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Emotion processing in schizophrenia is state and trait dependent

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ABSTRACT

Background: Substantial evidence exists about emotion processing (EP) impairments in schizophrenia patients. However, whether these deficits are present primarily during psychosis (i.e., state dependent) or an integral part of the disorder (i.e., trait dependent) remains unclear.
Methods: EP was assessed with the degraded facial affect recognition task in schizophrenia patients (N = 521) and healthy controls (N = 312) at baseline (T1) and after a three year follow-up (T2). In schizophrenia patients symptomatic remission was assessed with the Positive and Negative Syndrome Scale (PANSS) remission tool. Patients were divided into four groups: remission T1 and remission T2 (RR); remission T1 and non-remission T2 (RN); non-remission T1 and non-remission T2 (NN) and non-remission T1 and remission T2 (NR). Factorial repeated measures ANCOVA was used to compare EP performance over time between groups. Age, gender and general cognition were included as covariates.
Results: Schizophrenia patients performed worse than healthy controls on EP at T1 ($p = 0.001$). The patients that were in symptomatic remission at both time points (the RR group) performed worse than the healthy controls at T2 ($p < 0.001$). Significant group × time interactions were found between RR and RN ($p = 0.001$), and between NR and RN ($p = 0.04$), indicating a differential EP performance over time. No group × time interaction was found between NN and NR.
Conclusion: The results show relatively poor EP performance in schizophrenia patients compared to healthy controls. EP performance in schizophrenia patients was associated with symptomatic remission. The results provide support for the hypothesis that EP deficits in schizophrenia are both state and trait dependent.

1. Introduction

Schizophrenia is characterized by positive symptoms (e.g., delusions and hallucinations), negative symptoms (e.g., flat or blunted affect and emotion), and cognitive impairments (e.g., deficits in working memory, attention and social cognition) (American Psychiatric Association, 2000). Social cognition represents how people think about themselves and others (Penn et al., 2008) and is necessary for successful social interactions between people (Baron-Cohen et al., 1985). Emotion processing (EP) is an important domain of social cognition (Green et al., 2005) and has been described as the ability to infer emotional information from prosody or facial expressions, the latter being the focus of the current study (Couture et al., 2006). Not surprisingly, EP is found to be related to social problem solving and community functioning in

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schizophrenia (Hofer et al., 2009; Irani et al., 2012). Moreover, impairments in EP may even exceed the value of general cognition in explaining outcome in schizophrenia (Fett et al., 2011).

Schizophrenia patients differ as for the genetic patterns that predispose them to the illness (Gershon et al., 2011). A factor complicating the search for genes that underlie the disorder is that the course of the disease is usually characterized by different states of illness that fluctuate over time (i.e., a patient returns to a non-psychotic state in between psychotic episodes). An emerging area of genetic research in schizophrenia is that of so-called 'trait markers'. Trait markers refer to processes that play an antecedent, possibly causal, role in the susceptibility to the disease (Chen et al., 2009). These markers may be closer to the genotype than the symptoms of the illness (van Os and Kapur, 2009), and, therefore, can be useful targets for genetic studies. In addition, trait markers can be relevant if they have a high diagnostic specificity. A behavioral trait is an enduring characteristic that is associated with illness in the population. Numerous studies have shown deficits in EP performance in schizophrenia patients compared to healthy controls (Marwick and Hall, 2008; Penn et al., 2008; Chan et al., 2010; Kohler et al., 2010). Cross-sectional studies showed EP deficits to be present at the first onset of schizophrenia and to be stable over the course of illness in chronic patients (Pinkham et al., 2007; Green et al., 2012). Trait markers are most useful when they are also present in clinically unaffected relatives (Chen et al., 2009). Indeed, some studies found EP deficits in unaffected siblings of schizophrenia patients (Eack et al., 2009; de Achaval et al., 2010). Siblings performed worse on recognizing facial emotion compared to healthy controls, suggesting a trait dependent deficit in EP in schizophrenia.

