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SOCIAL COGNITION IN SCHIZOPHRENIA

Sociale cognitie bij schizofrenie

(met een samenvatting in het Nederlands)

Proefschrift

ter verkrijging van de graad van doctor aan de Universiteit Utrecht op gezag van de rector magnificus, prof.dr. G.J. van der Zwaan, ingevolge het besluit van het college voor promoties in het openbaar te verdedigen op dinsdag 30 september 2014 des middags te 12.45 uur

door

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Geboren op 21 december 1981 te Gouda

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TABLE OF CONTENTS

01

INTRODUCTION

1. INTRODUCTION

The term mental illness represents a wide range of different disorders. What unites these different conditions is that they all affect a person's emotions, thoughts and behavior. One of the most disabling psychiatric illnesses is schizophrenia (Addington and Addington, 2008). This disease is characterized among others by impairment of social cognition (Penn *et al*., 2008; Bora *et al*., 2009; Kohler *et al*., 2010). Social cognition has been defined as "a set of related processes applied to the recognition, understanding, accurate processing, and effective use of social cues and information in social situations" (Penn *et al*., 1997). Social cognitive deficits are associated with impaired social functioning (Irani *et al*., 2012). The research presented in this thesis investigates social cognition in schizophrenia in relation to 1) the symptomatology of the disease, 2) structural abnormalities of for social cognition relevant brain structures, and 3) quality of life (QOL) of the patients and anti-psychotic treatment.

1.1 SCHIZOPHRENIA

Schizophrenia is a psychiatric disorder with a life-time prevalence of 0.3%-0.66% (McGrath *et al*., 2008). The illness becomes chronic in most patients and causes immense human and economic costs (Van Os and Kapur, 2009).

Symptomatology

Schizophrenia is a complex syndrome, incorporating a wide range of symptoms that may occur at certain stages of the disease. The core symptoms can largely be divided into positive and negative symptoms (APA, 2012). Positive symptoms reflect an excess of normal function as compared to healthy subjects, i.e., hallucinations, delusions, catatonic behavior and thought disorder. The positive symptoms often have a fluctuating course, with periods of florid psychosis alternating with periods of remission. Negative symptoms, which are generally more chronic in nature, reflect the absence of normal function and include lack of initiative, lack of energy, social withdrawal, emotional flattening and poverty of speech.

Besides positive and negative symptoms, neurocognitive impairments, such as attention and memory problems or difficulties with planning and organization, are also considered a core component of schizophrenia. On average, neurocognitive impairment is severe to moderately severe compared to healthy controls, and almost all patients with schizophrenia demonstrate neurocognitive decrements compared to their expected level if they had not developed the illness (Keefe *et al*., 2008). Although, currently, neurocognitive impairment is not part of the official disease classification of schizophrenia, many psychiatrists have argued for its inclusion in the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-V), that was released in 2012 (Davidson, 2008; Keefe, 2008). Recently, research efforts have started to explore also the 'affective' or 'emotional' area of cognition, or so-called 'social cognition' (Green *et al*, 2008), in schizophrenia.

Antipsychotic drugs constitute the main treatment of schizophrenia. These drugs are effective against the positive symptoms of the disease. However, their efficacy against its negative and cognitive symptoms is disappointing (Leucht *et al*., 2009).

Etiology

Whereas the etiology of schizophrenia remains largely undetermined, an interaction between genetic and environmental factors is thought to play a role in this regard (Van Os and Kapur, 2009). The genetic component in schizophrenia is well documented to be substantial. Schizophrenia occurs at a higher rate in families, e.g., first degree relatives of affected people have a ten times higher risk of developing schizophrenia than individuals in the general population. Twin studies show a concordance rate of up to 50% for monozygotic twins and 10% for dizygotic twins (Tsuang *et al*., 2001). While the exact mechanisms are unknown, the overall incidence of schizophrenia is also attributable to certain environmental factors, which include pre-and perinatal complications, daily life stressors, and factors such as minority status, urbanicity, and cannabis use (Cahn *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 a 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 proper trait marker 1) distinguishes patients from healthy individuals, 2) is heritable, and 3) is state independent. Research in twins and first-degree relatives of patients suggests that genes predisposing to schizophrenia affect certain traits of the illness, e.g., structural brain abnormalities (Boos *et al*., 2007) and neurocognitive impairments (Toulopoulo *et al*., 2007).

The diagnosis of schizophrenia is associated with demonstrable alterations in brain structure and changes in dopamine neurotransmission (Van Os and Kapur, 2009). Structural brain imaging studies have consistently shown a decrease in gray matter volume and ventricular enlargement in schizophrenia patients (Haijma *et al*., 2013; Vita *et al*., 2006). Neurochemical imaging studies are consistent in showing that schizophrenia, in its acute psychotic state, is associated with an increase in dopamine synthesis, dopamine release, and synaptic dopamine concentrations (Guillin *et al*., 2007). Functional imaging studies show abnormal activity in the brains of schizophrenia patients in response to certain cognitive tasks (Fusar-Poli *et al*., 2007). It has been suggested that structural and neurochemical abnormalities may underlie these alterations in functional activity (van Os and Kapur, 2009). How altered brain function results in the actual experiences, such as paranoia or hearing voices, reported by schizophrenia patients remains unclear.

1.2. SOCIAL COGNITION

The study of social cognition examines the cognitive processing of social information (Pinkham *et al*., 2003). Social cognition has been defined as "a set of related processes applied to the recognition, understanding, accurate processing, and effective use of social cues and information in social situations (Penn *et al*., 1997)." The ability to correctly perceive and interpret a range of emotions is required to decode social signs and give them meaning. This social cognitive skill is known as emotion recognition (Penn *et al*., 1997). Another important social cognitive skill, 'theory of mind' (ToM), is the ability to take the perspective of another person and to make attributions about another person's intentions (Penn *et al*., 1997). Both emotion recognition and ToM are required for smooth social interactions and enable humans to function in the social community (Frith *et al*., 2008). In healthy individuals social cognition has been extensively studied using primarily functional imaging, and a network of brain regions subserving social cognition has been identified (Adolphs *et al*., 2009). In short, the processing of facial expressions depends critically on the amygdala, whereas in mentalizing tasks, such as ToM, the frontal cortices are critical. The temporal lobe, including the temporal poles, posterior superior temporal sulcus and temporal parietal junction, has also been associated with social cognition, specifically with social reward processing.

Social cognition in schizophrenia

Investigations of social cognition in schizophrenia reveal consistent impairments compared to healthy controls, particularly in emotion recognition and ToM (Bora *et al*., 2009; Kohler *et al*., 2010). Emotion recognition, i.e., the ability to infer emotional information from facial expressions, and ToM, i.e., the ability to infer the intentions and beliefs of other individuals, are for schizophrenia important domains of social cognition, because they appear to be valid predictors of social functioning in this disorder (Couture *et al*., 2006; Fett *et al*., 2011). Moreover, it has been argued that impairments in emotion recognition and ToM may trump the value of neurocognition

and symptoms in explaining outcome in schizophrenia (Pijnenborg *et al*., 2009; Fett *et al*., 2011). Therefore, social cognition may serve as an important treatment target for improving daily life of schizophrenia patients. Unfortunately, social cognitive abilities appear to be hardly influenced by the currently available antipsychotic medications (Harvey *et al*., 2006; Penn *et al*., 2009; Sergi *et al*., 2007). However, not all recently released anti-psychotics have been investigated in this respect.

Social cognition in schizophrenia: state or trait?

Recent research has suggested that social cognition could possibly serve as a trait marker for schizophrenia. Numerous studies have shown deficits in social cognitive performance in schizophrenia patients compared to healthy controls (Penn *et al*., 2008). Cross-sectional studies showed social cognitive deficits to be present at first onset of schizophrenia and to be stable over the course of illness (Green *et al*., 2012; Pinkham *et al*., 2007). In addition, some studies found social cognitive deficits in unaffected siblings of schizophrenia patients (de Achaval *et al*., 2010; Eack *et al*., 2009). However, the results of reports on social cognitive deficits in unaffected siblings of schizophrenia patients are inconsistent and the presence of social cognitive deficits at a prodromal stage of the illness remains questionable (Kee *et al*., 2004; Pinkham *et al*., 2007). Moreover, social cognitive performance might change over time according to an increase or decrease in clinical symptoms, i.e., is state dependent, which may imply that individuals in remission outperform individuals in an acute phase of the disorder (Edwards *et al*., 2002). Taken together, it remains unclear whether social cognitive impairment in schizophrenia should be considered a trait or a state characteristic.

The disrupted social brain in schizophrenia

Functional neuroimaging studies in schizophrenia patients have consistently demonstrated abnormal activity of the amygdala during processing of facial emotions compared to healthy controls (Aleman and Kahn, 2005; Pessoa, 2008). In addition, abnormal activation of the prefrontal cortex (PFC) has been shown in relation to

impaired performance on ToM-tasks (Hill *et al*., 2004; Dollfus *et al*., 2008). Only few studies have investigated the relationship between structural brain abnormalities and social cognitive deficits in schizophrenia. It may be hypothesized that structural alterations in the same regions, i.e., the amygdala and/or prefrontal cortex, are associated with the functional brain abnormalities observed in schizophrenia patients during the performance of social cognitive tasks.

1.3. AIMS AND OUTLINE

The objective of the research presented in this thesis was threefold. First (Part I, Chapters 2 and 3), we investigated whether social cognitive impairment in schizophrenia should be considered a trait and/or a state characteristic. Second (Part II, Chapter 4), structural brain correlates of social cognitive impairments in schizophrenia were examined. Third (Part III, Chapters 5 and 6), the impact of social cognitive deficits on quality of life (QOL) as well as the effect of anti-psychotic medication on social cognition in schizophrenia were explored.

Part I: Social cognition and symptomatology

Chapter 2 uses a genetically sensitive cross-trait cross-sibling design in a large sample of schizophrenia patients, their healthy siblings, and healthy control subjects that were recruited within the Genetic Risk and Outcome in Psychosis (GROUP) study, to investigate whether the overlap between symptoms and social cognitive deficits that is observed in patients is due to shared familial factors. The GROUP study is a large ongoing cohort study that consists of 1120 patients with non-affective psychosis, 1057 of their healthy siblings, and 590 control subjects. The study described in Chapter 3 uses the same cohort of schizophrenia patients and examines longitudinally whether social cognitive impairments are either present primarily during psychosis (i.e., state dependent) or form an integral part of the disorder (i.e., trait dependent), or are both state and trait dependent.

Part II: The disrupted social brain

The study described in Chapter 4 investigates whether social cognitive impairment in patients with schizophrenia is associated with structural abnormalities of the amygdala and/or the PFC. We use an automated parcellation method to examine amygdala and PFC gray matter volumes and their association with facial emotion recognition and ToM skills in a sample of patients and healthy controls recruited from the GROUP study.

Part III: Social cognition, quality of life and anti-psychotic treatment

Schizophrenia patients have a worse functional outcome as compared to healthy individuals, and also a poorer QOL (Ruggeri *et al.*, 2005). The study described in Chapter 5 investigates the association between social cognition and QOL in a large cross-sectional sample of the GROUP study. In Chapter 6 we test the hypothesis that treatment with aripiprazole, because of the unique action of this drug as a partial dopamine agonist in brain circuits underlying social cognition, would lead to a significant improvement in social cognitive processing compared to other antipsychotics. Therefore, we compare the effects of aripiprazole and the frequently prescribed atypical antipsychotic agent risperidone in an 8-week, randomized, multicenter, open-label study of 80 schizophrenia patients.

Chapter 7 provides a general discussion of the findings from Chapters 2 to 6.

REFERENCES

de Achával, D., Costanzo, E.Y., Villarreal, M., Jáuregui, I.O., Chiodi, A., Castro, M.N., Fahrer, R.D., Leiguarda, R.C., Chu, E.M., Guinjoan, S.M., 2010. Emotion processing and theory of mind in schizophrenia patients and their unaffected first-degree relatives. Neuropsychologia 48(5): p. 1209-1215.

Addington, J., Addington, D., 2008. Social and cognitive functioning in psychosis. Schizophr. Res. 99 (1-3), 176-81.

Adolphs, R., 2009. The social brain: neural basis of social knowledge. Annual Review of Psychology 60, 693–716.

Aleman, A., Kahn, R.S., 2005. Strange feelings: do amygdala abnormalities dysregulate the emotional brain in schizophrenia? Progress in Neurobiology 77 (5), 283-98.

American Psychiatric Association, 2012. Diagnostic and Statistical Manual of Mental Disorders, fifth ed., American Psychiatric Association, Washington, DC.

Boos, H.B., Aleman, A., Cahn, W., Hulshoff Pol, H., Kahn, R.S., 2007. Brain volumes in relatives of patients with schizophrenia: a meta-analysis. Arch Gen Psychiatry 64: 297-304.

Bora, E., Yucel, M., Pantelis, C., 2009. Theory of mind impairment in schizophrenia: meta-analysis. Schizophrenia Research 109, 1–9.

Cahn, W., Krabbendam, L., Myin-Germeys, I., Bruggeman, R., de Haan, L., 2011. Handboek schizofrenie. De Tijdstroom, Utrecht, the Netherlands.

Chen Y., Norton, D., McBain, R., 2009. Trait and State Markers of Schizophrenia in Visual Processing, in: Ritsner M.S. (Ed.), The Handbook of Neuropsychiatric Biomarkers, Endophenotypes and Genes. Springer Science + Business Media BV., pp. 211-220.

Couture, S.M., Penn, D.L., Roberts, D.L., 2006. The functional significance of social cognition in schizophrenia: a review. Schizophrenia Bulletin 32 (S1), S44–S63.

Davidson, M., 2008. Reflections on the inclusion of cognitive impairment in the diagnostic criteria for schizophrenia. World Psychiatry 7(1): 33–34.

Dollfus, S., Razafimandimby, A., Maiza, O., Lebain, P., Brazo, P., Beaucousin, V., Lecardeur, L., Delamillieure, P., Mazoyer, B., Tzourio-Mazoyer, N., 2008. Functional deficit in the medial prefrontal cortex during a language comprehension task in patients with schizophrenia. Schizophrenia Research 99 (1–3), 304–311.

Eack, S.M., Mermon, D.E., Montrose, D.M., Miewald, J., Gur, R.E., Gur, R.C., Sweeney, J.A., Keshavan, M.S., 2010. Social cognition deficits among individuals at familial high risk for schizophrenia. Schizophrenia Bulletin. 36(6): p. 1081-1088.

Edwards, J., Jackson, H.J., Pattison, P.E., 2002. Emotion recognition via facial expression and affective prosody in schizophrenia: a methodological review. Clin. Psychol. Rev. 22, 789 – 832.

Fett, A.K., Viechtbauer, W., Dominguez, M.D., Penn, D.L., van Os, J., Krabbendam, L., 2011. The relationship between neurocognition and social cognition with functional outcomes in schizophrenia: a meta-analysis. Neurosci. Biobehav. Rev. 35 (3), 573–588.

Frith, C.D., 2008. Social cognition. Philosophical Transactions of the Royal Society B: Biological Sciences. 363: p. 2033-2039.

Fusar-Poli, P., Perez, J., Broome, M., Borgwardt, S., Placentin, A., Caverzasi, E., Cortesi, M., Veggiotti, P., Politi, P., Barale, F., McGuire, P., 2007. Neurofunctional correlates of vulnerability to psychosis; a systematic review and meta-analysis. Neurosci. Biobehav Rev 31: 465-84.

Gershon, E.S., Alliey-Rodriguez, N., Liu, C., 2011. After GWAS: searching for genetic risk for schizophrenia and bipolar disorder. Am J Psychiatry. 168(3):253-6.

Green, M.F., Leitman, D.I., 2008. Social cognition in schizophrenia. Schizophr Bull. 34, 670-2.

Green, M.F., Bearden, C.E., Cannon, T.D., Fiske, A.P., Hellemann, G.S., Horan, W.P., Kee, K., Kern, R.S., Lee, J., Sergi, M.J., Subotnik, K.L., Sugar, C.A., Ventura, J., Yee, C.M., Nuechterlein, K.H., 2012. Social cognition in schizophrenia, part 1: performance across phase of illness. Schizophr. Bull. 38, 845 – 864.

