. Social perception as a mediator of the influence of early visual processing on functional status in schizophrenia. *Am J Psychiatry.* 2006;163(3):448-54.

15. Vaskinn A, Sundet K, Friis S, Simonsen C, Birkenaes AB, Jonsdottir H, Ringen PA, Andreassen OA. Emotion perception and learning potential: mediators between neurocognition and social problem-solving in schizophrenia? *J Int Neuropsychol Soc.* 2008;14(2):279-88.

16. Addington J, Girard TA, Christensen BK, Addington D. Social cognition mediates illness-related and cognitive influences on social function in patients with schizophrenia-spectrum disorders. *J Psychiatry Neurosci. 2*010;35(1):49-54.

17. Dickinson D, Bellack AS, Gold JM. Social/communication skills, cognition, and vocational functioning in schizophrenia. *Schizophr Bull.* 2007;33(5):1213-20.

18. Krabbendam L, Marcelis M, Delespaul P, Jolles J, Van Os J. Single or multiple familial cognitive risk factors in schizophrenia? *Am J Med Gene*t. 2001;105(2): 183-8.

19. Braff DL. Information processing and attention dysfunctions in schizophrenia. *Schizophr Bull.* 1993;19(2):233-59.

20. Dickinson D, Ramsey ME, Gold JM. Overlooking the obvious: A meta-analytic comparison of digit symbol coding tasks and other cognitive measures in schizophrenia. *Arch Gen Psychiatry.* 2007;64(5):532-42.

21. Heinrichs RW, Zakzanis KK. Neurocognitive deficit in schizophrenia: A quantitative review of the evidence. Neuropsychology 1998;12(3):426-45.

22. Morice R, Delahunty A. Frontal/executive impairments in schizophrenia. *Schizophr Bull.* 1996;22(1):125-37.

23. Nuechterlein KH, Dawson ME. Information processing and attentional functioning in the developmental course of schizophrenic disorders. *Schizophr Bull.* 1984;10(2):160-203.

24. Kohler CG, Walker JB, Martin EA, Healey KM, Moberg PJ. Facial emotion perception in schizophrenia: A meta-analytic review. *Schizophr Bu*ll. 2009;36(5):1009-19.

25. Garety PA, Kuipers E, Fowler D, Freeman D, Bebbington PE. A cognitive model of the positive symptoms of psychosis. *Psychol Med.* 2001;31(2):189-95.

26. Galdos PM, Van Os JJ, Murray RM. Puberty and the onset of psychosis. *Schizophr Res.* 1993;10(1):7-14.

27. Kapur S. Psychosis as a state of aberrant salience: a framework linking biology, phenomenology, and pharmacology in schizophrenia. *Am J Psychiatry.* 2003;160(1):13-23.

28. van 't Wout M, Aleman A, Kessels RP, Laroi F, Kahn RS. Emotional processing in a non-clinical psychosis-prone sample. *Schizophr Res.* 2004;68(2-3):271-81.

29. Eysenck HJ, Eysenck SBG. *Manual of the eysenck personality questionnaire*. London: Hodder & Stoughton; 1975.

30. Galdos M, Simons C, Fernandez-Rivas A, Wichers M, Peralta C, Lataster T, Amer G, Myin-germeys I, Allardyce J, Gonzalez Torres MA, Van Os J. Affectively salient meaning in random noise: A task sensitive to psychosis liability. *Schizophr Bull.* In press 2010.

31. Wechsler D. *WAIS-III administration and scoring manual*. San Antonia, TX: The Psychological Corporation; 1997.

32. Lopez JM, Santin C, Torrico E. Utilidad de las formas cortas de la Escala de Inteligencia de Wechler para adultos (WAIS). *Anales Psicología*. 2003;1:53-63.

33. Eriksen BA, Eriksen CW. Effects of noise letters upon the identification of a target letter in a nonsearch task. Percept Psychophys 1974;16:143-9.

34. Posner MI, Inhoff AW, Friedrich FJ, Cohen A. Isolating attentional systems: A cognitive-anatomical analysis. Psychobiology 1987;15:107-21.

35. Rey A. *Clinical assessment in psychology.* Paris: Presses Universitaires de France; 1964.

36. Spreen O, Strauss E. *A compendium of neuropsychological tests.* Adminstration, norms, and commentary. 2nd ed. New York: Oxford University Press; 1998.