However, results on EP deficits in unaffected siblings of schizophrenia patients are inconsistent and the presence of EP deficits at a prodromal stage of the illness remains questionable (Kee et al., 2004). Although some studies found EP deficits in people at clinical high risk for psychosis (Amminger et al., 2012; Green et al., 2012), other studies found that subjects at increased risk for psychosis performed similarly to healthy controls (Pinkham et al., 2007). Moreover, EP performance might change over time according to an increase or decrease in clinical symptoms, as one study reviewing 24 studies on EP suggested that individuals in remission outperform individuals at an acute phase of the disorder (Edwards et al., 2002). In addition, several studies showed that poor EP performance in schizophrenia was related to more severe schizophrenia symptoms (Kohler et al., 2000, 2010; Marwick and Hall, 2008; Laroi et al., 2010; Huang et al., 2013; Tseng et al., 2013; Ventura at al., 2013). A longitudinal study by Kucharska-Pietura et al. showed EP deficits in schizophrenia patients to worsen with progression of illness (Kucharska-Pietura et al., 2005). Although it remains uncertain if the decline in EP ability seen in patients over time was entirely due to an increase in illness severity, the results at least indicate that EP deficits in schizophrenia patients fluctuate over time.

To the best of our knowledge, no longitudinal study to date has investigated whether EP impairments are either present primarily during psychosis (i.e., state dependent) or form an integral part of the disorder (i.e., trait dependent), or a combination of the two (i.e., state as well as trait dependent). Typically, though not necessarily, a state characteristic is transient and a trait characteristic is enduring (Chen et al., 2009). Therefore, longitudinal research is essential to elucidate whether EP deficits are state or trait dependent in schizophrenia, because these studies follow the natural course of illness within the same patient, whereas cross-sectional studies do not. The present study was outlined to examine EP performance, i.e., facial emotion recognition ability, longitudinally in a large cohort of schizophrenia patients and healthy controls over three years' time. Assessments of EP, general cognition (IQ) and schizophrenia symptoms were performed at baseline and after a three year follow-up. First, EP performance was compared between schizophrenia patients and healthy controls. Second, schizophrenia patients were divided into four groups, based on their symptomatic state of illness at both measurements, i.e. remission or non-remission at baseline and remission or non-remission at follow-up. The severity of schizophrenia symptoms served as a basis for defining state of illness within the patients. EP scores were compared between the four patient groups over time. In the literature to date there is still debate concerning emotion specific EP deficits in schizophrenia patients. Although some studies suggest a negative-emotion specific deficit (Edwards et al., 2001; Bediou et al., 2005; van 't Wout et al., 2007), other more recent studies suggest that facial emotion recognition impairment in schizophrenia may reflect a more generalized deficit (Mendoza et al., 2011; Huang et al., 2013).

In the context of previous evidence of social cognitive impairments in schizophrenia patients, we expected the EP scores to be different between patients and healthy controls. Besides being related to the disorder (trait dependent), we also expected EP performance to vary within the patient group depending on state of illness, in other words, for the patient groups we hypothesized EP performance to be state dependent. Specifically, 1) for the patients in non-remission at baseline we expected an improvement on EP performance over time if they achieved a remission state at follow-up, and 2) for patients in remission at baseline, we expected a decrease in EP performance over time, if they returned to a non-remission state at follow-up.

2. Method

2.1. Procedure and sample

The data originate from measures of the ongoing longitudinal multicenter study 'Genetic Risk and Outcome in Psychosis' (GROUP). Assessments were performed at baseline and after a three year follow-up. The procedure of recruitment, informed consent, approval by the accredited Medical Ethics Review Committee (METC) and population characteristics of the participants have been described in a previous report on the GROUP study (Korver et al., 2012). The full GROUP sample at baseline consisted of 1120 patients with a non-affective psychotic disorder, 1057 of their siblings, 919 of their parents, and 590 healthy controls. For this study, we included patients and healthy controls for whom assessments were available at baseline and follow-up.

The patient group had to meet the criteria for non-affective psychotic disorder of the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM IV) (American Psychiatric Association, 2000), as assessed by the Comprehensive Assessment of Symptoms and History (CASH) interview (Andreasen et al., 1992). Further inclusion criteria for patients were: age between 15 and 60; good command of the Dutch language; ability and willingness to give informed consent and having had the first psychotic episode up to ten years before baseline.