Guillin, O., Abi-Dargham, A., Laruelle, M., 2007. Neurobiology of dopamine in schizophrenia. Int Rev Neurobiol; 78: 1-39.

Haijma, S.V., Van Haren, N., Cahn, W., Koolschijn, C.P., Hulshoff Pol, H.E., Kahn, R.S., 2013. Brain Volumes in Schizophrenia: A Meta-Analysis in Over 18 000 Subjects. Schizophrenia Bulletin 39 (5), 1129–1138.

Harvey, P.D., Patterson, T.L., Potter, L.S., Zhong, K., Brecher, M., 2006. Improvement in social competence with short-term atypical antipsychotic treatment: a randomized, double-blind comparison of quetiapine versus risperidone for social competence, social cognition, and neuropsychological functioning. Am. J. Psychiatry. 163 (11), 1918-1925.

Hill, K., Mann, L., Laws, K.R., Stephenson, C.M., Nimmo-Smith, I., McKenna, P.J., 2004. Hypofrontality in schizophrenia: a metaanalysis of functional imaging studies. Acta psychiatrica Scandinavica 110, 243–256.

Irani, F., Seligman, S., Kamath, V., Kohler, C., Gur, R.C., 2012. A meta-analysis of emotion perception and functional outcomes in schizophrenia. Schizophr Res. 137(1-3):203-11.

Kee, K.S., Horan, W.P., Mintz, J., Green, M.F., 2004. Do siblings of schizophrenia patients
demonstrate affect perception deficits? Schizophr. Res. 67, 84 – 94.

Keefe, R.S., 2008. Should cognitive impairment be included in the diagnostic criteria for schizophrenia? World Psychiatry. 7(1):22-8.

Kohler CG, Walker JB, Martin EA, Healey KM, Moberg PJ, 2010. Facial emotion perception in schizophrenia: a meta-analytic review. Schizophrenia Bulletin 36, 1009–1019.

Leucht, S., Corves, C., Arbter, D., Engel, R.R., Davis, J.M., 2009. Second-generation versus first-generation anti-psychotic drugs for schizophrenia: a meta-analysis. Lancet 373: 31-41.

McGrath, J., Saha, S., Chant, D., Welham, J., 2008. Schizophrenia: a concise overview of incidence, prevalence, and mortality. Epidemiol Rev. 30:67-76.

Penn, D.L., Corrigan, P.W., Bentall, R.P., Racenstein, J.M., Newman, L., 1997. Social cognition in schizophrenia. Psychol. Bull. 121 (1), 114-132.

Penn D.L., Lawrence, L.S., Roberts, D.L., 2008. Social cognition in schizophrenia: an overview. Schiz Bull 34 (3): 408-411.

Penn, D.L., Keefe, R.S., Davis, S.M., Meyer, P.S., Perkins, D.O., Losardo, D., Lieberman, J.A., 2009. The effects of antipsychotic medications on emotion perception in patients with chronic schizophrenia in the CATIE trial. Schizophr. Res. 115 (1), 17-23.

Pessoa, L., 2008. On the relationship between emotion and cognition. Nature reviews. Neuroscience. 9, 148–158.

Pijnenborg, G.H., Withaar, F.K., Evans, J.J., van den Bosch, R.J., Timmerman, M.E., Brouwer, W.H., 2009. The predictive value of measures of social cognition for community functioning in schizophrenia: implications for neuropsychological assessment. Journal of the International Neuropsychological Society 15 (2), 239-47.

Pinkham, A.E., Lieberman, J., 2003. Implications for the neural basis of social cognition for the study of schizophrenia. American Journal of Psychiatry 160 (5), 815-24.

Pinkham, A.E., Penn, D.L., Perkins, D.O., Graham, K.A., Siegel, M., 2007. Emotion perception and social skill over the course of psychosis: a comparison of individuals at risk for psychosis and individuals with early and chronic schizophrenia. Cogn. Neuropsych. 12 (3), 198 – 212.

Ruggeri, M., Nose, M. Bonnetto, C., Cristafalo, D., Lasalvia, A., Salvi, G., Stefani, B., Malchiodi, F., Tansella, M., 2005. Changes and predictors of change in objective and subjective quality of life: multiwave follow-up study in community psychiatric practice. Br. J. Psychiatry 187, 121-130.

Sergi, M.J., Green, M.F., Widmark, C., Reist, C., Erhart, S., Braff, D.L., Kee, K.S., Marder, S.R., Mintz, J., 2007. Social cognition [corrected] and neurocognition: effects of risperidone, olanzapine, and haloperidol. Am. J. Psychiatry. 164 (10), 1585-1592.

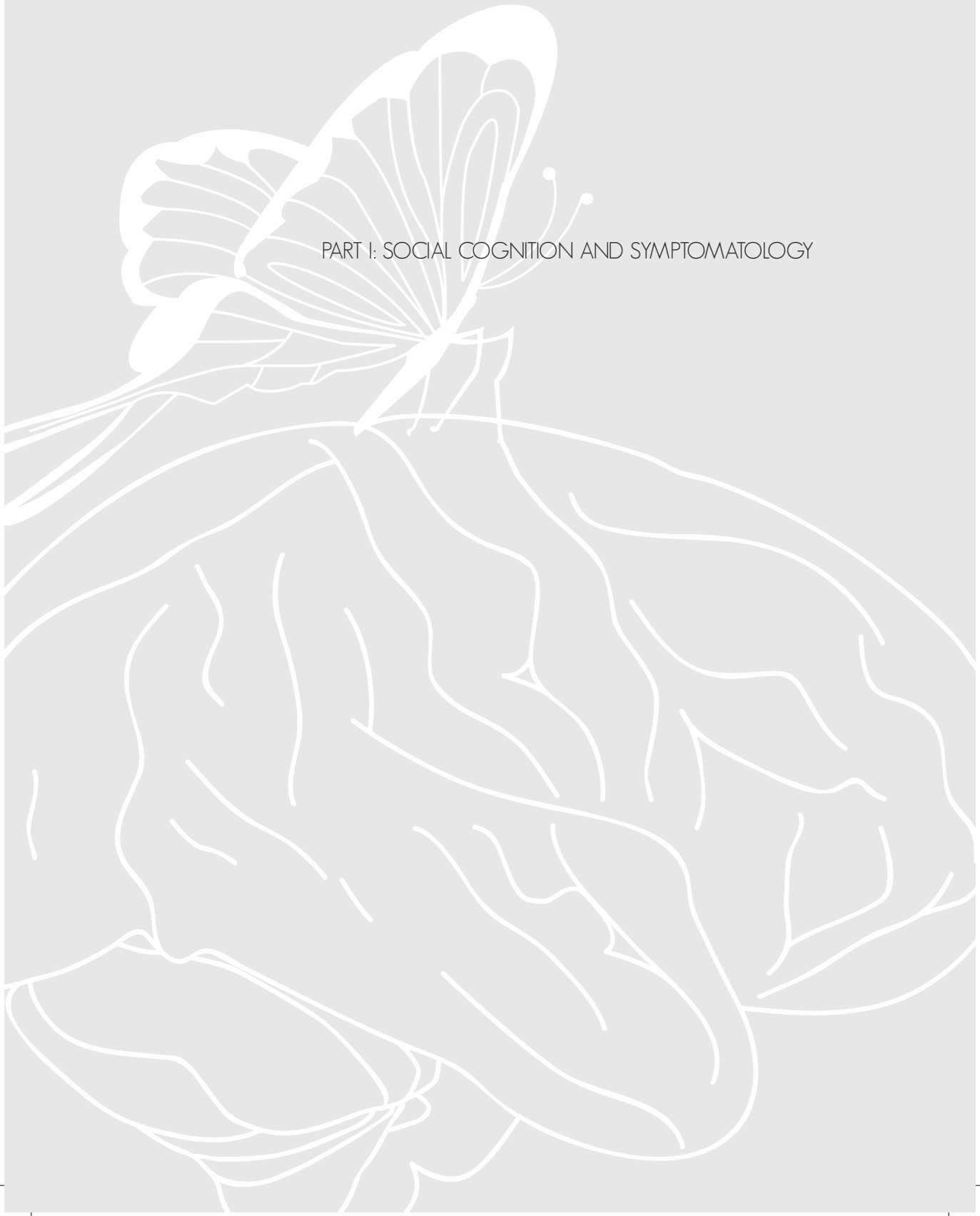
Toulopoulou, T., Picchioni, M., Rijsdijk, F., Hua-Hall, M., Ettinger, U., Sham, P., Murray, R., 2007. Substantial genetic overlap between neurocognition and schizophrenia: genetic modeling in twin samples. Arch Gen Psychiatry. 64(12):1348-55.

Tsuang, M.T., Stone ,W.S., Faraone, S.V., 2001. Genes, environment and schizophrenia. Br J Psychiatry Suppl. 40:s18-24.

Van Os, J. and Kapur, S., 2009. Schizophrenia. Lancet. 374 :635-45.

Vita, A., De Peri, L., Silenzi, C., Dieci, M., 2006. Brain morphology in first-episode schizophrenia: a meta-nalysis of quantitative magnetic resonance imaging studies. Schiz. Res. 82, 75-88.

PART I: SOCIAL COGNITION AND SYMPTOMATOLOGY



02

SOCIAL COGNITIVE IMPAIRMENTS AND PSYCHOTIC SYMPTOMS: WHAT IS THE NATURE OF THEIR ASSOCIATION?

Anne-Kathrin J. Fett, Arija Maat, GROUP Investigators (René S. Kahn, Don H. Linszen, Jim van Os, Durk Wiersma, Richard Bruggeman, Wiepke Cahn, Lieuwe de Haan, Lydia Krabbendam, Inez Myin-Germeys)

Schizophrenia Bulletin 2013; 39(1): 77-85

ABSTRACT

Social cognitive deficits are associated with psychotic symptoms, but the nature of this association remains unknown. This study uses a genetically sensitive cross-trait cross-sibling design to investigate the nature of the overlap between both phenotypes. A sample of 1032 patients, 1017 of their healthy siblings and 579 control subjects were recruited within the Dutch Genetic Risk and Outcome in Psychosis (GROUP) study. Participants completed a battery of cognitive tests, including two social cognitive tests on theory of mind (ToM) and emotion recognition. Within siblings, symptoms were assessed with the Structured Interview for Schizotypy-Revised. The Positive and Negative Syndrome Scale was used to assess patients' symptoms. Within patients social cognitive performance was consistently and significantly associated with disorganized and, to a lesser degree, with negative symptoms. Associations with positive symptoms were significant, but smaller. Suggestive of a shared aetiology, both social cognitive factors showed significant familial clustering. The associations between patients' ToM and subclinical symptoms in siblings were non-significant, suggesting that their overlap within patients is due to individual rather than shared familial factors. Indicative of a shared aetiology, familial co-variation was present between patients' emotion recognition ability and disorganized and, albeit to a lesser degree, positive but not negative subclinical symptoms in siblings.

KEYWORDS

Cross-sibling Design, Family Study, Schizophrenia, Social Cognition

1. INTRODUCTION

Schizophrenia is accompanied by significant functional impairment in different social cognitive domains (Bora *et al*., 2009; Edwards *et al*., 2002). The impairments are associated with psychotic symptoms (Doody *et al*., 1998; Marjoram *et al*., 2005; Shean *et al*., 2005). This association may reflect a shared aetiopathology with a possible genetic basis. Alternatively, both traits may be on a causal pathway such that psychotic symptoms are the consequence of impaired social cognition (or vice versa), or both traits may be secondary to another, possibly disease-related factor (e.g. general cognitive impairment). These explanations are not mutually exclusive, and the present study set out to investigate the evidence for a shared familiar aetiology. If symptoms and social cognition co-vary because of a similar familiar aetiology, social cognitive abnormalities could be useful intermediate phenotypes in the search for the genetic causes of the symptoms of psychosis.

There is some evidence in favour of a genetic aetiology of the social cognitive impairment in psychosis. For example, higher rates of social cognitive impairment have been reported in first-degree relatives as compared to the general population (de Achával *et al*., 2010; Addington *et al*., 2008; Anselmetti *et al*., 2009; Janssen *et al*., 2003; Vermissen *et al*., 2008). However, higher rates of subclinical symptoms in relatives and familial clustering of symptoms have also been reported (Cardno *et al*., 2001). There is evidence that in non-clinical individuals higher positive schizotypy is associated with worse ToM performance (Pickup *et al*., 2006). Other studies suggested that associations between social cognitive performance and symptoms are also present during prodromal states and remission of the illness (Eack *et al*., 2010; Langdon *et al*., 1999). Studies to date have not been able to rule out alternative explanations for the symptom cognition association, for example that the presence of social cognitive deficits is secondary to subclinical or residual psychotic experiences. Therefore, the current study applied a genetically sensitive cross-trait cross-sibling design to investigate the nature of the association between social

cognitive abnormalities and psychotic symptoms.

Social cognition is a multidimensional construct (Van Hooren *et al*., 2008) and the nature of the associations between symptoms and social cognition may differ across social cognitive domains (Penn *et al*., 2008). Here, we focused on two core domains of social cognition that are impaired in schizophrenia and have previously been suggested to play a role in the formation of psychotic symptoms: 1) theory of mind and 2) emotion processing (de Achával *et al*., 2010; Penn *et al*., 2008). We used a cross-trait cross-sibling design (see Figure 1) in a large sample of patients with non-affective psychosis, their unaffected siblings and healthy controls to investigate social cognitive impairment and psychotic symptoms and the nature of their association. First, the associations between the different social cognitive functions and symptom clusters were analysed within patients and their relatives to confirm the assumption of overlap between the two domains. Second, familial clustering of social cognitive functioning was investigated using within-trait cross-sibling analyses. Finally, we investigated all cross-trait cross-sibling associations between subclinical symptomatic expression in siblings and social cognitive functioning in patients. The presence of such associations suggests a common familial aetiology of both traits. Alternatively, finding symptom-cognition associations within affected individuals only suggests that the frequently reported overlap between symptoms and social cognitive deficits is due to individual (e.g. illness related) factors rather than shared familial aetiology.

2. METHOD

Procedure and sample

The data pertains to baseline measures of the ongoing longitudinal multicenter study 'Genetic Risk and Outcome in Psychosis' (GROUP). The sample was recruited in the Netherlands and Belgium. Participants with non-affective psychosis were identified via clinicians working in regional psychotic disorder mental health services. Family

members were recruited through participating patients. Healthy volunteers were recruited through random community mailings in the catchment area. The full GROUP sample consisted of 1120 patients with a non-affective psychotic disorder, 1057 of their siblings, 919 of their parents and 590 unrelated controls from the general population. The current inclusion criteria were: 1) age between 16 and 60; 2) good command of the Dutch language and 3) being able and willing to give informed consent. Patients had to meet the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV-TR) (APA, 2000) criteria for a non-affective psychotic disorder, as assessed by the Comprehensive Assessment of Symptoms and History Interview (Andreasen et al., 1992). Additional inclusion criteria for the control group were not having a 1) lifetime psychotic disorder and/or 2) a first-degree family member with a lifetime psychotic disorder. The project was approved by the local Research Ethics Committee and all participants gave written informed consent in accordance with the committee's guidelines.

Measures of social cognition

Degraded Facial Affect Recognition Task (DFAR). The DFAR (van 't Wout et al., 2004) uses photographs of four different actors (two male, two female) depicting the four emotions: angry, happy, fearful and neutral. The task comprises 64 trials consisting of 16 face presentations in each emotion category. The emotions were shown with 100% and 75% intensity in order to increase the difficulty of the task. Subjects were asked to indicate the emotional expression of each face with a button press and to respond as accurately as possible. Outcomes were the proportion correctly recognized as neutral, happy, fearful and angry emotions and the overall proportion correct.