37. Amer G, García Soriano MT, García A, Tarongí S, Barceló I. Registro automatizado del test de aprendizaje auditivo-verbal de Rey. Descripción e implementación en una consulta de neurología cognitiva y de la conducta. *Neurologia.* 2001;16:456-7.

38. Wohlberg GW, Kornetsky C. Sustained attention in remitted schizophrenics. *Arch Gen Psychiatry.* 1973;28(4):533-7.

39. Nuechterlein KH, Dawson ME. Information processing and attention in the development of schizophrenic disorders. *Schizophr Bull.* 1984;10(2):160-203.

40. Wang Q, Chan R, Sun J, Yao J, Deng W, Sun X, Liu X, Sham PC, Ma X, Meng H, Murray RM, Collier DA, Li T.. Reaction time of the continuous performance test is an endophenotypic marker for schizophrenia: A study of first-episode neuroleptic-naive schizophrenia, their non-psychotic first-degree relatives and healthy population controls. *Schizophr Res.* 2007;89(1-3):293-8.

41. Bilder RM, Turkel E, Lipschutz-Broch L, Lieberman JA. Antipsychotic medication effects on neuropsychological functions. *Psychopharmacol Bull.* 1992;28(4):353-66.

42. Nolan KA, Bilder RM, Lachman HM, Volavka J. Catechol O-Methyltransferase Val158Met polymorphism in schizophrenia: Differential effects of val and et Alleles on cognitive stability and flexibility. *Am J Psychiatry.* 2004;161(2):359-61.

43. Meiran N, Levine J, Meiran N, Henik A. Task set switching in schizophrenia. *Neuropsychology.* 2000;14(3):471-82.

44. Bilder RM, Turkel E, Lipschutz-Broch L, Lieberman JA. Antipsychotic medication effects on neuropsychological functions. *Psychopharmacol Bull.* 1992;28(4):353-66.

45. McGuffin P, Farmer A, Harvey I. A polydiagnostic application of operational criteria in studies of psychotic illness. Development and reliability of the OPCRIT system. *Arch Gen Psychiatry*. 1991;48(8):764-70.

46. Kay SR, Fiszbein A, Opler LA. The positive and negative syndrome scale (PANSS) for schizophrenia. *Schizophr Bull.* 1987;13(2):261-76.

47. StataCorp. *STATA Statistical Software: Release 11.* Texas: College Station; 2009.

48. Abdel-Hamid M, Lehmkamper C, Sonntag C, Juckel G, Daum I, Brune M. Theory of mind in schizophrenia: the role of clinical symptomatology and neurocognition in understanding other people's thoughts and intentions. *Psychiatry Res.* 2009;165(1-2):19-26.

49. Shur S, Shamay-Tsoory SG, Levkovitz Y. Integration of emotional and cognitive aspects of theory of mind in schizophrenia and its relation to prefrontal neurocognitive performance. *Cogn Neuropsychiatry.* 2008;13(6):472-90.

50. Dickinson D, Ragland JD, Gold JM, Gur RC. General and specific cognitive deficits in schizophrenia: Goliath defeats David? *Biol Psychiatry.* 2008;64(9):823-7.

51. Galdos M, Simons C, Fernandez-Rivas A, Wichers M, Peralta C, Lataster T, et al. Psychosis and affectively salient meaning in random noise: A brief, specific and sensitive aberrant salience test. Submitted Manuscript 2010.

52. McGurk SR, Twamley EW, Sitzer DI, McHugo GJ, Mueser KT. A meta-analysis of cognitive remediation in schizophrenia. *Am J Psychiatry.* 2007;164(12):1791-802.

53. Dickinson D, Tenhula W, Morris S, Brown C, Peer J, Spencer K, Li L, Zold JM, Bellack AS.. A randomized, controlled trial of computer-assisted cognitive remediation for schizophrenia. *Am J Psychiatry*. 2009;167(2):170-80.

54. Corcoran R, Mercer G, Frith CD. Schizophrenia, symptomatology and social inference: investigating "theory of mind" in people with schizophrenia. *Schizophr Res.* 1995;17(1):5-13.