For the healthy control group inclusion criteria were: not having any diagnosis according to DSM IV (American Psychiatric Association, 2000), as assessed by the CASH (Andreasen et al., 1992); age between 15 and 60; good command of the Dutch language; ability and willingness to give informed consent and no first degree family members with a psychotic disorder at baseline.

2.2. Measures

All measures used in the GROUP project were selected on the basis of established validity, reliability and on their feasibility for use in multisite studies.

2.2.1. The Positive and Negative Syndrome Scale (PANSS)

In the GROUP project, current severity of symptoms was measured with the PANSS (Kay et al., 1987). The PANSS consists of 30 items. Each item is scored on a scale ranging from 1 (absent) to 7 (extreme), the behavioral effect of symptoms and their severity are incorporated in item rating. Three domains are described for the PANSS, measuring positive, negative or general symptoms.

2.2.2. The PANSS remission tool

We used the PANSS remission tool (Andreasen et al., 2005) as a measure for symptomatic remission. Based on the PANSS described above, Andreasen et al. identified eight main PANSS symptoms to serve as the basis for defining symptomatic remission in schizophrenia (Andreasen et al., 2005). For remission, a score of 3 or lower on the following items is required (PANSS items are placed between brackets): delusions (P1), unusual thought content (G9), hallucinatory behavior (P3), conceptual disorganization (P2), mannerisms/posturing (G5), blunted affect (N1), social withdrawal (N4) and lack of spontaneity (N6).

2.2.3. Degraded facial affect recognition (DFAR) task

The degraded facial affect recognition task (van 't Wout et al., 2004) uses photographs of faces of four different actors (two females and two males) representing four emotions: angry, fearful, happy, and neutral. The task consists of 64 trails with 16 face presentations in each emotion category. In order to increase the difficulty of the task, the emotions were shown with 75% intensity. Subjects were asked to indicate the emotional expression of each face with a button press. Outcome was the proportion of correctly recognized facial expressions (DFAR total), range: 0–100%. The DFAR is an experimental task, nevertheless the characteristics of the test are largely identical to other facial recognition tests used in the field (for an overview see Ventura et al., 2013). Previous studies specifically using the DFAR, have found valid results for differential EP performance between schizophrenia patients and healthy controls (van 't Wout et al., 2004), as well as between schizophrenia patients and their relatives (van 't Wout, et al., 2007). We evaluated test–retest reliability of the DFAR with data from the present study by calculating Pearson's correlation between DFAR performance at T1 and DFAR performance at T2, indicating robust test–retest reliability ($r = 0.58$, $p < 0.001$). In addition, because we had a healthy control group in our study, that did not improve significantly over 3 years' time (see paragraph 3.1), learning effects caused by repeated administration could be largely ruled out.

2.2.4. Wechsler Adult Intelligence Scale (WAIS III), short form

The digit symbol–coding (processing speed), arithmetic (working memory), information (verbal comprehension) and block design (reasoning and problem solving) subtests of the WAIS III were administered as an indication of general cognitive ability (Wechsler, 1997; Blyer et al., 2000). The sum of the four subtests yields a measure of estimated IQ.

2.3. Statistical analyses

First, the normality of the data was interpreted by visually examining the distribution curves. Data on all study variables was normally distributed, and there were no significant outliers. To assess differences between study completers and non-completers, baseline characteristics were compared between patients who completed the trial and study drop-outs using χ^2-tests or *t*-tests. Patients were divided into four groups, based on their symptomatic state of illness at baseline and after a three year follow-up: i.e.; remission at baseline–remission at follow-up (RR), remission at baseline–non-remission at follow-up (RN), non-remission at baseline–non-remission at follow-up (NN) and non-remission at baseline–remission at follow-up (NR). One-way ANOVAs and independent *t*-tests were used to compare demographic and clinical characteristics between both the schizophrenia patients and the healthy controls, as well as between the four patient groups (i.e.; RR, RN, NR, NN). For descriptive purposes, within-group improvement on EP performance was evaluated with paired-sample *t*-tests. Effect sizes (*d*) were calculated using Cohen's formula (Cohen, 1988).