Hinting Task (HT). Theory of mind was assessed with the HT (Corcoran et al., 1995; Janssen et al., 2003; Vermissen et al., 2008). The task tests the ability of subjects to infer the real intentions behind indirect speech utterances. It comprises ten short passages presenting an interaction between two characters that end with one of

the characters dropping a hint. The subject is then asked what the character really meant. Correctly identified hints are scored with two points. In cases of an incorrect response, a more obvious hint is added. A subsequent correct response is scored with one point; an incorrect response is scored as zero. The outcome range is 0-20.

Measures of neurocognition

Benton Facial Recognition Test (BFRT). The short form of the BFRT (Benton et al., 1983), a measure of the ability to match unfamiliar faces, was used to assess whether deficits in facial affect recognition are not mediated by differences in general facial recognition ability.

Wechsler Adult Intelligence Scale (WAIS III). The Arithmetic, Digit Symbol-Coding, Block Design and Information subtests of the WAIS III were administered as an indicator of IQ (Blyler et al., 2000; Wechsler, 1997).

Symptom assessment

The Positive and Negative Syndrome Scale (PANSS). The PANSS (Kay et al, 1987) has been used to assess symptoms in patients. Originally, the PANSS consisted of a positive and negative syndrome scale and a general psychopathology scale. However, a specific model has been formulated on the social cognitive basis of disorganized symptoms (Hardy-Baylé et al., 2003) and research to date shows the most robust association between poor mental state attribution and disorganization symptoms (Bruene et al., 2010; Sprong et al., 2007). Recently, van der Gaag and colleagues developed a more fine-grained model of symptoms. Among other factors, the model captures disorganized symptoms (van der Gaag et al., 2006). The positive, negative and disorganized symptom factors of the model were used in the current analyses.

Structured Interview for Schizotypy–Revised (SIS-R). The SIS-R (Kendler et al., 1989; Vollema and Ormel, 2000) was administered to assess subclinical symptoms in siblings. It is a semi-structured interview that contains 20 schizotypal symptoms

and 11 schizotypal signs. Guided by our a-priori theoretical considerations for the classification of symptoms within patients and previous research (Hardy-Baylé et al., 2003), we reduced the item scores to the three dimensions of 1) positive (referential thinking, magical ideation, illusions and suspiciousness); 2) negative (social isolation, social anxiety, introversion and restricted affect); and 3) disorganization schizotypy (goal directness of thinking, loosening of associations and oddness).

Statistical analyses

Statistical analyses were performed using STATA version 11.0 statistical software. Linear regression analyses were used to investigate group differences and within-group symptom-cognition associations within siblings and patients. It has been argued that social cognitive impairment in schizophrenia is non-specific and that any association with symptoms may be due to confounding by neurocognitive impairment (Dickinson et al., 2004; Kerr and Neale, 1993). We therefore adjusted all between group analyses for IQ (for intercorrelations between IQ and the social cognitive tasks see Table 1). The potentially confounding factors age and gender were controlled in all between group analyses. Between group linear regression analyses on DFAR performance were also adjusted for general face recognition ability. Some families contributed more than one patient or sibling. All possible patient-sibling pairs were included in the analysis. To account for the observations of multiple siblings within one family, multilevel random regression analyses (XTREG) were used to analyse within-trait cross-sibling associations, i.e. the familial clustering of cognitive performance. Cross-trait cross-sibling associations between cognitive performance in patients and subclinical symptoms in siblings were analysed using the same routine. All cross-trait cross-sibling analyses were adjusted for the corresponding trait within the patient and sibling groups. Effect sizes are expressed as the standardized regression coefficient β for linear regression analyses and the regression coefficient b with the 95% confidence intervals.

3. RESULTS

Sample

The current study incorporated a subset of participants from the full GROUP sample. This sub-sample included 1032 patients, 1017 of their healthy siblings and 579 controls. Sample characteristics and test statistics are displayed in Table 2.

Social cognition

Patients had a worse HT performance than controls and siblings. The means of controls and siblings differed into the expected direction but this difference was not significant. Patients also performed worse on the DFAR than controls and siblings. Again, the performance of controls and siblings differed into the expected direction but was not significant. All groups recognized happy emotion best; followed by neutral; angry and fearful emotion with the lowest rate of correct recognitions. Analyses per emotion category showed no differences between controls and siblings for any of the four categories. Patients did not perform worse than controls and siblings in recognizing neutral and happy emotions. They did, however, perform significantly worse than controls and siblings with respect to angry and fearful emotions (see Table 3). All analyses were controlled for age, gender and IQ. DFAR analyses were also controlled for general face recognition ability.

Cross-trait within-group analyses

Within patients HT performance was consistently and significantly associated with disorganized and, to a lesser extent, with negative symptoms. The association with positive symptoms was smaller but also significant. DFAR performance was significantly associated with disorganized and, to a lesser extent, with negative and positive symptoms. Within siblings, HT performance was weakly but significantly associated with subclinical disorganized symptoms only. The associations with subclinical negative and positive symptoms were non-significant. DFAR performance

was significantly associated with subclinical negative symptoms only. The associations with subclinical disorganized and positive symptoms were non-significant (Table 4).

Within-trait cross-sibling analyses

The analyses between at least 674 patient-sibling pairs showed significant within-trait familial clustering of HT performance, DFAR performance and IQ (Table 4). All within-trait cross-sibling analyses were controlled for age, gender and IQ.

Cross-trait cross-sibling analyses

None of the associations between HT performance in patients and subclinical symptoms in siblings were significant. DFAR performance in patients and subclinical disorganized symptoms in siblings were significantly associated. The associations between patients' DFAR performance and siblings' subclinical symptoms were marginally significant for positive subclinical symptoms and non-significant for negative subclinical symptoms (Table 4). All cross-trait cross-sibling analyses were controlled for age, gender and IQ and the respective symptom domain and cognitive task across siblings.

4. DISCUSSION

Our results showed no familial co-variation of the association between ToM performance and psychotic symptoms across siblings, suggesting that the overlap between the two phenotypes, which is seen in patients, does not reflect a shared familial aetiology. However, indicative of a shared aetiology, familial co-variation was present between patients' emotion recognition ability and disorganized and, to a lesser degree, positive, but not negative subclinical symptoms in siblings.

Social cognitive impairment over the psychosis continuum

In line with earlier evidence (Sprong *et al*., 2007), a worse performance in ToM and emotion recognition ability was weakly associated with a higher psychosis risk. Patients performed worse on the hinting task than siblings and controls and siblings mean values were intermediate. Yet, in contrast to what had been expected on the basis of previous research (Alfimova *et al*., 2009; Anselmetti *et al*., 2009; Bediou *et al*., 2007; Janssen *et al*., 2003; Vermissen *et al*., 2008;) the difference between siblings and controls was small and not significant. A similar pattern of results was present for emotion recognition. Despite their overall impairment, the valence-related performance pattern of patients was similar to that of siblings and controls, with a superior recognition of happy and neutral emotions as compared to fearful and angry emotions (Silver *et al*., 2009). Analyses per emotion category indicated that the overall effect was mainly driven by differences in the recognition of angry and fearful emotion. The finding of unimpaired recognition of neutral and happy affect, but impaired recognition of negative affect is consistent with previous reports on the disproportionate impairment in the identification of negative emotions and lends further support to emotion-specific processing deficits in schizophrenia (Alfimova *et al*., 2009; Bediou *et al*., 2007; Edwards *et al*., 2001; Kohler *et al*., 2003; van 't Wout *et al*., 2007).

Symptoms and social cognition

To investigate the nature of the associations between symptoms and social cognitive impairment in patients and siblings we carried out cross-trait within-group analyses first. Within patients, poorer ToM performance was consistently and significantly associated with all three symptom clusters. The strongest association was present with disorganized symptoms. The association with negative symptoms was intermediate and the weakest association was present with positive symptoms. Emotion recognition was significantly associated with disorganized and negative symptoms, albeit to a lesser degree than ToM. Within siblings significant associations were present between ToM and subclinical disorganized symptoms, but not negative symptoms. Emotion recognition, in turn, was significantly associated with subclinical negative symptoms, but not disorganized symptoms. Associations between both social cognitive domains and positive symptoms were entirely specific to patients. In the next step, we investigated whether social cognitive performance clusters within families. The within-trait cross-sibling analyses revealed considerable familial clustering of ToM and emotion recognition, although to a slightly lesser degree. The social cognitive clusters remained significant when controlled for IQ, supporting a substantial independence from the neurocognitive domain (Van Hooren *et al*., 2008). The cross-trait, cross-sibling investigations revealed no significant associations between ToM in patients and any subclinical symptoms in their siblings. No significant association was present between patients' emotion recognition and negative symptoms in siblings. However, indicative of a common aetiological transmission, patients' emotion recognition ability was significantly associated with siblings' disorganized subclinical symptoms and, although to a lesser degree, with their positive subclinical symptoms.

The results confirmed previously observed associations between symptoms and social cognitive performance within the patients. Only two significant cognition-symptom associations were present within the sibling group. This finding may be due to constricted variation within siblings. Alternatively, other symptom cognition associations may only come into effect once the disorder has been developed.

Our findings corroborated the potential role of both social cognitive functions as intermediary phenotypes of the illness. Familial clustering indicates a possible shared aetiological basis underlying impaired social cognition in siblings and patients. Obviously, the two phenotypes may also have been acquired in a shared environment (e.g. parental neglect). However, research suggests that the familial liability to schizophrenia strongly represents the influence of shared genes, so a partly genetic transmission of the phenotypes is therefore likely (Cardno *et al*., 2002; Gur *et al*., 2007).

The differential cross-trait cross-sibling associations between social cognitive functioning and the specific symptom clusters point toward partly differential aetiological substrates. The aetiology of emotion recognition deficits and symptoms seems to vary between the three clusters. Emotion recognition deficits may be useful endophenotypes in the search for the genetic causes of disorganized symptoms and possibly to a lesser degree of positive, but not negative symptoms. Alternatively, it could be argued that these differences are due to a lower sensitivity of the SIS-R to positive and even more strongly to negative symptoms. However, previous evidence proved the SIS-R is sensitive to family-specific variation in positive and negative subclinical symptoms (Hanssen *et al*., 2006).

Our results did not substantiate a shared aetiology of ToM deficits and any of the three symptom clusters. In this case the overlap seems to originate at an individual level. In line with previous research (Van Hooren *et al*., 2008), the present findings suggest a substantial heterogeneity and multicomponent structure of social cognition. Analogous to other (genetic) predispositions that appear in the phenotype under particular conditions (e.g. sunburn and skin cancer), manifold factors may bring the associations between ToM impairment and symptoms to expression. A dynamic interplay of symptoms, cognitive processes, behavioural and environmental factors may offer a suitable explanation for our findings. Patients' ToM deficits may play a role in the formation, exacerbation and maintenance of psychotic

symptoms (Garety *et al*., 2001; Laroi *et al*., 2010). Specifically, impaired ToM could lead to a paranoid interpretation of other persons' intentions as malevolent. Also, impaired emotion recognition, although possibly to a lesser degree, may cause negative misinterpretations of social-emotional cues. Misperceptions may lead to the avoidance of social situations or contacts and problematic social behaviour, which may be partially reflected in negative symptoms. Disorganized symptoms and social cognitive deficits, moreover, could be associated on a level of conceptual understanding rather than misinterpretation of social situations.

Strengths and limitations

The current study used a uniquely large sample with adequate power to detect even delicate effects. Also, the patient-sibling based design has the important advantage of automatically controlling for confounds that are associated with the illness, such as residual symptoms or the effects of antipsychotic medication. Sibling based designs also have the advantage of low confounding by unobserved factors that may affect case-control comparisons in unrelated subjects, such as shared socioeconomic and developmental conditions.

The findings should be considered keeping the following limitations in mind. First, our data cannot completely clarify whether any abnormalities in social cognition are present prior to the illness onset (i.e. potentially causal) or whether they are co-varying epiphenomena of the clinical picture. However, in line with previous research our results indicate that the association between social cognitive impairment and symptoms is not only present during acute psychosis (Sprong *et al*., 2007). Second, we had to use different measures to assess the clinical phenotypes in patients and siblings. The SIS-R is not suitable for the use in patients, because it may underlie ceiling effect. The PANSS interview, in turn, may be subject to floor effects when used in relatives. However, we aimed to establish concurrent validity between the two measures by structuring the items along the same symptom dimensions. Third, as reported by previous research, the social cognitive performance differences between

siblings and controls were subtle (Alfimova *et al*., 2009; Baas *et al*., 2008). This may partly be due to the nature of the social cognitive tasks that we employed. The Hinting Task is specifically prone to ceiling effects. It also needs to be noted that our measure may only reflect part of the broader domain that it belongs to. Other ToM tasks possibly tap into different mentalising capacities and future studies should aim to include more tasks to get a better representation of the domain. Another possible explanation for the relatively small effects could be a self-selection bias, in which only relatively stable patients volunteer to participate in demanding research. Also, biased answering of siblings who are highly aware of the symptoms of psychosis and who may want to appear healthy may have reduced the effects. Obviously, it is difficult to translate statistical effect sizes and p-values into clinical significance one to one. Even though effect sizes on some tasks are small, the work of our group and others (Couture *et al*., 2006; Fett *et al*., 2011) has shown that social cognitive performance in the domains of ToM and emotion perception and processing is associated with functional outcome, possibly to a higher degree than many other cognitive factors. These findings imply a substantial clinical significance of the degree of social cognitive impairment that is typically seen in schizophrenia.

Conclusion

ToM and emotion recognition impairments are associated with the liability to non-affective psychosis and cluster within families. Our findings support the idea that both traits could be suitable intermediary phenotypes for genetic studies. The cross-trait cross-sibling analyses did not support a familial continuity between subclinical symptoms and ToM. However, a shared familial aetiology may underlie the overlap between emotion recognition deficits and disorganized and positive psychotic symptoms. Emotion recognition deficits could therefore be useful intermediate phenotypes in the identification of the familial causes of specific symptoms of psychosis.

REFERENCES

de Achával, D., et al., Emotion processing and theory of mind in schizophrenia patients and their unaffected first-degree relatives. Neuropsychologia, 2010. 48(5): p. 1209-1215.

Addington, J., et al., Facial affect recognition in individuals at clinical high risk for psychosis. The British Journal of Psychiatry, 2008. 192: p. 67-68.

Alfimova, M.V., et al., Facial affect recognition deficit as a marker of genetic vulnerability to schizophrenia. The Spanish Journal of Psychology, 2009. 12(1): p. 46-55.

Andreasen, N.C., M. Flaum, and S. Arndt, The Comprehensive Assessment of Symptoms and History (CASH). An instrument for assessing diagnosis and psychopathology. Archives of General Psychiatry, 1992. 49: p. 615-623.

Anselmetti, S., et al., 'Theory' of mind impairment in patients affected by schizophrenia and in their parents. Schizophrenia Research, 2009. 115(2-3): p. 278-285.

APA, ed. Diagnostic and statistical manual of mental disorders. 4th rev ed. 2000, American Psychiatric Association: Washington DC.

Baas, D., et al., Social judgement in clinically stable patients with schizophrenia and healthy relatives: Behavioural evidence of social brain dysfunction. Psychological Medicine, 2008. 38(5): p. 747-754.

Bediou, B., et al., Emotion recognition and genetic vulnerability to schizophrenia. The British Journal of Psychiatry, 2007. 191(2): p. 126-130.

Benton, A.L., et al., Benton's Test of Facial Recognition. 1983, New York: Oxford University Press.

Blyler, C.R., et al., Short form of the WAIS-III for use with patients with schizophrenia. Schizophrenia Research, 2000. 46(2-3): p. 209-215.

Bora, E., M. Yucel, and C. Pantelis, Theory of mind impairment in schizophrenia: Meta-analysis. Schizophrenia Research, 2009. 109(1-3): p. 1-9.

Bruene, M., et al., Social skills and behavioral problems in schizophrenia: The role of mental state attribution, neurocognition and clinical symptomatology. Psychiatry Research, 2010.

Cardno, A.G., et al., Twin study of symptom dimensions in psychoses. British Journal of Psychiatry, 2001. 179(1): p. 39-45.

Cardno, A.G., et al., A twin study of genetic relationships between psychotic symptoms. American Journal of Psychiatry, 2002. 159(4): p. 539-545.

Corcoran, R., G. Mercer, and C.D. Frith, Schizophrenia, symptomatology and social inference: Investigating "theory of mind" in people with schizophrenia. Schizophrenia Research, 1995. 17: p. 5-13.

Couture, S.M., D.L. Penn, and D.L. Roberts, The functional significance of social cognition in schizophrenia: a review. Schizophrenia Bulletin, 2006. 32 Suppl 1: p. S44-63.

Dickinson, D., et al., General and specific cognitive deficits in schizophrenia. Biological Psychiatry, 2004. 55: p. 826-833.

Doody, G.A., et al., Theory of mind and psychoses. Psychological Medicine, 1998. 28(02): p. 397-405.

Eack, S.M., et al., Social cognition deficits among individuals at familial high risk for schizophrenia. Schizophrenia Bulletin, 2010. 36(6): p. 1081-1088.

Edwards, J., et al., Facial affect and affective prosody recognition in first-episode schizophrenia. Schizophrenia Research, 2001. 48: p. 235-253.

Edwards, J., H.J. Jackson, and P.E. Pattison, Emotion recognition via facial expression and affective prosody in schizophrenia: A methodological review. Clinical Psychology Review, 2002. 22: p. 789–832.

Fett, A.-K.J., et al., The relationship between neurocognition and social cognition with functional outcomes in schizophrenia: A meta-analysis. Neuroscience & Biobehavioral Reviews, 2011. 35(3): p. 573-588.

van der Gaag, M., et al., The five-factor model of the Positive and Negative Syndrome Scale II: A ten-fold cross-validation of a revised model. Schizophrenia Research, 2006. 85(1-3): p. 280-287.

Garety, P.A., et al., A cognitive model of the positive symptoms of psychosis. Psychological Medicine, 2001. 31(02): p. 189-195.

Gur, R.E., et al., Neurocognitive Endophenotypes in a Multiplex Multigenerational Family Study of Schizophrenia. American Journal of Psychiatry, 2007. 164(5): p. 813-819.

Hanssen, M., et al., Evidence for instrument and family-specific variation of subclinical psychosis dimensions in the general population. Journal of Abnormal Psychology, 2006. 115(1): p. 5-14.

Hardy-Baylé, M.C., Y. Sarfati, and C. Passerieux, The cognitive basis of disorganization symptomatology in schizophrenia and its clinical correlates: Toward a pathogenic approach to disorganization. Schizophrenia Bulletin, 2003. 29: p. 459-471.

Janssen, I., et al., Alterations in theory of mind in patients with schizophrenia and non-psychotic relatives. Acta Psychiatrica Scandinavica, 2003. 108: p. 110-117.

Kay, S.R., A. Fiszbein, and L.A. Opler, The Positive and Negative Syndrome Scale (PANSS) for Schizophrenia. Schizophrenia Bulletin, 1987. 13(2): p. 261-276.

Kendler, K.S., J.A. Liebermann, and D. Walsh, The structured interview for schizotypy (SIS): a preliminary report. Schizophrenia Bulletin, 1989. 15(4): p. 559-571.

Kerr, S.L. and J.M. Neale, Emotion perception in schizophrenia: Specific deficit or further evidence of generalized poor performance? Journal of Abnormal Psychology, 1993. 102: p. 312-318.

Kohler, C.G., et al., Facial emotion recognition in schizophrenia: Intensity effects and error pattern. American Journal of Psychiatry, 2003. 160: p. 1768–1774.

Langdon, R. and M. Coltheart, Mentalising, schizotypy, and schizophrenia. Cognition, 1999. 71(1): p. 43-71.

Laroi, F., et al., Basic Emotion Recognition and Psychopathology in Schizophrenia. Journal of Nervous & Mental Disease, 2010. 198: p. 79-81.

Marjoram, D., et al., Symptomatology and social inference: A theory of mind study of schizophrenia and psychotic affective disorder. Cognitive Neuropsychiatry, 2005. 10: p. 347-359.

Penn, D.L., L.J. Sanna, and D.L. Roberts, Social cognition in schizophrenia: An overview. Schizophrenia Bulletin, 2008. 34: p. 408–411.

Pickup, G., Theory of mind and its relation to schizotypy. Cognitive Neuropsychiatry, 2006. 11: p. 177-192.

Shean, G., A. Murphy, and J. Meyer, Social Cognition and Symptom Dimensions. The Journal of Nervous and Mental Disease, 2005. 193: p. 751-755.

Silver, H., W. Bilker, and C. Goodman, Impaired recognition of happy, sad and neutral expressions in schizophrenia is emotion, but not valence, specific and context dependent. Psychiatry Research, 2009. 169(2): p. 101-106.

Sprong, M., et al., Theory of mind in schizophrenia: A meta-analysis. British Journal of Psychiatry, 2007. 191: p. 5-13.

Van Hooren, S., et al., Social cognition and neurocognition as independent domains in psychosis. Schizophrenia Research, 2008. 103: p. 257-265.

Versmissen, D., et al., Evidence for a relationship between mentalising deficits and paranoia over the psychosis continuum. Schizophrenia Research, 2008. 99(1-3): p. 103-10.

Vollema, M. and J. Ormel, The Reliability of the Structured Interview for Schizotypy-Revised. Schizophrenia Bulletin, 2000. 26(3): p. 619-629.

Wechsler, D., WAIS-III: Wechsler Adult Intelligence Scale (3rd ed.) Administration and Scoring Manual. 1997, San Antonio, TX: Psychological Corporation.

van 't Wout, M., et al., Emotional processing in a non-clinical psychosis-prone sample. Schizophrenia Research, 2004. 68(2-3): p. 271-81.

van 't Wout, M., et al., Exploring the nature of facial affect processing deficits in schizophrenia. Psychiatry Research, 2007. 150: p. 227-235.

Table 1 | Intercorrelations between the (social) cognitive tasks by group

	Overall		Controls		Siblings		Patients	
	HT	DFAR	HT	DFAR	HT	DFAR	HT	DFAR
DFAR	0.23		0.12		0.10		0.25	
IQ	0.35	0.21	0.17	0.09	0.23	0.13	0.37	0.22

Table 3 | Group differences on the social cognitive tests

	Controls vs. Patients		Controls vs. Relatives		Patients vs. Relatives	
	β	p	β	p	β	p
HT	-0.17	< 0.001	0.01	0.61	-0.18	< 0.001
DFAR	-0.13	< 0.001	-0.03	0.30	-0.10	< 0.001
Neutral	-0.04	0.12	-0.01	0.80	-0.04	0.11
Happy	0.02	0.51	0.04	0.13	-0.02	0.36
Anger	-0.13	< 0.001	-0.04	0.12	-0.09	< 0.001
Fear	-0.10	< 0.001	-0.03	0.21	-0.07	0.002

Note β = adjusted for age, gender, IQ and face recognition ability (for the DFAR only).

Table 2 | Demographic and clinical sample characteristics

	Controls		Siblings		Patients			
Variable	n = 579 Mean (SD)	n	n = 1017 Mean (SD)	n	n = 1032 Mean (SD)	n	Test statistic	p-value
Age (yrs)	30.4 (10.6)[a]	579	27.8 (8.2)[b]	1017	27.3 (7.2)[c]	1032	F(2, 2624) = 26.84	< 0.001
Male (%)	45[a]		46[a]		77[b]		$\chi^2(2) = 257.53$	< 0.001
Education (%)								
None/primary only	2.4	576	7.4	994	13	1008	$\chi^2(16) = 246.54$	< 0.001
Lower secondary	14.8		19.7		30.7			
Lower vocational	15.6		22.4		17.4			
Higher secondary	31.7		20.5		25.5			
Higher vocational	25.5		18.5		9.1			
University	10		11.5		4.3			
IQ	109.7 (15.1)[a]	579	102.7 (15.6)[b]	1017	94.9 (16)[c]	1032	F(4, 2623) = 95.40	< 0.001
Hinting Task (range 0-20)	19.1 (1.3)[a]	573	18.8 (1.7)[a]	1009	17.5 (2.8)[b]	1008	F(5, 2584) = 114.25	< 0.001
DFAR total	73.2 (9.1)[a]	542	72.5 (9.4)[a]	943	68.6 (10.7)[b]	934	F(6, 2398) = 63.61	< 0.001
neutral	81.3 (15.1)		80.4 (15)		77.8 (17.5)		F(6, 2398) = 17.41	< 0.001
happy	87.4 (11.1)		88.2 (10.7)		86.8 (12.7)		F(6, 2398) = 14.17	< 0.001
angry	70.5 (18.6)		68.8 (19.3)		62.3 (20.9)		F(6, 2398) = 30.61	< 0.001
fearful	53.9 (18.1)		52.7 (19.7)		47.5 (19.7)		F(6, 2398) = 34.17	< 0.001
SIS-R								
Disorganized	0.03 (0.12)[a]	571	0.05 (0.19)[b]	1006			F(4, 1573) = 6.78	< 0.001
Negative	0.45 (0.43)[a†]	571	0.5 (0.47)[b]	1006			F(4, 1574) = 1.91	0.005

Table 2 | continued

Positive	0.31 (0.35)[a]	571	0.38 (0.42)[b]	1006			F(4, 1574) = 14.72	< 0.001
PANSS								
Disorganized					16.7 (6.2)	971		
Negative					15 (6.6)	970		
Positive					13.9 (6.6)	979		

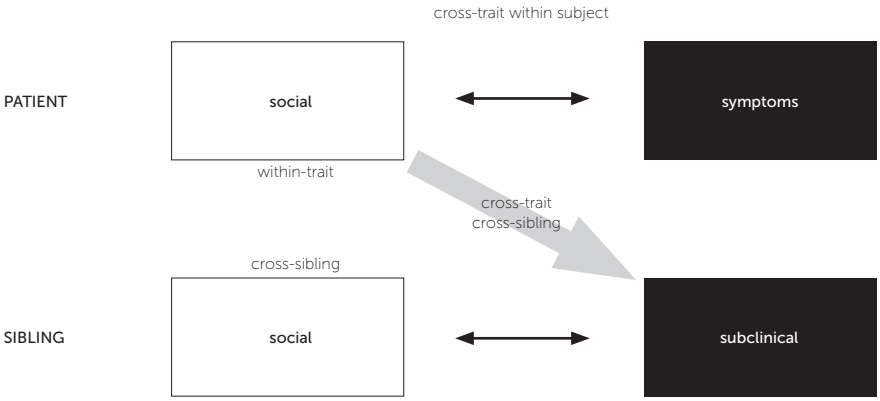
Note Different superscripts indicate significant group differences with $p < 0.05$. † indicates $p < 0.06$. Group differences in the specific emotion categories of the DFAR are displayed in Table 3.

Table 4 | Cross-trait within-patients/siblings, within-trait cross-sibling and cross-trait cross-sibling analyses

Analysis	n	Association	β	b	p-value	95%C.I. lb / ub
Cross-trait within-patients analysis	948	HT-disorganized symptoms	-0.33	-0.73	< 0.001	-0.91 / -0.56
	946	HT-negative symptoms	-0.21	-0.51	< 0.001	-0.70 / -0.32
	957	HT-positive symptoms	-0.11	-0.27	< 0.001	-0.46 / -0.07
	880	DFAR-disorganized symptoms	-0.21	-0.12	< 0.001	-0.17/ -0.07
	875	DFAR-negative symptoms	-0.11	-0.07	< 0.001	-0.12/ -0.02
	885	DFAR-positive symptoms	-0.09	-0.05	0.008	-0.11 / -0.001
Cross-trait within-siblings analysis	1001	HT-disorganized symptoms	-0.09	-0.01	0.006	-0.02 / 0.001
	1001	HT-negative symptoms	-0.04	-0.01	0.17	-0.04 / 0.01
	1001	HT-positive symptoms	-0.04	-0.01	0.22	-0.03 / 0.01
	935	DFAR-disorganized symptoms	-0.02	-0.0004	0.55	-0.002 / 0.001
	935	DFAR -negative symptoms	-0.07	-0.003	0.04	-0.01 / 0.001
	935	DFAR -positive symptoms	-0.02	-0.001	0.60	-0.005 / 0.003
	Families*					
Within-trait cross-sibling analysis	755	HT		0.08	< 0.001	0.02 / 0.13
	674	DFAR		0.09	0.002	0.02 / 0.17
	766	IQ		0.42	< 0.001	0.35 / 0.51
Cross-trait cross-sibling analysis	715	HT patients-disorganized symptoms siblings		0.001	0.87	-0.01 / 0.01
	717	HT patients-negative symptoms siblings		0.01	0.30	-0.01 / 0.02
	721	HT patients-positive symptoms siblings		0.002	0.75	-0.01 / 0.02
	640	DFAR patients -disorganized symptoms siblings		0.001	0.02	-0.0002/ 0.003
	639	DFAR patients -negative symptoms siblings		0.003	0.10	-0.002 / 0.01
	643	DFAR patients -positive symptoms siblings		0.003	0.06	-0.001 / 0.01

Note *All analyses are adjusted for age, gender, IQ and the respective relevant traits (i.e. social cognition in siblings and symptoms in patients); 95%CI = confidence interval for b; lb = lower bound, ub = upper bound.

Figure 1 | Cross-trait cross-sibling design



03

EMOTION PROCESSING IN SCHIZOPHRENIA IS STATE AND TRAIT DEPENDENT

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Under review for Schizophrenia Research

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 three years 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 assess the effect of group on EP performance over time. Age, gender and general cognition were included as covariates. Results: Schizophrenia patients performed worse than healthy controls on EP at T1 ($p = 0.001$). Significant group x time interactions were found between RR and RN ($p = 0.001$), and between NR and RN ($p = 0.042$), indicating a differential EP performance over time. No group x 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 state- , as well as trait- dependent.

KEYWORDS

Emotion Processing, Cognition, Psychosis, Remission, Schizophrenia, Social Cognition

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) (APA, 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 facial expressions (Couture *et al*., 2006). Not surprisingly, EP is found to be related to social problem solving and community functioning in 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).

State markers for schizophrenia refer to the status of clinical manifestations in patients (e.g, psychosis), whereas trait markers for schizophrenia refer to properties of the behavioral and biological processes that play an antecedent, possibly causal, role in the predisposition to the disorder (e.g., working memory deficits) (Chen *et al*., 2009; de Leeuw *et al*., 2013). A behavioral trait is an enduring characteristic that distinguishes schizophrenia patients from healthy individuals. Numerous studies have shown deficits in EP performance in schizophrenia patients compared to healthy controls (Chan *et al*., 2010; Kohler *et al*., 2010; Marwick and Hall, 2008; Penn *et al*., 2008). Cross-sectional studies showed EP deficits to be present at first onset of schizophrenia and to be stable over the course of illness in chronic patients (Green *et al*., 2012; Pinkham *et al*., 2007). Trait markers are most useful when they are present in clinically unaffected relatives of schizophrenia patients (Chen *et al*., 2009). Indeed, some studies found EP deficits in unaffected siblings of schizophrenia patients (de Achaval *et al*., 2010; Eack *et al*., 2009). 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 were 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; Laroi *et al*., 2010; Marwick and Hall, 2008; Tseng *et 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 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 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 state of illness at both measurements, i.e. remission or non-remission at baseline and remission or non-remission at follow-up. EP scores were compared between the four patient groups over time.

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, 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 multicentre study 'Genetic Risk and Outcome in Psychosis' (GROUP). Assessments were performed at baseline and after three years 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) (APA, 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 (APA, 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.

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.

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 behaviour (P3), conceptual disorganization (P2), mannerisms/posturing (G5), blunted affect (N1), social withdrawal (N4) and lack of spontaneity (N6).

Degraded Facial Affect Recognition Task (DFAR). 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).

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 (Blyer *et al*., 2000; Wechsler, 1997). The sum of the four subtests yields a measure of estimated IQ.

2.3 STATISTICAL ANALYSES

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 state of illness at baseline and after three years 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).