Differences in EP performance may be subject to confounding by age, gender and IQ (Scholten et al., 2005; Dickinson et al., 2008). Therefore, we evaluated differences in EP performance between the four patient groups adjusted for gender and baseline assessments of age and IQ. However, because differences in IQ between patients and healthy controls may remove variance associated with group status (Dennis et al., 2009), we did not include IQ as a covariate in our analyses comparing schizophrenia patients to healthy controls. First, to investigate whether EP is trait dependent, an ANCOVA was conducted to compare performance at baseline between schizophrenia patients and healthy controls. In addition, to further investigate whether EP is trait dependent, an ANCOVA was conducted to compare performance at follow-up between schizophrenia patients that were in symptomatic remission at both time points (the RR group) and healthy controls. Second, to investigate whether EP performance is state dependent, a factorial repeated measures ANCOVA was conducted within the patient group, assessing the effects of 'group', 'time' and 'group × time'. This analysis was performed to compare performance over time between 1) the NR versus the RN group, because these groups made a reversal transition in state of illness over time, 2) the RR versus the RN group, because both groups were in remission at baseline; the RN group made a transition in state of illness over time while the RR group did not, and 3) the NN versus the NR group, because both groups were not in remission at baseline; the NR group made a transition in state of illness over time while the NN group did not. Only when significant interaction effects for EP as measured with the DFAR Total were revealed, post-hoc analyses for each emotion category independently were performed, i.e., for DFAR happy, neutral, angry and fearful. Exploratory correlational analyses examined the relationship between EP performance and symptoms.

Statistical analyses were performed using SPSS version 20.0. For our analysis to investigate trait dependency, the significance level was set at $0.05/2 = 0.025$, controlling for the total number of tests relevant to this specific research question. Similarly, the significance level of the test for state dependency was set at $0.05/3 = 0.017$, controlling for the total number of tests of this analysis. Differences with $p < 0.05$ were considered as differences at trend level.

3. Results

3.1. Sample characteristics

The current study incorporated a subset of participants from the full GROUP sample. This subsample included 521 schizophrenia patients and 312 healthy controls for whom assessments were available at baseline and follow-up. Table 1 summarizes the demographic and clinical characteristics of patients who completed the study (N = 521) and those who only completed the baseline assessment (N = 243).

Schizophrenia patients who completed both baseline and follow-up assessment had significantly higher IQ-scores, had lower symptom scores and were less likely to use atypical antipsychotics, as compared to patients who only completed the baseline assessment (Table 1). There was no difference in EP performance at baseline between drop-outs and completers (Table 1). The main reason for drop-out was inability to track the participant.

Table 2 shows the demographic and clinical characteristics of all groups. The distribution of age, gender and IQ was different in the patient group (N = 521) compared to the healthy control group (N = 312). Patients were younger, were more frequently male and had a significantly lower IQ (Table 2). The four patient groups i.e., RR (N = 195), RN (N = 54), NN (N = 151) and NR (N = 121), showed similar age of onset, illness duration and number of psychotic episodes, but showed significant differences in age, gender and IQ (Table 2). Paired *t*-tests revealed that EP performance changed over time for all groups, however this change was not necessarily significant HC: $t\ (310) = -1.70$, $p = 0.09$, $d = -9.09$; NN: $t\ (150) = -0.62$, $p = 0.54$, $d = -0.05$; NR: $t\ (120) = -1.61$, $p = 0.06$, $d = -0.11$; RN: $t\ (53) = -1.80$, $p = 0.04$, $d = 0.28$; RR: $t\ (194) = -3.17$, $p < 0.01$, $d = -0.23$.

Table 1
Demographic and clinical characteristics of schizophrenia patients who completed baseline and follow-up assessment (N = 521) and those who only completed baseline assessment (N = 243).