Differences in EP performance may be subject to confounding by age, gender and IQ (Dickinson *et al*., 2008; Scholten *et al*., 2005). Therefore, we evaluated differences in EP performance adjusted for gender and baseline assessments of age and IQ. First, to investigate whether EP was trait dependent, an ANCOVA was conducted to compare performance at baseline between schizophrenia patients and healthy controls. Second, to investigate whether EP was state dependent, a factorial repeated measures ANCOVA was conducted within the patient group 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.

Statistical analyses were performed using SPSS version 20.0. For our primary analysis the significance level was set at 0.05/4 = 0.013, controlling for the total number of tests. 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 DFAR performance at baseline between drop-outs and completers (Table 1).

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 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).

3.2 EP PERFORMANCE BETWEEN SCHIZOPHRENIA PATIENTS AND HEALTHY CONTROLS

An ANCOVA was used to analyse differences between the patient group and the healthy control group on EP performance at baseline, as measured with the DFAR. After controlling for age, gender and IQ, a significant difference between both groups was found, $F(1,797) = 10.272$, $p = 0.001$. The patient group ($M = 69.48$, $SD = 9.75$) performed worse on EP as compared to the healthy control group ($M = 73.60$, $SD = 9.75$).

3.3 EP PERFORMANCE BETWEEN PATIENT GROUPS OVER TIME

To investigate whether EP is state dependent, we used factorial repeated measure ANCOVAs, with age, gender and IQ as covariates. We performed the following comparisons on EP performance over time: i.e., 1) NR vs. RN, 2) RR vs. RN and 3) NN vs. NR.

3.3.1 EP performance of NR versus RN over time

An interaction effect of time x group on DFAR total score on trend level was found, $F(1,161) = 4.202$, $p = 0.042$ (Figure 1 & Table 3). 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 x group on DFAR total score was found, F(1,235) = 11.360, p = 0.001 (Figure 1 & Table 3). 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.

3.3.3 EP performance of NN versus NR over time

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

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 three years 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 (Chan *et al*., 2010; Kohler *et al*., 2010; Marwick and Hall, 2008; Penn *et al*., 2008), we found relatively poor EP performance in schizophrenia patients compared to healthy controls at baseline. Second, 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; Laroi *et al*., 2010; Marwick and Hall, 2008; Tseng *et al*., 2013) and with a previous study demonstrating that remitted patients outperform acutely ill patients on EP (Edwards *et al*., 2002). 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 figure 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 performance of the NR group, possibly enabling less dramatic improvement on EP over time (Figure 1). Besides the difference in EP performance between the NR and NN 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 (Green *et al*., 2012; Pinkham *et al*., 2007). 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 remission status at either assessment as well as it's dynamics over time, 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 years 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 state of illness.

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

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.

REFERENCES

de Achaval, D., Constanzo, E.Y., Villareal, M., Jauregui, I.O., Chiodi, A., Castro, M.N., Fahrer, R.D.,Leiguarda, R.C., 2010. Emotion processing and theory of mind in schizophrenia patients and their unaffected first-degree relatives. Neuropsychologia 48, 1209 – 1215.

Aleman, A., Kahn, R.S., 2005. Strange feelings: Do amygdala abnormalities dysregulate the emotional brain in schizophrenia? Prog. Neurobiology 77, 283 - 298.

American Psychiatric Association, 2000. Diagnostic and statistical manual of mental Disorders, fourth ed. text revision. American Psychiatric Association, Washington, DC.

Amminger, G.P., Schäfer, M.R., Papegeourgiou, K., Klier, C.M., Schögelhofer, M., Mossaheb, N., Werneck-Rohrer, S.,Nelson, B., 2012. Emotion recognition in individuals at clinical high-risk for schizophrenia. Schizophr. Bull. 38, 1030 – 1039.

Andreasen, N.C., Flaum, M., Arndt, S., 1992. The Comprehensive Assessment of Symptoms and History (CASH). An instrument for assessing diagnosis and psychopathology. Arch. Gen. Psychiatry 49 (8), 615 – 623.

Andreasen, N.C., Carpenter, W.T., Kane, J.M., Lasser, R.A., Marder, S.R., Weinberger, D.R., 2005. Remission in schizophrenia: proposed criteria and rational for consensus. Am. J. Psychiatry 162, 441 - 449.

Baron-Cohen, S., Leslie, A.M., Frith, U., 1985. Does the autistic child have a 'theory of mind'? Cognition 21, 37 – 46.

Blyer, C.R., Gold, J.M., Iannone, V.N., Buchanan, R.W., 2000. Short form of the WAIS-III for use with patients with schizophrenia. Schizophr. Res. 46, 209 – 215.

Chan, R.C.K., Li, H., Cheung, E.F.C., Gong, Q., 2010. Impaired facial emotion perception in Schizophrenia. Psych. Res. 178, 381 – 390.

Chen Y., Norton D., McBain R., 2009. Trait and State Markers of Schizophrenia in Visual Processing, in: Ritsner M.S. (Ed.), The Handbook of Neuropsychiatric Biomarkers, Endophenotypes and Genes. Springer Science + Business Media BV. , pp. 211-220.

Couture, S.M., Penn, D.L., Roberts, D.L., 2006. The functional significance of social cognition in schizophrenia: a review. Schizophr. Bull. 31 (S1), S44 – 63.

Dickinson, D., Ragland, J.D., Gold, J.M., Gur, R.C., 2008. General and specific cognitive deficits in schizophrenia: goliath defeats david? Biol. Psych. 64, 823 – 827.

Eack, S.M., Mermom, D.E., Montrose, D.M., Miewald, J., Gur, R.E., Gur, R.C., Sweeney, J.A., Keshavan, S., 2009. Social cognition deficits among individuals at familial high risk for schizophrenia. Schizophr. Bull. 36, 1081 – 1088.

Edwards, J., Jackson, H.J., Pattison, P.E., 2002. Emotion recognition via facial expression and affective prosody in schizophrenia: a methodological review. Clin. Psychol. Rev. 22, 789 – 832.

Fett, A.K., Viechtbauer, W., Dominguez, M.D., Penn, D.L., van Os, J., Krabbendam, L., 2011. The relationship between neurocognition and social cognition with functional outcomes in schizophrenia: a meta-analysis. Neurosci. Biobehav. Rev. 35 (3), 573–588.

Green, M.F., Olivier, B., Crawley, J.N., Penn, D.L., Silverstein, S., 2005. Social cognition in schizophrenia: recommendations from the measurement and treatment research to improve cognition in schizophrenia new approaches conference. Schizophr. Bull. 31, 882 –887.

Green, M.F., Bearden, C.E., Cannon, T.D., Fiske, A.P., Hellemann, G.S., Horan, W.P., Kee, K., Kern, R.S., Lee, J., Sergi, M.J., Subotnik, K.L., Sugar, C.A., Ventura, J., Yee, C.M., Nuechterlein, K.H., 2012. Social cognition in schizophrenia, part 1: performance across phase of illness. Schizophr. Bull. 38, 845 – 864.

Hofer, A., Benecke, C., Edlinger, M., Huber, R., Kemmler, G., Rettenbacher, M.A., Schleich, G., Fleishhacker, W.W., 2009. Facial emotion recognition and its relationship to symptomatic, subjective and functional outcomes in outpatients with chronic schizophrenia. Eur. Psych. 24, 27 – 32.

Irani, F.I., Seligman, S., Kamath, V., Kohler, C., Gur, R.C., 2012. A meta-analysis of emotion perception and functional outcomes in schizophrenia. Schizophr. Res. 137, 203 – 211.

Kay, S.R., Fiszbein, A., Opler, L.A., 1987. The positive and negative syndrome scale (PANSS) for schizophrenia. Schizophr. Bull. 24, 399 – 412.

Kee, K.S., Horan, W.P., Mintz, J., Green, M.F., 2004. Do siblings of schizophrenia patients demonstrate affect perception deficits? Schizophr. Res. 67, 84 – 94.

Kohler, C.G., Bilker, W., Hagendoorn, M., Gur, R.E., Gur, R.C., 2000. Emotion recognition deficit in schizophrenia: association with symptomatology and cognition. Soc. Biol. Psych. 48, 127 – 136.

Kohler, C.G., Walker, J.B., Martin, E.A., Healey, K.M., Mober, P.J., 2010. Facial emotion perception in schizophrenia. Schizophr. Bull. 36, 1009 – 1019.

Korver, N., Quee, P.J., Boos, H.B.M., Simons, C.J.P., de Haan, L., & GROUP investigators, 2012. Genetic Risk and Outcome of Psychosis (GROUP), a multi-site longitudinal cohort study focused on gene-environment interactions: objectives, sample characteristics, recruitment and assessment methods. Int. J. Methods in Psych. Res. 21, 205 – 221.

Kucharska-Pietura, K., David, A.S., Masiak, M., Phillips, M.L., 2005. Perception of facial and vocal affect by people with schizophrenia in early and late stages of illness. Brit. J. Psych. 187, 523 – 528.

Laroi, F., Fonteneau, B., Mourad, H. & Raballo, A., 2010. Basic emotion recognition and psychopathology in schizophrenia. J. Of Nerv. And Ment. Disease 198, 79 – 81.

de Leeuw, M., Kahn, R.S., Zandbelt, B.B., Widschwendter, C.G., Vink, M., 2013. Working memory and default mode network abnormalities in unaffected siblings of schizophrenia patients. Schizophr Res. 150 (2-3), 555-62.

Li, H., Chan, R.C.K., McAlonan, G.M., Gong, Q.Y., 2010. Facial emotion processing in schizophrenia: a meta-analysis of functional neuroimaging data. Schizophr. Bull. 36, 1029 – 1039.

Marwick, K., Hall, J., 2008. Social cognition in schizophrenia: a review of face processing. Brit. Med. Bull. 88, 43 – 58.

Penn, D.L., Sanna, L.J., Roberts, D.L., 2008. Social cognition in schizophrenia: an overview. Schizophr. Bull. 34, 408 – 411.

Pinkham, A.E., Penn, D.L., Perkins, D.O., Graham, K.A., Siegel, M., 2007. Emotion perception and social skill over the course of psychosis: a comparison of individuals at risk for psychosis and individuals with early and chronic schizophrenia. Cogn. Neuropsych. 12 (3), 198 – 212.

Rosenfeld, A.J., Lieberman, J.A., Jarskog, L.F., 2011. Oxytocin, dopamine, and the amygdala: a neurofunctional model of social cognitive deficits in schizophrenia. Schizophr. Bull. 37 (5), 1077-87.

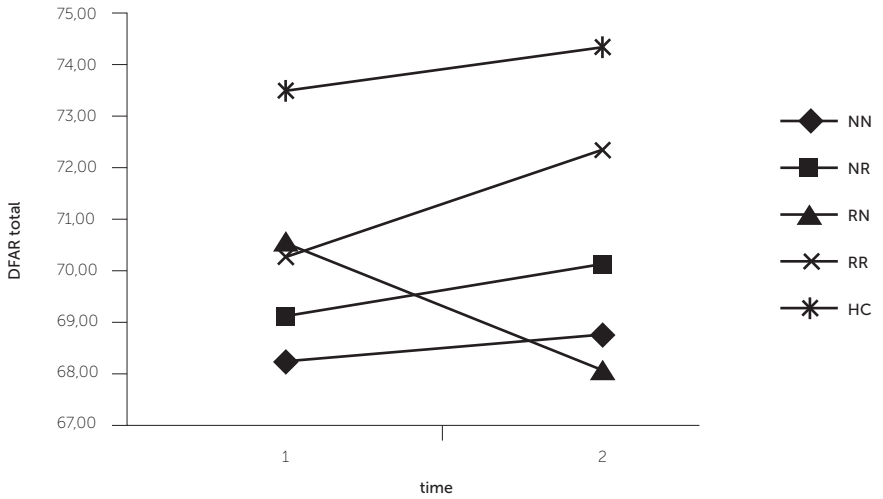
Scholten, M., Aleman, A., Montagne, B., Kahn, R.S., 2005. Schizophrenia and processing of facial emotions: sex matters. Schizophr. Res. 78, 61-67.

Tseng, H.H., Chen, S.H., Liu, C.M., Howes, O., Huang, Y.L., Hsieh, M.H., Liu, C.C., Shan, J.C., Lin, Y.T, Hwu, H.G., 2013. Facial and prosodic recognition deficits associate with specific clusters of psychotic symptoms in schizophrenia. Plos One 8, 1 – 7.

Wechsler, D., 1997. WAIS-III: Wechsler Adult Intelligence Scale, administration and scoring manual, third edition. Psychological Corporation, San Antonio, TX.

van 't Wout, M., Aleman, A., Kessels, R.P., Laroi, F., Kahn, R.S., 2004. Emotional processing in a non-clinical psychosis-prone sample. Schizophr. Res. 113, 189 – 199.

Figure 1 | DFAR total performance of schizophrenia patients and healthy controls at baseline and follow-up.



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.

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) = 0.631	0.529
Gender				
M (%)	77	79	X^2 (1) = 0.108	0.743
F (%)	23	21		
IQ	96.82 ± 15.23	91.29 ± 15.84	t (418) = 4.393	<0.001
Illness duration (years)	4.29 ± 3.90	3.90 ± 3.59	t (468) = 1.329	0.185
Age of onset (years)	22.57 ± 6.88	22.67 ± 6.64	t (453) = -0.194	0.846
Episodes (n)	1.65 ± 0.95	1.85 ± 1.33	t (750) = -2.443	0.015
PANSS POS	12.21 ± 5.00	13.46 ± 5.16	t (404) = -3.025	0.003
PANSS NEG	13.29 ± 5.53	15.76 ± 6.44	t (728) = -5.192	<0.001
PANSS GEN	28.84 ± 8.51	32.29 ± 8.88	t (397) = -4.861	<0.001
Medication				
Typical (%)	86	81	X^2 (3) = 26.78	0.031
Atypical (%)	14	19		
DFAR total	69.41 ± 9.794	68.40 ± 9.810	t (472) = 1.331	0.185

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 (years)	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	X^2 (1) = 119.62	<0.001	69	78	85	81	X^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 (years)	-	4.29 ±3.90	-	-	4.33 ±3.74	4.61 ±3.37	4.75 ±3.97	3.86 ±4.62	F (4) = 1.23	0.297
Age of onset (years)	-	22.57 ±6.88	-	-	22.55 ±6.52	23.62 ±6.75	22.93 ±6.93	21.27 ±6.31	F (4) = 2.19	0.088
Episodes (n)	-	1.65 ±0.95	-	-	1.60 ±0.82	1.68 ±0.91	1.74 ±1.10	1.55 ±0.93	X^2 (3) = 30.59	0.213
PANSS POS Baseline	-	12.21 ±5.00	-	-	9.15 ±2.38	9.69 ±2.38	15.82 ±5.20	13.79 ±4.87	F (4) = 88.50	<0.001
PANSS POS Follow-up	-	10.87 ±4.40	-	-	8.47 ±2.09	13.35 ±5.12	14.53 ±4.87	9.13 ±2.18		
PANSS NEG Baseline	-	13.29 ±5.53	-	-	9.70 ±3.13	10.73 ±3.13	17.07 ±5.67	16.17 ±5.04	F (4) = 96.51	<0.001
PANSS NEG Follow-up	-	11.60 ±5.02	-	-	8.94 ±2.52	14.52 ±6.11	15.41 ±5.64	10.05 ±2.80		
PANSS GEN Baseline	-	28.84 ±8.51	-	-	23.39 ±5.06	25.43 ±5.52	34.79 ±8.22	32.15 ±7.85	F (4) = 90.47	<0.001
PANSS GEN Follow-up	-	25.32 ±7.50	-	-	21.34 ±5.18	30.80 ±8.76	30.97 ±7.25	22.84 ±4.40		
Typical (%)	-	86	-	-	88	91	81	87	X^2 (3) = 2.85	0.416
Atypical (%)	-	14	-	-	10	9	15	10		

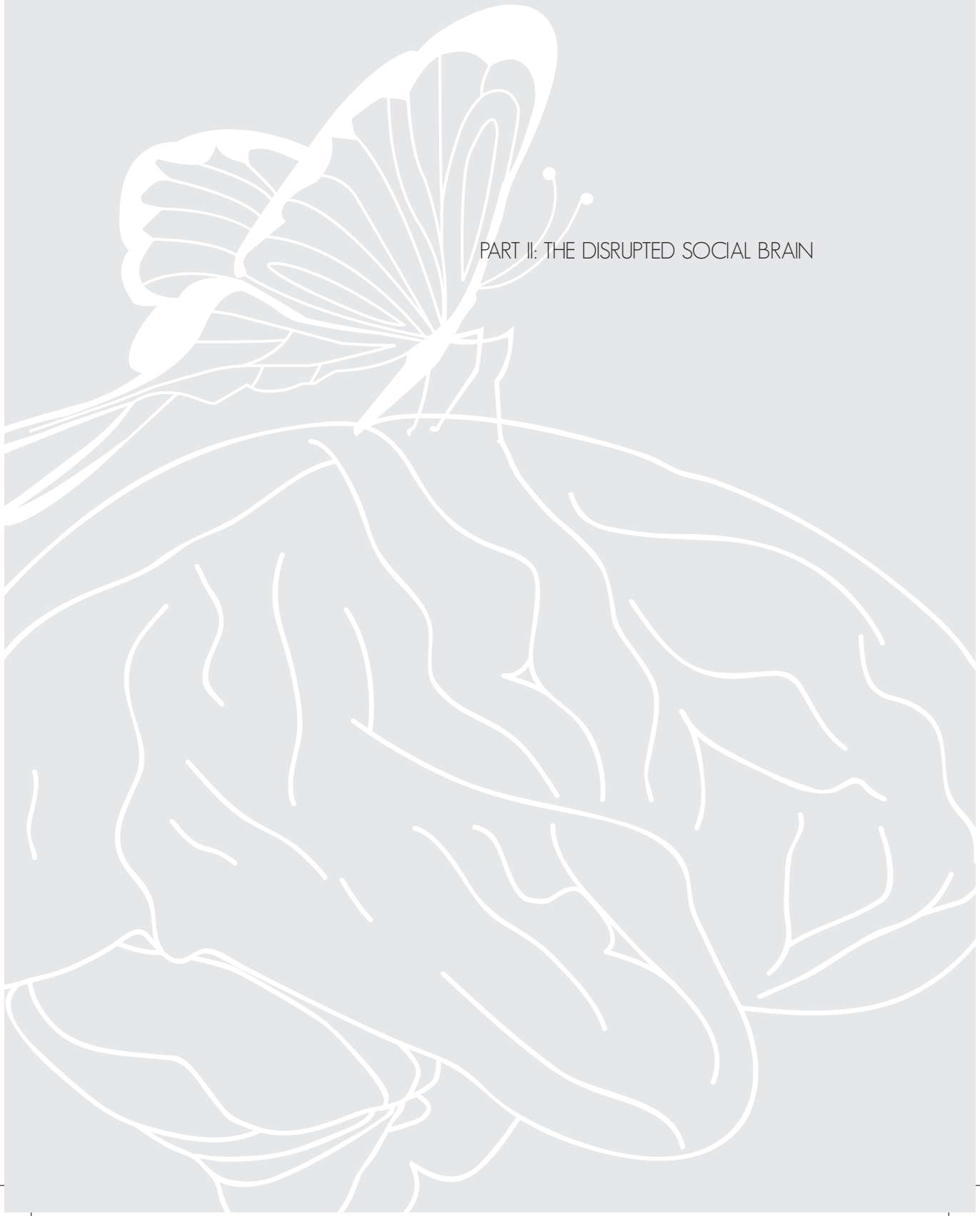
Abbreviations: HC = healthy controls, PT = schizophrenia patients, RR = schizophrenia patients in remission at baseline and in remission at follow-up, RN = schizophrenia patients in remission at baseline and in non-remission at follow-up, NN = schizophrenia patients in non-remission at baseline and in 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, Typical = typical antipsychotic, Atypical = atypical antipsychotic.

Table 3 | DFAR total performance of schizophrenia patients and healthy controls at baseline and follow-up

	DFAR total Baseline	DFAR total Follow-up
Group	Mean ± SD	Mean ± SD
HC	73.55 ±9.14	74.34 ±9.24
Total PT	69.41 ±9.79	70.34 ±9.72
RR	70.30 ±9.37	72.40 ±9.12
RN	70.55 ±9.11	68.07 ±8.52
NN	68.25 ±10.17	68.77 ±10.50
NR	69.12 ±10.20	70.16 ±9.60

Abbreviations: DFAR total = total score on the degraded facial affect recognition task, 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.

PART II: THE DISRUPTED SOCIAL BRAIN



04

EMOTION RECOGNITION AND THEORY OF MIND ARE RELATED TO GRAY MATTER VOLUME OF THE PREFRONTAL CORTEX IN SCHIZOPHRENIA

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ABSTRACT

Background: Investigations of social cognition in schizophrenia have demonstrated consistent impairments compared to healthy controls. Functional imaging studies in schizophrenia patients and healthy controls have revealed that social cognitive processing depends critically on the amygdala and the prefrontal cortex (PFC). However, the relationship between social cognition and structural brain abnormalities in these regions in schizophrenia patients is less well examined. Methods: Measures of facial emotion recognition and theory of mind (ToM), two key social cognitive abilities, as well as face perception and IQ, were assessed in 166 patients with schizophrenia and 134 healthy controls, and MRI brain scans were acquired. Automated parcellation of the brain to determine gray matter volume of the amygdala and the superior, middle, inferior and orbital PFC was performed. Results: Between-group analyses showed poorer recognition of angry faces and ToM performance, and decreased amygdala and PFC gray matter volumes in schizophrenia patients as compared to healthy controls. Moreover, in schizophrenia patients, recognition of angry faces was associated with inferior PFC gray matter volume, particularly the pars triangularis ($p= 0.006$), with poor performance being related to reduced pars triangularis gray matter volume. In addition, ToM ability was related to PFC gray matter volume, particularly middle PFC ($p= 0.001$), in that poor ToM skills in schizophrenia patients were associated with reduced middle PFC gray matter volume. Conclusions: Reduced PFC, but not amygdala, gray matter volume is associated with social cognitive deficits in schizophrenia.

KEYWORDS

Amygdala, Emotion Recognition, Magnetic Resonance Imaging, Prefrontal Cortex, Schizophrenia, Social cognition, Theory of mind

1. INTRODUCTION

Emotional dysfunction is one of the core clinical features of schizophrenia, already described by Emil Kraepelin, who first delineated the disorder (Kraepelin, 1893). Emotional expression, perception and experience are part of the construct of "social cognition", which refers to the cognitive processing of social information (Pinkham, 2003). Investigations of social cognition in schizophrenia reveal consistent impairments compared to healthy controls, particularly in emotion recognition and theory of mind (ToM) (Bora *et al*., 2009; Kohler *et al*., 2010). Emotion recognition, i.e., the ability to infer emotional information from facial expressions (Couture *et al*., 2006), and ToM, i.e., the ability to infer the intentions and beliefs of other individuals (Baron-Cohen *et al*., 2001), are important domains of social cognition, because they appear to be valid predictors of social functioning (Couture *et al*., 2006; Fett *et al*., 2011; Green *et al*., 2005). Moreover, it has been argued that impairments in emotion recognition and ToM may even trump the value of general cognition and symptoms in explaining outcome in schizophrenia (Fett *et al*., 2011; Pijnenborg *et al*., 2009).

In healthy individuals social cognition has been extensively studied using primarily functional imaging, and a network of brain regions subserving social cognition has been identified (Adolphs *et al*., 2009; Brothers *et al*., 1990). In short, the processing of facial expressions depends critically on the amygdala and the orbitofrontal cortex (Adolphs *et al*., 2002; Hornak *et al*., 1996), whereas in mentalizing-tasks, such as ToM, the medial and orbitofrontal cortices are critical (Adolphs *et al*., 2009; Baron-Cohen *et al*., 1994; Fletcher *et al*., 1995; Gallagher *et al*., 2000; Vogeley *et al*., 2001).

In schizophrenia, functional neuroimaging studies have consistently demonstrated reduced activity of the amygdala during processing of facial emotions compared to healthy controls (Aleman and Kahn, 2005; Pessoa, 2008) and reduced activation of the prefrontal cortex (PFC) has been related to impaired performance on ToM-tasks (Brunet *et al*., 2003; Dollfus *et al*., 2008; Hill *et al*., 2004; Walter *et al*., 2009). Indeed,

a recent meta-analysis of functional imaging studies comprising 450 schizophrenia patients and 422 healthy controls has shown reduced amygdala and PFC activity during social cognitive tasks in schizophrenia (Taylor *et al*., 2012).

In contrast to the numerous functional neuroimaging studies in schizophrenia, only few structural imaging studies investigated the relationship between abnormalities of the amygdala and PFC, in relation to social cognitive deficits seen in patients. Specifically, volume reductions of the amygdala were found in relation to emotion recognition deficits (Exner *et al*., 2004; Namiki *et al*., 2007). In addition, volume reductions of the PFC were found in relation to ToM deficits in schizophrenia, particularly in the middle PFC (Bertrand *et al*., 2008; Yamada *et al*., 2007), the ventral PFC (Hirao *et al*., 2008; Hooker *et al*., 2011) and orbitofrontal cortex (Herold *et al*., 2009). So far, samples have been small (between 16 and 38 schizophrenia patients), and all but one of these studies (Namiki *et al*., 2007) used Voxel Based Morphometry (VBM) as a method to survey the whole brain for gray matter volume alterations. Usually, no specific regions of interest (ROI's) were defined and a correction for multiple comparisons was not applied. Furthermore, the influence of IQ and symptomatology was often disregarded. Although general cognition (IQ) and social cognition appear separable domains (van Hooren *et al*., 2008), it has been argued that social cognitive impairment in schizophrenia is non-specific and estimates of variance in social cognition accounted for by general cognition range from 34 to 83% (Sergi *et al*., 2007; Vauth *et al*., 2004). Also, despite consistent evidence that severity of symptoms is negatively associated with gray matter volume (Boos *et al*., 2012; Cahn *et al*., 2009), most studies on the association between social cognition and gray matter volume did not correct for schizophrenia symptom severity.

In the present study we use an automated parcellation method (Freesurfer 5.1) to examine amygdala and PFC volumes and their association with facial emotion recognition and ToM skills in a large sample of schizophrenia patients and healthy controls, controlling for IQ and symptom severity. We hypothesize that social

cognitive deficits in schizophrenia are related to a reduction of gray matter volume in the amygdala and PFC.

2. METHOD

2.1. PARTICIPANTS

A total of 166 schizophrenia patients and 134 healthy controls were included. Participants were recruited at the University Medical Center Utrecht, the Netherlands, as part of a large cohort 'Genetic Risk and Outcome in Psychosis' (GROUP) study. The procedure of recruitment, informed consent and approval by the accredited Medical Ethics Review Committee (METC) has been described in a previous report on the GROUP study (Korver *et al*., 2012).

Study participants were between 16 and 60 years of age and were fluent in Dutch. Subjects with a history of head trauma or major medical or neurological illness were excluded. Patients had to meet the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (APA, 2000) criteria for a non-affective psychotic disorder, as assessed by the Comprehensive Assessment of Symptoms and History Interview (CASH) (Andreasen *et al*., 1992). Symptom severity was assessed using the Positive and Negative Syndrome Scale (PANSS; Kay *et al*., 1987); and the type and current dose of antipsychotic therapy was documented. The healthy control group had no current or lifetime psychiatric disorder, as assessed by the CASH (Andreasen *et al*., 1992), and no first or second degree family member with a lifetime psychotic disorder.

2.2. COGNITIVE MEASURES

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

2.2.1 Emotion Perception

Degraded Facial Affect Recognition Task. The facial affect recognition task (van 't Wout *et al*., 2004) uses black and white photographs of four different actors (two male, two female) depicting four emotions: angry, happy, fearful and neutral. The task comprises 64 trials consisting of 16 face presentations in each emotion category. The emotions are shown with 75% intensity in order to increase the difficulty of the task. Subjects are asked to indicate the emotional expression of each face with a button press and to respond as accurately as possible. Outcome is the proportion of faces correctly recognized as neutral, happy, fearful and angry emotions (range: 0-100%).

2.2.2. General facial recognition ability

Benton facial recognition test (short form). The Benton facial recognition test (Benton *et al*., 1983) measures the ability to match unfamiliar faces. It is used to assess whether deficits in facial affect recognition are mediated by differences in general facial recognition ability. Subjects are presented with a target face above six test faces, and they are asked to indicate which of the six images match the target face. The outcome range is 0–27.

2.2.3 Theory of mind

Hinting task. Theory of mind was assessed with the hinting task (Corcoran *et al*. 1995; Janssen *et al*. 2003; Vermissen *et al*. 2008). The task tests the ability of subjects to infer the real intentions behind indirect speech utterances. It comprises ten short passages presenting an interaction between two characters that end with one of the characters dropping a hint. The subject is then asked to indicate what the character really meant. Correctly identified hints are scored with two points. In case of an incorrect response a more obvious hint is added. A subsequent correct response is scored with one point; an incorrect response is scored as zero. The score range is 0-20.

2.2.4 Cognition

Wechsler Adult Intelligence Scale (WAIS III). The Arithmetic (working memory), Digit Symbol-Coding (processing speed), Block Design (reasoning and problem solving) and Information subtests (verbal comprehension) of the WAIS III were administered to estimate IQ (Blyler *et al*. 2000; Wechsler, 1997). The sum of the four subtests yields a measure of estimated IQ.

2.3 IMAGING

Magnetic resonance imaging (MRI) data were obtained on a 1.5 T Achieva scanner (Philips Medical Systems, Best, The Netherlands). Three-dimensional T1-weighted scans (FFE pulse sequence, TR/TE=30 ms/4.6 ms, flip-angle 30°, FOV 256×256 mm^2, voxelsize 1×1×1.2 mm^3, 160–180 contiguous slices) of the whole brain were acquired. T1-images were processed using Freesurfer software (version 5.1.0; http://surfer.nmr.mhg.harvard.edu; Dale *et al*. 1999; Fischl *et al*. 1999). The Freesurfer suite was used for automatic segmentation of subcortical gray matter regions and for automatic parcellation of the cortical surface into cortical gray matter regions. Thirty-four cortical structures were labeled per hemisphere using the Desikan–Killiany atlas (Desikan *et al*. 2006). This study focused on a priori defined amygdala and PFC regions. The eight bilateral PFC regions produced by Freesurfer were used to compute four bilateral prefrontal cerebral lobes: 1) superior PFC, 2) middle PFC (rostral and caudal part), 3) inferior PFC (pars triangularis and pars operculum) and 4) orbitofrontal cortex (lateral and medial part and pars orbitalis). The quality of the parcellation was checked by AM, blind to subject identity and clinical information. Segmentations were deemed unfit for analysis when visual inspection of the volumes clearly showed a segmentation fault, either by not including the whole structure or by clearly exceeding the structure boundary. As a result of this procedure not one PFC volume was discarded, and four amygdala volumes were discarded.

2.4. ANALYSES

Statistical analyses were performed using SPSS version 20.0. First, the normality of the

data was tested using Kolmogrov-Smirnov analysis. All ROIs as well as the behavioral data were normally distributed, except for the hinting task. Statistical testing of group-differences in demographic characteristics was performed using analysis of variance (ANOVA) for continuous and chi-squared tests for categorical variables.

2.4.1 Between-group differences in social cognition and gray matter volume

Differences in social cognition between schizophrenia patients and healthy controls may be confounded by general cognitive performance, age and gender. Therefore, we evaluated the differences in social cognitive impairments with ANCOVA adjusted for estimated IQ, age and gender. Performance on the degraded facial affect recognition task was also adjusted for general facial recognition ability. Further analyses were limited to the social cognitive variables where patients differed significantly from healthy controls.