	Study completers (N = 521)	Study drop-outs (N = 243)	Statistics	*p*
	Mean ± SD	Mean ± SD		
Age (years)	27.34 ± 7.33	26.99 ± 7.18	t (481) = 0.63	0.53
Gender	77	79	χ^2 (1) = 0.11	0.74
M (%)	23	21		
F (%)				
IQ	96.82 ± 15.23	91.29 ± 15.84	t (418) = 4.39	<0.001
Illness duration (years)	4.29 ± 3.90	3.90 ± 3.59	t (468) = 1.33	0.19
Age of onset (years)	22.57 ± 6.88	22.67 ± 6.64	t (453) = −0.19	0.85
Episodes (N)	1.65 ± 0.95	1.85 ± 1.33	t (750) = −2.44	0.02
PANSS POS	12.21 ± 5.00	13.46 ± 5.16	t (404) = −3.03	0.003
PANSS NEG	13.29 ± 5.53	15.76 ± 6.44	t (728) = −5.19	<0.001
PANSS GEN	28.84 ± 8.51	32.29 ± 8.88	t (397) = −4.86	<0.001
Medication	86	81	χ^2 (3) = 26.78	0.03
Typical (%)	14	19		
Atypical (%)				
DFAR total	69.41 ± 9.79	68.40 ± 9.81	t (472) = 1.33	0.19

Abbreviations: M = males, F = females, episodes = number of psychotic episodes, PANSS = Positive and Negative Syndrome Scale, POS = positive, NEG = negative, GEN = general, Typical = typical antipsychotic, Atypical = atypical antipsychotic, DFAR total = total score on the degraded facial affect recognition task.

Table 2
Demographic and clinical characteristics of schizophrenia patients and healthy controls.

	HC (312)	PT (521)	Statistics *PT vs. HC*	p	RR (195)	RN (54)	NN (151)	NR (121)	Statistics *PT groups*	*p*
	Mean ± SD	Mean ± SD			Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD		
Age (y)	30.13 ± 10.73	27.34 ± 7.33	t (830) = -4.45	<0.001	27.57 ± 6.97	28.81 ± 7.86	27.83 ± 7.50	25.70 ± 7.24	F (4) = 6.56	<0.001
Gender										
M (%)	50	77	χ^2 (1) = 119.62	<0.001	69	78	85	81	χ^2 (1) = 30.59	<0.001
F (%)	50	23			31	22	15	19		
IQ	111.70 ± 15.61	96.82 ± 15.23	t (634) = -13.32	<0.001	100.26 ± 14.28	95.77 ± 14.71	93.55 ± 15.85	95.67 ± 15.29	F (4) = 49.39	<0.001
Illness duration (y)	-	4.29 ± 3.90	-	-	4.33 ± 3.74	4.61 ± 3.37	4.75 ± 3.97	3.86 ± 4.62	F (4) = 1.23	0.30
Age of onset (y)	-	22.57 ± 6.88	-	-	22.55 ± 6.52	23.62 ± 6.75	22.93 ± 6.93	21.27 ± 6.31	F (4) = 2.19	0.09
Episodes (N)	-	1.65 ± 0.95	-	-	1.60 ± 0.82	1.68 ± 0.91	1.74 ± 1.10	1.55 ± 0.93	χ^2 (3) = 30.59	0.21
PANSS POS										
Baseline		12.21 ± 5.00			9.17 ± 2.54	9.62 ± 2.44	15.96 ± 5.20	13.68 ± 4.88	F (4) = 88.50	<0.001
Follow-up		10.87 ± 4.40			8.48 ± 2.11	13.06 ± 4.69	14.64 ± 4.94	9.10 ± 2.22		
PANSS NEG										
Baseline		13.29 ± 5.53			9.61 ± 3.00	10.68 ± 3.08	16.97 ± 5.62	15.99 ± 5.04	F (4) = 96.51	<0.001
Follow-up		11.60 ± 5.02			8.91 ± 2.45	14.46 ± 6.19	15.40 ± 5.63	10.05 ± 2.80		
PANSS GEN										
Baseline	-	28.84 ± 8.51	-	-	23.35 ± 5.17	25.31 ± 5.59	34.88 ± 8.19	31.88 ± 7.97	F (4) = 90.47	<0.001
Follow-up		25.32 ± 7.50			21.45 ± 5.07	30.24 ± 8.65	31.04 ± 7.29	22.80 ± 4.61		
Remission										
Baseline					0	0	2.35 ± 1.38	1.95 ± 1.11	F(1,268)=10.85	0.001
Follow-up						1.65 ± 0.84	2.13 ± 1.30	0	F (1,199)=6.08	0.02
DFAR TOT	73.55 ± 9.14	69.41 ± 9.79			70.30 ± 9.39	70.60 ± 9.04	68.16 ± 10.31	69.01 ± 10.00		
Baseline										
Follow-up	74.34 ± 9.24	70.34 ± 9.72			72.20 ± 9.28	68.08 ± 8.44	68.69 ± 10.40	70.39 ± 9.62		
Medication										
Typical (%)	-	86	-	-	88	91	81	87	χ^2 (3) = 2.85	0.42
Atypical (%)	-	14			10	9	15	10		
SZ subtype (%)										
Disorganized					4	4	2	4		
Catatonic					1	-	1	-		
Paranoid					45	60	63	45		
Undiff.					6	2	10	10		
Residual					1	4	3	7		