ANCOVA's were used to assess the effect of group (patient/ healthy control) on amygdala gray matter volume and gray matter volume of the four sub regions of the PFC; 1) superior PFC; 2) middle PFC; 3) inferior PFC, and 4) orbitofrontal cortex. Age, gender and intracranial volume were included as covariates in the structural brain analyses. For those sub regions of the PFC that showed a significant group difference, we further specified our results by analyzing the individual sub cortices of that region (i.e., for the middle PFC the rostral and caudal part, for the inferior PFC the pars triangularis and the pars operculum, and for the orbitofrontal cortex the lateral and medial part and the pars orbitalis).

2.4.2 Regression analyses of social cognition and gray matter volume

For those social cognitive measures where patients performed significantly worse than controls, linear regression analyses were conducted to investigate the association between gray matter volume of the ROI's and test-performance. Participant age and gender were entered as covariates, as well as intracranial volume. First, we investigated if gray matter volume of the amygdala and PFC had a main effect on social cognitive

performance in healthy controls. Second, we investigated if gray matter volume of the amygdala and PFC had a main effect on social cognitive performance in patients. To control for the influence of symptom severity and antipsychotic medication, this analysis was repeated using Total PANSS score and antipsychotic medication dose, in a haloperidol equivalent, as covariates. Third, to identify whether a possible association between the two variables differed between the groups, we conducted a regression analysis on gray matter volume, in which we added the interaction between group (patient/ healthy control) and social cognitive measure as well as both main effects. To verify that the findings were not explained by differences in general cognition between healthy controls and patients, this analysis was repeated controlling for IQ.

As often is the case (Fett *et al*. 2013; Hooker *et al*. 2011), the performance data for the hinting task (range: 0-20) were skewed towards perfect performance in healthy controls (M = 18.88, SD = 1.25), and to a lesser extent also in patients (M = 16.51, SD = 3.21), thereby violating the assumption of normal distribution. Therefore, two subgroups were created within the patient group; i.e., 'poor' and 'good' performers. The lowest hinting task score in the healthy control group (score = 15) was used as upper thresholds for 'poor'- performers among schizophrenia patients. An ANCOVA was conducted to examine whether 'poor' and 'good'- performers differed in gray matter volume of the ROI's, i.e., amygdala, superior -, middle-, and inferior PFC, and orbitofrontal cortex. In line with our analysis on emotion recognition described above, the analyses for the hinting task were repeated controlling for schizophrenia symptoms (i.e., total PANSS score), antipsychotic medication intake, and general cognition (i.e., IQ). A type-I error rate of p=0.05 was used for all analyses.

3. RESULTS

Demographic and clinical characteristics of all participants and the statistical significance of group-differences are provided in Table 1. Patients were not significantly different in age, but were more frequently male and had significantly lower IQ, as

compared to the healthy controls.

3.1 BETWEEN-GROUP DIFFERENCES ON SOCIAL COGNITION

Schizophrenia patients performed significantly worse than healthy controls on the hinting task. In addition, performance in recognition of angry faces was significantly worse in schizophrenia patients compared to healthy controls. Performance in recognition of neutral, happy and fearful faces was not different between patients and healthy controls. See table 1.

3.2 BETWEEN-GROUP DIFFERENCES ON GRAY MATTER VOLUME

Gray matter volume was reduced in schizophrenia patients as compared to healthy controls for all ROI's; i.e, amygdala, superior PFC, middle PFC (rostral and caudal part), inferior PFC (pars triangularis and pars operculum) and orbitofrontal cortex (lateral part and pars orbitalis, but not the medial orbitofrontal cortex). See table 1.

3.3 RELATIONSHIP BETWEEN SOCIAL COGNITION AND GRAY MATTER VOLUME

Schizophrenia patients showed a significant association between angry face recognition and inferior PFC gray matter volume, in that poorer performance was associated with reduced inferior PFC gray matter volume (B = 18.10, ß = 0 .16, t (141) = 2.19, p = 0.03). In particular, a reduction of pars triangularis gray matter volume of the inferior PFC, was related to poorer recognition of angry faces in schizophrenia patients (B = 11.07, ß = 0.17, t (141) = 2.29, p = 0.02). Repeated analyses that corrected for the effects of symptom severity and current dose of antipsychotic medication, did not affect these findings. In healthy controls, we found a trend level significant negative association between angry face recognition and pars triangularis gray matter volume (B =-12.32, ß = -0.14, t (118) = -1.87, p = 0.06). The interaction analysis showed that the relationship between pars triangularis gray matter volume and angry face recognition was significantly different in schizophrenia patients compared to healthy

controls (Group*anger: B = 22.46, ß = 0.54, t (262) = 6.11, p = 0.006), see figure 1. When adding IQ to the regression as a covariate, the findings remained essentially the same (Group*anger: B = 18.85, ß = 0.46, t (261) = 2.36, p = 0.02). Both patients and healthy controls did not show a significant relationship between angry face recognition and amygdala volume.

Table 2 shows between group differences in demographic variables between 'poor' and 'good' hinting task performance among schizophrenia patients. Poor performers had significantly lower IQ and more severe negative symptoms. Significant differences between 'poor' and 'good' performers were found for gray matter volume of the superior PFC (F (1, 146) = 4.66, p = 0.03) and middle PFC (i.e, the rostral part; F (1, 146) = 11.38, p = 0.001), even after controlling for IQ (Table 2). When controlling for schizophrenia symptoms, only the rostral middle PFC remained significantly related to performance on the hinting task (F(1, 138) = 6.94, p = 0.01) (Figure 2). There was no difference in amygdala gray matter volume between the two subgroups.

4. DISCUSSION

This study investigated the relationship of emotion recognition and theory of mind (ToM) with gray matter volumes of the amygdala and prefrontal cortex (PFC) in 166 schizophrenia patients and 134 healthy controls. Schizophrenia patients showed poorer recognition of angry faces and impaired ToM performance, as well as decreased amygdala and PFC gray matter volumes, compared to healthy controls. PFC, but not amygdala, gray matter volume was related to emotion recognition and ToM performance in schizophrenia. Specifically, a reduction of pars triangularis gray matter volume was related to poorer emotion recognition, while a reduction of middle PFC gray matter volume was related to poorer ToM skills. The association between PFC gray matter volume and these aspects of social cognition was not present in healthy controls.

The finding that schizophrenia patients showed poorer recognition of angry faces compared to healthy controls is consistent with previous reports of impairment of negative affect recognition in schizophrenia, showing that the ability of patients to attribute negative emotions to facial expressions is significantly compromised (Bediou *et al*. 2005; Mandal *et al*. 1998). Furthermore, in line with previous studies showing that schizophrenia patients are impaired in their ability to infer the intentions of other people (Bora *et al*. 2009), patients performed worse than healthy controls on the ToM-task.

Also, schizophrenia patients demonstrated significant volume deficits in the amygdala and PFC as compared to healthy controls. This is in line with results from a recent meta-analysis reporting, among others, on reduction in both the amygdala and PFC in schizophrenia patients relative to healthy controls (Haijma *et al*., 2013).

Our finding of a relationship between social cognition and reduced PFC gray matter volume is consistent with neuroimaging studies using VBM (Bertrand *et al*., 2008; Herold *et al*., 2009; Hirao *et al*., 2008; Hooker *et al*., 2011; Yamada *et al*., 2007). The PFC is a heterogeneous structure; the subregions of the PFC differ in their cytoarchitecture as well as connectivity to other parts of the brain (Fuster, 1989). The specific link between gray matter volume of the pars triangularis and emotion recognition on the one hand, and gray matter volume of the middle PFC and ToM skills on the other, lends further support to previous evidence from structural imaging studies that individual sub-regions of the PFC mediate different cognitive processes (Buchanan *et al*., 1998; Crespo-Facorro *et al*., 2000; Venkatasubramanian *et al*., 2008; Wiegand *et al*., 2004).

The PFC, which constitutes one third of the neocortex, is one of the last parts of the cortex to develop in the human brain (Fuster, 2001; Fuster, 2002). The late maturation of this region of the brain is consistent with behavioral evidence that the PFC is critical for those higher cognitive functions that develop later in life, like

complex linguistics and mentalizing skills, such as ToM (Venkatasubramanian *et al*., 2008). Also, the phylogenetic recentness of the PFC supports the observation that it is crucial in complex social cognitive functions, a faculty in which humans are considered to be more specialized than most other primates (Povinelli and Preuss, 1995; Semendeferi, 2012). We specifically found volumes of two regions of the PFC, i.e., the pars triangularis and the middle PFC, to be related to social cognition. Both regions contain so called 'mirror neurons' (Bertrand *et al*., 2008; Johnson-Frey *et al*., 2003; Nieuwenhuys *et al*., 2008), discharging when a person observes another individual performing an action that is similar to that encoded by this neuron (Nieuwenhuys *et al*., 2008). A recent study on the biological underpinnings of empathy in schizophrenia showed an abnormal functioning mirror neuron system as measured using electroencephalography (McCormick *et al*., 2012). In this context, we speculate that the volume deficits in the pars triangularis and middle PFC and their association with social cognitive deficits observed in this study, might reflect mirror neuron loss in schizophrenia patients.

Although we found reduced amygdala volume and poorer social cognition in schizophrenia patients compared to healthy controls, we did not demonstrate an association between amygdala volume and either measure of social cognition. The absence of this relationship, especially with emotion recognition, contrasts with results from one previous study that used manual tracing and reported an association between amygdala volume and sadness emotion recognition (Namiki *et al.,* 2007), and another study that used VBM, which found an association between amygdala volume and emotional learning (Exner *et al.,* 2004). This inconsistency with our findings could be explained by differences in patient characteristics, as our patients were relatively young and had a shorter duration of illness than the patients in these studies. Perhaps in earlier illness stages the amygdala, while seemingly reduced in volume relative to healthy controls, is not at the level where it translates to a secondary effect on performance. Accordingly, the amygdala volume of the patients in the above mentioned studies was relatively small, i.e., M = 2730.00 mm^3 (Exner *et*

al., 2004) and M = 2199.81 mm^3 (Namiki *et al.,* 2007), as compared to the amygdala volume of the patients in the present study, i.e., M = 3229.43 mm^3. In earlier stages of illness, emotion recognition deficits may be partially explained by reduced PFC gray matter volume, rather than reduced amygdala gray matter volume.

Neuroimaging studies examining functional brain connectivity show that the amygdalae are strongly connected to prefrontal areas (Aleman and Kahn, 2005; Iidaka *et al*., 2001; Kim *et al*., 2011; Mukherjee *et al*., 2013; Stein *et al*., 2007). Two fMRI studies examining frontolimbal connectivity during social cognitive tasks demonstrated significantly weaker amygdala-prefrontal cortical coupling in schizophrenia patients as compared to healthy controls (Anticevic *et al*., 2012; Das *et al*., 2007). The regional volume reductions in the PFC in schizophrenia patients might be related to hypofunction in these specific parts of the PFC (Hill *et al*., 2004; Russell *et al*., 2000). The volumetric and functional changes of the PFC in schizophrenia patients might reduce the connectivity between the PFC and the amygdala, and consequently induce altered functional processing in the amygdala during social cognitive tests, as shown in previous functional MRI research (Aleman and Kahn, 2005). Our findings suggest that the reduced amygdala activity seen in schizophrenia during social cognitive tasks is not the result of reduced amygdala gray matter volume, but could be explained by the loss of PFC gray matter volume.

Some limitations should be noted. First, all the patients in the study were medicated, and many were mildly symptomatic at the time of scanning. However, including current dose of antipsychotic medication or symptom severity as a covariate in our analyses did not change the main results. Nevertheless, for the ToM task, the superior frontal cortex did not remain statistically significant when controlling for schizophrenia symptoms. This might be explained by previous studies suggesting an association between illness severity and reduced gray matter volume (Boos *et al*., 2012; Cahn *et al*., 2009). Second, we did not examine other brain regions such as the temporal lobe, which has been found related to social cognition in at least

one structural ROI study (Goghari *et al*., 2011). Third, the hinting task, that was used to assess ToM, was too easy for healthy controls, which resulted in a ceiling effect. However, we took this into account by limiting the analysis for the hinting task to schizophrenia patients only.

In summary, this is the largest study in schizophrenia patients to date, examining the relationship between two aspects of social cognition, i.e., emotion recognition and ToM, and two previously established key regions of the social brain, i.e., the amygdala and the PFC. The results show that reduced PFC gray matter volume, but not amygdala gray matter volume, is associated with social cognitive deficits in schizophrenia. Further research, combining structural imaging and functional connectivity analysis of the brain, is needed to investigate whether disrupted amygdala-prefrontal connectivity underlies abnormal social cognition in schizophrenia.

REFERENCES

Adolphs R., Baron-Cohen S., Tranel, 2002. Impaired recognition of social emotions following amygdala damage. Journal of Cognitive Neuroscience 14, 1264–1274.

Adolphs R., 2009. The social brain: neural basis of social knowledge. Annual Review of Psychology 60, 693–716.

Aleman A., Kahn R.S., 2005. Strange feelings: do amygdala abnormalities dysregulate the emotional brain in schizophrenia? Progress in Neurobiology 77 (5), 283-98.

American Psychiatric Association, 2000. Diagnostic and Statistical Manual of Mental Disorders, fourth ed., text revision. American Psychiatric Association: Washington, DC.

Andreasen N.C., Flaum M., Arndt S., 1992. The Comprehensive Assessment of Symptoms and History (CASH). An instrument for assessing diagnosis and psychopathology. Archives of General Psychiatry 49 (8), 615–623.

Anticevic A., Repovs G., Barch D.M., 2012. Emotion Effects on Attention, Amygdala Activation, and Functional Connectivity in Schizophrenia. Schizophrenia Bulletin 38 (5), 967–980.

Baron-Cohen S., Ring H., Moriarty J., Schmitz B., Costa D., Ell P., 1994. Recognition of mental state terms. Clinical findings in children with autism and a functional neuroimaging study of normal adults. British Journal of Psychiatry 165 (5), 640–649.

Baron-Cohen S., Wheelwright S., Hill J., Raste Y., Plumb I., 2001. The "Reading the Mind in the Eyes" Test revised version: a study with normal adults, and adults with Asperger syndrome or high-functioning autism. Journal of child psychology and psychiatry 42, 241–251.

Bediou B., Franck N., Saoud M., Baudouin J.Y., Tiberghien G., Dalery J., d'Amato T., 2005. Effects of emotion and identity on facial affect processing in schizophrenia. Psychiatry Research 133, 149–157.

Benton A.L., Sivan A.B., Hamsher K.D., Varney N.R., Spreen O., 1983. Benton's Test of Facial Recognition. Oxford University Press: New York, NY.

Bertrand M.C., Achim A.M., Harvey P.O., Sutton H., Malla A.K., Lepage M., 2008. Structural neural correlates of impairments in social cognition in first episode psychosis. Social Neuroscience 3 (1), 79–88.

Blyler C.R., Gold J.M., Iannone V.N., Buchanan R.W., 2000. Short form of the WAIS-III for use with patients with schizophrenia. Schizophrenia Research 46, 209–215.

Boos H.B., Cahn W., van Haren N.E., Derks E.M., Brouwer R.M., Schnack H.G., Hulshoff Pol H.E., Kahn R.S., 2012. Focal and global brain measurements in siblings of patients with schizophrenia. Schizophrenia Bulletin 38 (4), 814-25.

Bora E., Yucel M., Pantelis C., 2009. Theory of mind impairment in schizophrenia: meta-analysis. Schizophrenia Research 109, 1–9.

Brothers L., 1990. The social brain: a project for integrating primate behaviour and neurophysiology in a new domain. Concepts Neuroscience 1, 27–51.

Brunet E., Sarfati Y., Hardy-Baylé M.C., Decety J., 2003. Abnormalities of brain function during a nonverbal theory of mind task in schizophrenia. Neuropsychologia 41 (12), 1574–1582.

Buchanan R.W., Vladar K., Barta P.E., Pearlson G.D., 1998. Structural evaluation of the prefrontal cortex in schizophrenia. American Journal of Psychiatry 155, 1049–1055.