Abbreviations: HC = healthy controls, PT = schizophrenia patients, RR = schizophrenia patients in remission at baseline and in remission at follow-up, RN = schizophrenia patients in remission at baseline and in non-remission at follow-up, NN = schizophrenia patients in non-remission at baseline and in non-remission at follow-up, NR = schizophrenia patients in non-remission at baseline and in remission at follow-up, M = males, F = females, Episodes = number of psychotic episodes, PANSS = Positive and Negative Syndrome Scale, POS = positive, NEG = negative, GEN = general, Remission = number of PANSS remission tool items, i.e., delusions (P1), unusual thought content (G9), hallucinatory behaviour (P3), conceptual disorganization (P2), mannerisms/posturing (G5), blunted affect (N1), social withdrawal (N4) and lack of spontaneity (N6), with a score higher than 3, DFAR TOT = total score on the degraded facial affect recognition task, Typical = typical antipsychotic, Atypical = atypical antipsychotic, SZ subtype = subtypes of schizophrenia, Undiff. = Undifferentiated subtype.

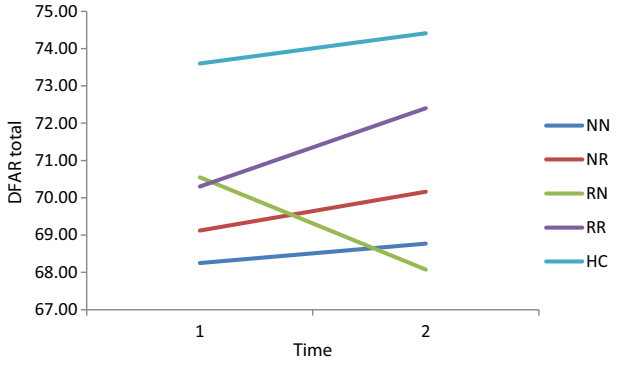

Fig. 1. Title: DFAR total performance of schizophrenia patients and healthy control at baseline and follow-up. Description: The graph presents relatively poor DFAR total performance in schizophrenia patients compared to healthy controls. Furthermore, the graph shows that DFAR total performance in schizophrenia patients is not stable over time and is associated with the patients' state of illness, i.e., symptomatic remission or non-remission. Abbreviations: DFAR total = total score (%) on the degraded facial affect recognition task, HC = healthy controls, RR = schizophrenia patients in remission at baseline and in remission at follow-up, RN = schizophrenia patients in remission at baseline and in non-remission at follow-up, NN = schizophrenia patients in non-remission at baseline and in non-remission at follow-up, NR = schizophrenia patients in non-remission at baseline and in remission at follow-up.

3.2. EP performance between schizophrenia patients and healthy controls

An ANCOVA was used to analyze differences between the patient group and the healthy control group on EP performance at baseline, as measured with the DFAR. After controlling for age and gender, a significant difference between both groups was found, $F(3,828) = 25.70$, $p < 0.001$. The patient group performed worse on EP as compared to the healthy control group (Table 2). The ANCOVA that was used to compare schizophrenia patients that were in symptomatic remission at both time points (the RR group) and the healthy control group, revealed a significant difference between the two groups on EP performance at follow-up $F(3,502) = 15.60$, $p < 0.001$ (Table 2, Fig. 1).

3.3. EP performance between patient groups over time

To investigate whether EP is state dependent, we used factorial repeated measures ANCOVAs, with age, gender and IQ as covariates. We performed the following comparisons on EP performance over time; 1) NR vs. RN, 2) RR vs. RN and 3) NN vs. NR. A sensitivity analysis was performed to test whether excluding IQ as a covariate would have an impact on the results. The main findings did not change.

3.3.1. EP performance of NR versus RN over time

An interaction effect of time × group on DFAR total score on trend level was found, $F(1,161) = 4.20$, $p = 0.04$ (Fig. 1). The NR group showed an improvement on EP performance over time whereas the RN group showed a decrease in EP performance over time. No main effect of group or time was found.

3.3.2. EP performance of RR versus RN over time

A significant interaction effect of time × group on DFAR total score was found, $F(1,235) = 11.36$, $p = 0.001$ (Fig. 1). The RR group showed an increase in EP performance over time, whereas the RN group showed a decrease in EP performance over time. No main effect of group or time was found. Since a significant interaction effect was revealed, we conducted post-hoc analyses per emotion category, revealing that the interaction was only significant for angry face recognition ($F(1,237) = 7.65$, $p = 0.006$).

3.3.3. EP performance of NN versus NR over time

No significant interaction effect or significant main effects were found. The NN and the NR group did not change differently over time.

3.4. Correlational analysis

Pearson's correlations were calculated between EP performance (i.e., DFAR total) and symptoms (i.e., PANSS positive, negative and general scale) at baseline. For the positive and negative scales, significant correlations were found, however these correlations were very weak ($r \approx 0.1$). For the general scale no significant correlations with EP performance were found. This implies that relatedness of EP and symptoms was not of major concern for a correct interpretation of the interaction analysis.

4. Discussion

In a longitudinal study in a large sample of schizophrenia patients we investigated whether EP deficits in schizophrenia are present primarily during psychosis (i.e., state dependent) or associated with the disorder (i.e., trait dependent). We compared EP performance between schizophrenia patients across different stages of illness, i.e. remission versus non-remission, at baseline and after a three year follow-up. We took general cognition into account and applied a conservative correction for multiple comparisons to our analyses. Besides being trait dependent, we show that EP performance in schizophrenia patients is also significantly associated with severity of symptoms.

First, in line with previous evidence (Marwick and Hall, 2008; Penn et al., 2008; Chan et al., 2010; Kohler et al., 2010), we found relatively poor EP performance in schizophrenia patients compared to healthy controls at baseline. In addition, we now show that even patients that appear to be rather stable in remission (RR), perform worse than healthy controls on EP at a three year follow-up. These findings support a trait dependent view on EP deficits in schizophrenia patients and, therefore, EP impairment may be a useful target for genetic studies in schizophrenia. However, in support of a more state dependent view of the illness, we demonstrate that patients who stay in remission for three years (RR) improve on EP performance over time, whereas patients, who return to a non-remission state after three years (RN), perform worse at follow-up compared to baseline. These findings are in agreement with previous reports showing that EP performance is significantly related to symptom severity (Kohler et al., 2000; Marwick and Hall, 2008; Laroi et al., 2010; Tseng et al., 2013) and with a previous study demonstrating that remitted patients outperform acutely ill patients on EP (Edwards et al., 2002). Analyses per emotion category indicated that the overall effect was mainly driven by differences in the recognition of angry emotion. This finding is in line with previous reports on the disproportionate impairment in the identification of negative emotions (Edwards et al., 2001; van 't Wout et al., 2004; Bediou et al., 2005) and lends further support to emotion-specific processing deficits in schizophrenia. Third, we extend previous findings by showing that the patient group in remission at baseline and in non-remission at follow-up (RN) had a worse EP performance at follow-up compared to baseline, whereas the patient group in non-remission at baseline and in remission at follow-up (NR) improved on EP performance over time. Although this last interaction effect was just below statistical threshold after correction for multiple testing, together with the other results, our findings indicate that EP performance is state dependent, as depicted in Fig. 1.

In contrast to our above mentioned findings supporting a state dependent view on EP performance in schizophrenia, we failed to show a difference in EP performance over time between the group in non-remission at baseline and in non-remission at follow-up (NN) and the group in non-remission at baseline and in remission at follow-up (NR). This might be explained by the relatively high baseline EP

performance of the NR group, possibly enabling less dramatic improvement on EP over time (Fig. 1). Besides the difference in EP performance between the NN and the NR group at baseline, the NR group also had less severe positive symptoms compared to the NN group at this time point, as measured with the PANSS (Table 2). Possibly, part of the patients in the NR group was already almost in remission at baseline, which could explain the lack of state dependent EP performance of the NR group.

Our results are in contrast with studies showing that EP is a stable deficit in schizophrenia (Pinkham et al., 2007; Green et al., 2012). A possible explanation for this discrepancy might be that in previous studies "state of illness", i.e. remission vs. non-remission, was not taken into account. Considering symptomatic remission status at either assessment, we showed that remission status was related to higher EP scores compared to patients who are not in remission.

The results show that EP performance in schizophrenia is not stable over time and relies heavily on the patients' state of illness, i.e. symptomatic remission or non-remission. This might be related to abnormal amygdala activation during social cognitive processing in symptomatic schizophrenia patients (Aleman and Kahn, 2005; Pessoa, 2008). EP appears to be related to abnormal activity of the amygdala (Li et al., 2010), and at the same time amygdala processing is found to be influenced by schizophrenia symptoms (Marwick and Hall, 2008). Therefore, altered amygdala activation might be the underlying mechanism of state dependent EP performance, i.e., a decrease in EP performance when schizophrenia symptoms are more severe and an increase in EP performance when schizophrenia symptoms are less severe. Further support for this explanation is provided by recent PET studies in symptomatic schizophrenia patients showing abnormalities in dopaminergic signaling in the amygdala that result in social cognitive deficits (Rosenfeld et al., 2011).

The findings of this study should be interpreted in view of the following limitations. First, the high percentage of subjects who did not receive the follow-up assessment may limit the generalizability of the results. However, the lack of a baseline difference in EP performance between drop-outs and completers is reassuring and may imply that the results apply more broadly to patients with schizophrenia. Second, there were only two measurement points in this study, i.e., baseline and three year follow-up. In between measurements, symptoms were not registered, so it is unclear if patients switched from remission to non-remission or vice versa during this period of time. For further research, we suggest a replication of our study with more measurement points, in order to establish a more valid monitoring of symptomatic state of illness. Third, we did not consider possible confounding effects of medication. Nevertheless, all patients included in the current study were medicated (Table 1) and there was no difference between the four patient groups with respect to type of antipsychotic medication used, i.e., atypical or typical antipsychotic medication (Table 2). Moreover, previous trials comparing different antipsychotic medications in relation to social cognitive performance, reported no difference among treatment groups (Harvey et al., 2006; Sergi et al., 2007; Penn et al., 2009; Maat et al., 2014). Fourth, although it has been suggested that depressive symptoms are associated with EP performance in schizophrenia (Brennan et al., 2014), we did not control for this in our analyses. However, we conducted a correlational analysis between PANSS item G6, i.e., the PANSS item measuring depressive symptoms, and EP. The results of this analysis showed a small and non-significant correlation between PANSS item G6 and EP (Pearson's $r = 0.03$, $p = 0.34$). Therefore, it is unlikely that a difference in depressive symptoms between the subgroups, explains our results.

In summary, this is the first large longitudinal study investigating whether EP performance is state dependent in schizophrenia. Our study shows that EP performance in schizophrenia is trait dependent, but also relies significantly on the symptomatic state of illness, i.e. remission or non-remission. Stage of illness in schizophrenia may contribute to social cognitive deficits. Therefore improving the symptomatic course of schizophrenia may impact on social cognitive ability and social functioning.

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Contributors

AM and SM managed the literature searches. AM, SM, WC and ED undertook the statistical analysis. AM and SM wrote the complete first draft of the manuscript. All authors made meaningful contributions to the writing. All authors contributed to and have approved the final manuscript.

Conflict of interest

There are no conflicts of interest.

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