Cahn W., Rais M., Stigter F.P., 2009. Psychosis and brain volume changes during the first five years of schizophrenia. European Journal of Neuropsychopharmacology 19, 147-151.

Crespo-Facorro B., Kim J., Andreasen N.C., O' Leary D.S., Magnotta V., 2000. Regional frontal abnormalities in schizophrenia: a quantitative gray matter volume and cortical surface size study. Biological Psychiatry 48, 110–119.

Corcoran R., Mercer G., Frith C.D., 1995. Schizophrenia, symptomatology and social inference: investigating "theory of mind" in people with schizophrenia. Schizophrenia Research 17, 5–13.

Couture S.M., Penn D.L., Roberts D.L., 2006. The functional significance of social cognition in schizophrenia: a review. Schizophrenia Bulletin 32 (S1), S44–S63.

Dale A.M., Fischl B., Sereno M.I., 1999. Cortical surface-based analysis. I. Segmentation and surface reconstruction. Neuroimage 9 (2), 179–194.

Das P., Kemp A.H., Flynn G., Harris A.W.F., Liddell B.J., Whitford T.J., Peduto A., Gordon E., Williams L.M., 2007. Functional disconnections in the direct and indirect amygdala pathways for fear processing in schizophrenia. Schizophrenia Research 90, 284-294.

Desikan R.S., Ségonne F., Fischl B., Quinn B.T., Dickerson B.C., Blacker D., Buckner R.L., Dale A.M., Maguire R.P., Hyman B.T., Albert M.S., Killiany R.J., 2006. An automated labeling system for subdividing the human cerebral cortex on MRI scans into gyral based regions of interest. Neuroimage 31, 968–980.

Dollfus S., Razafimandimby A., Maiza O., Lebain P., Brazo P., Beaucousin V., Lecardeur L., Delamillieure P., Mazoyer B., Tzourio-Mazoyer N., 2008. Functional deficit in the medial prefrontal cortex during a language comprehension task in patients with schizophrenia. Schizophrenia Research 99 (1–3), 304–311.

Exner C., Boucsein K., Degner D., Irle E., Weniger G., 2004. Impaired emotional learning and reduced amygdala size in schizophrenia: a 3-month follow-up. Schizophrenia Research 71 (2-3), 493-503.

Fett A.K., Viechtbauer W., Dominguez M.D., Penn D.L., van Os J., Krabbendam L., 2011. The relationship between neurocognition and social cognition with functional outcomes in schizophrenia: a meta-analysis. Neuroscience and biobehavioral reviews 35 (3), 573-88.

Fett A.K., Maat A.; GROUP Investigators, 2013. Social cognitive impairments and psychotic symptoms: what is the nature of their association? Schizophrenia Bulletin 39 (1), 77-85.

Fischl B., Sereno M.I., Dale A.M., 1999. Cortical surface-based analysis. II: inflation, flattening, and a surface-based coordinate system. Neuroimage 9 (2), 195–207.

Fletcher P.C., Happe F., Frith U., Baker S.C., Dolan R.J., Frackowiak R.S., Frith C.D., 1995. Other minds in the brain: a functional imaging study of "theory of mind" in story comprehension. Cognition 57 (2), 109–128.

Fuster J.M., 1989. The prefrontal cortex, second ed. Raven Press: New York.

Fuster J.M., 2002. Frontal lobe and cognitive development. Journal of Neurocytology 31 (3-5), 373-85.

Fuster J.M., 2001. The prefrontal cortex--an update: time is of the essence. Neuron 30 (2), 319-33.

Gallagher H.L., Happe F., Brunswick N., Fletcher P.C., Frith U., Frith C.D., 2000. Reading the mind in cartoons and stories: an fMRI study of 'theory of mind' in verbal and nonverbal tasks. Neuropsychologia 38 (1), 11–21.

Goghari V.M., Macdonald A.W. 3rd, Sponheim S.R., 2011. Temporal lobe structures and facial emotion recognition in schizophrenia patients and nonpsychotic relatives. Schizophrenia Bulletin 37 (6), 1281-94.

Green M.F., Olivier B., Crawley J.N., Penn D.L., Silverstein S., 2005. Social cognition in schizophrenia: recommendations from the measurement and treatment research to improve cognition in schizophrenia new approaches conference. Schizophrenia Bulletin 31, 882–887.

Haijma S.V., Van Haren N., Cahn W., Koolschijn C.P., Hulshoff Pol H.E., Kahn R.S., 2013. Brain Volumes in Schizophrenia: A Meta-Analysis in Over 18 000 Subjects. Schizophrenia Bulletin 39 (5), 1129–1138.

Herold R., Feldmann A., Simon M., Tényi T., Kövér F., Nagy F., Varga E., Fekete S., 2009. Regional gray matter reduction and theory of mind deficit in the early phase of schizophrenia: a voxel-based morphometric study. Acta psychiatrica Scandinavica 119 (3), 199-208.

Hill K., Mann L., Laws K.R., Stephenson C.M., Nimmo-Smith I., McKenna P.J., 2004. Hypofrontality in schizophrenia: a metaanalysis of functional imaging studies. Acta psychiatrica Scandinavica 110, 243–256.

Hirao K., Miyata J., Fujiwara H., Yamada M., Namiki C., Shimizu M., Sawamoto N., Fukuyama H., Hayashi T., Murai T., 2008. Theory of mind and frontal lobe pathology in schizophrenia: a voxel-based morphometry study. Schizophrenia Research 105 (1–3), 165–174.

Hooker C.I., Bruce L., Lincoln S.H., Fisher M., Vinogradov S., 2011. Theory of mind skills are related to gray matter volume in the ventromedial prefrontal cortex in schizophrenia. Biological Psychiatry 70 (12), 1169-78.

van Hooren S., Versmissen D., Janssen I., Myin-Germeys I., à Campo J., Mengelers R., van Os J., Krabbendam L., 2008. Social cognition and neurocognition as independent domains in psychosis. Schizophrenia Research 103 (1-3), 257-65.

Hornak J., Rolls E.T., Wade D., 1996. Face and voice expression identification in patients with emotional and behavioural changes following ventral frontal lobe damage. Neuropsychologia 34 (4), 247–261.

Iidaka T., Omori M., Murata T., Kosaka H., Yonekura Y., Okada T., Sadato N., 2001. Neural interaction of the amygdala with the prefrontal and temporal cortices in the processing of facial expressions as revealed by fMRI. Journal of Cognitive Neuroscience 13, 1035–1047.

Janssen I., Krabbendam L., Jolles J., van Os J., 2003. Alterations in theory of mind in patients with schizophrenia and non-psychotic relatives. Acta psychiatrica Scandinavica 108 (2), 110–117.

Johnson-Frey S.H., Maloof F.R., Newman-Norlund R., Farrer C., Inati S., Grafton S.T., 2003. Actions or hand-object interactions? Human inferior frontal cortex and action observation. Neuron 39 (6), 1053-8.

Kay S.R., Fiszbein A., Opler L.A., 1987. The positive and negative syndrome scale (PANSS) for schizophrenia. Schizophrenia Bulletin 13, 261–276.

Kim M.J., Loucks R.A., Palmer A.L., Brown A.C., Solomon K.M., Marchante A.N., Whalen P.J., 2011. The structural and functional connectivity of the amygdala: from normal emotion to pathological anxiety. Behavioural brain research 223, 403–410.

Kohler C.G., Walker J.B., Martin E.A., Healey K.M., Moberg P.J., 2010. Facial emotion perception in schizophrenia: a meta-analytic review. Schizophrenia Bulletin 36, 1009–1019.

Korver N., Quee P.J., Boos H.B., Simons C.J., de Haan L.; GROUP investigators, 2012. Genetic Risk and Outcome of Psychosis (GROUP), a multi-site longitudinal cohort study focused on gene-environment interaction: objectives, sample characteristics, recruitment and assessment methods. International journal of methods in psychiatric research 21 (3), 205-21.

Kraepelin E., 1893. Die richtung der Psychiatrischen forschung. Leipzig: Barth, Germany.

Mandal M.K., Pandey R., Prasad A.B., 1998. Facial expressions of emotions and schizophrenia: a review. Schizophrenia Bulletin 24, 399–412.

McCormick L.M., Brumm M.C., Beadle J.N., Paradiso S., Yamada T., Andreasen N., 2012. Mirror neuron function, psychosis, and empathy in schizophrenia. Psychiatry Research 201 (3), 233-9.

Mukherjee P., Whalley H.C., McKirdy J.W., Sprengelmeyer R., Young A.W., McIntosh A.M., Lawrie S.M., Hall J., 2014. Altered Amygdala Connectivity Within the Social Brain in Schizophrenia. Schizophrenia Bulletin 40 (1), 152-60.

Namiki C., Hirao K., Yamada M., Hanakawa T., Fukuyama H., Hayashi T., Murai T., 2007. Impaired facial emotion recognition and reduced amygdalar volume in schizophrenia. Psychiatry Research 156 (1), 23-32.

Nieuwenhuys R., Voogd J., Van Huijzen C., 2008. The human central nervous system, fourth ed. Springer: Berlin Heidelberg.

Pessoa L., 2008. On the relationship between emotion and cognition. Nature reviews. Neuroscience. 9, 148–158.

Pijnenborg G.H., Withaar F.K., Evans J.J., van den Bosch R.J., Timmerman M.E., Brouwer W.H., 2009. The predictive value of measures of social cognition for community functioning in schizophrenia: implications for neuropsychological assessment. Journal of the International Neuropsychological Society 15 (2), 239-47.

Pinkham A.E., Lieberman J., 2003. Implications for the neural basis of social cognition for the study of schizophrenia. American Journal of Psychiatry 160 (5), 815-24.

Povinelli D.J., Preuss T.M., 1995. Theory of mind: evolutionary history of a cognitive specialization. Trends in Neuroscience 18 (9), 418-24.

Russell T.A., Rubia K., Bullmore E.T., Soni W., Suckling J., Brammer M.J., Simmons A., Williams S.C., Sharma T., 2000. Exploring the social brain in schizophrenia: left prefrontal underactivation during mental state attribution. American Journal of Psychiatry 157 (12), 2040-2.

Semendeferi K., 2012. Human prefrontal cortex: evolution, development, and pathology. Progress in Brain Research 195, 191-218.

Sergi M.J., Rassovsky Y., Widmark C., Reist C., Erhart S., Braff D.L., Marder S.R., Green M.F., 2007. Social cognition in schizophrenia: relationships with neurocognition and negative symptoms. Schizophrenia Research 90, 316–324.

Stein J.L., Wiedholz L.M., Bassett D.S., Weinberger D.R., Zink C.F., Mattay V.S., Meyer-Lindenberg A., 2007. A validated network of effective amygdala connectivity. Neuroimage 36, 736–745.

Taylor S.F., Kang J., Brege I.S., Tso I.F., Hosanagar A., Johnson T.D., 2012. Meta-analysis of functional neuroimaging studies of emotion perception and experience in schizophrenia. Biological Psychiatry 71 (2), 136-45.

Vauth R., Rüsch N., Wirtz M., Corrigan, P.W., 2004. Does social cognition influence the relation between neurocognitive deficits and vocational functioning in schizophrenia? Psychiatry Research 128 (2), 155–165.

Venkatasubramanian G., Jayakumar P.N., Keshavan M.S., 2008. Automated MRI parcellation study of regional volume and thickness of prefrontal cortex (PFC) in antipsychotic-naïve schizophrenia. Acta psychiatrica Scandinavica 117 (6), 420-31.

Versmissen D., Janssen I., Myin-Germeys I., Mengelers R., Campo J.A., van Os J., Krabbendam L., 2008. Evidence for a relationship between mentalising deficits and paranoia over the psychosis continuum. Schizophrenia Research 99, 103–110.

Vogeley K., Bussfeld P., Newen A., Herrmann S., Happe F., Falkai P., Maier W., Shah N.J., Fink G.R., Zilles K., 2001. Mind reading: neural mechanisms of theory of mind and self-perspective. NeuroImage 14, 170–181.

Walter H., Ciaramidaro A., Adenzato M., Vasic N., Ardito R.B., Erk S., Bara B.G., 2009. Dysfunction of the social brain in schizophrenia is modulated by intention type: an fMRI study. Social Cognitive and Affective Neuroscience 4 (2), 166–176.

Wechsler D., 1997. WAIS-III: Wechsler Adult Intelligence Scale, Administration and Scoring Manual, third ed. Psychological Corporation: San Antonio, TX.

Wiegand L.C., Warfield S.K., Levitt J.J. Hirayasu Y., Salisbury D.F., Heckers S., Dickey C.C., Kikinis R., Jolesz F.A., McCarley R.W., Shenton M.E., 2004. Prefrontal cortical thickness in first-episode psychosis: a magnetic resonance imaging study. Biological Psychiatry 55, 131–140.

van 't Wout, M., Aleman A., Kessels R.P., Laroi F., Kahn R.S., 2004. Emotional processing in a non-clinical psychosis-prone sample. Schizophrenia Research 68, 271–281.

Yamada M., Hirao K., Namiki C., Hanakawa T., Fukuyama H., Hayashi T., Murai T., 2007. Social cognition and frontal lobe pathology in schizophrenia: a voxel-based morphometric study. Neuroimage 35 (1), 292–298.

Figure 1 | Relationship between Pars Triangularis GMV and angry face recognition in schizophrenia patients and healthy controls. GMV corrected for age, gender and ICV. GMV, Gray Matter Volume; ICV, Intracranial Volume

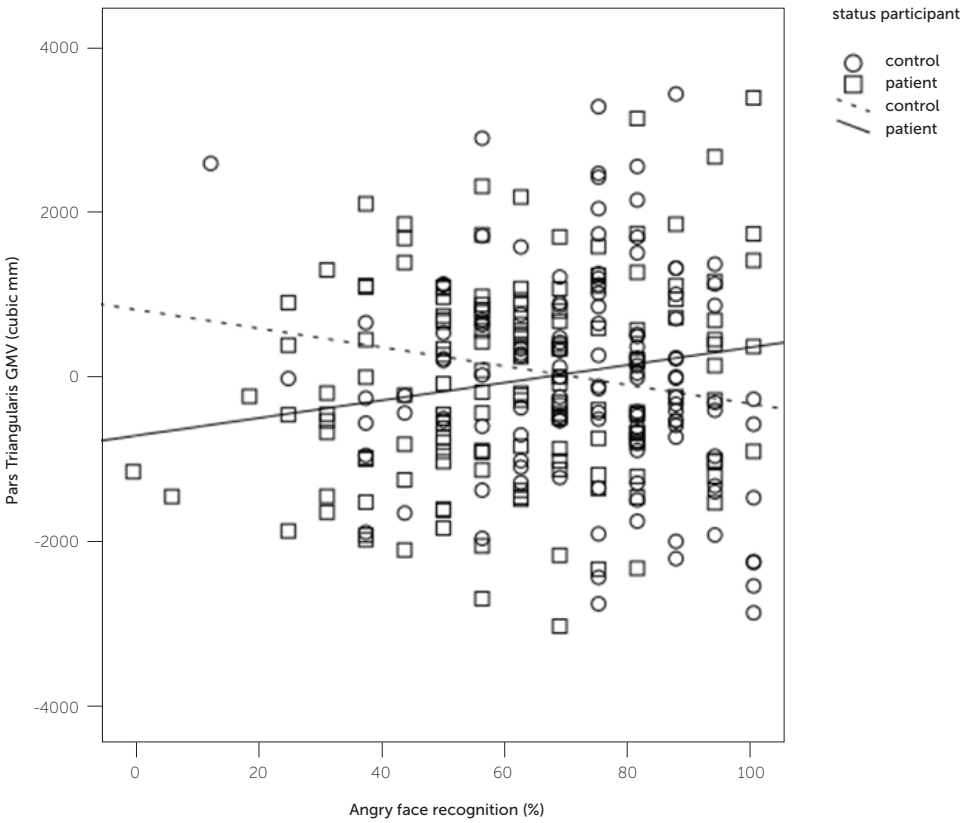


Figure 2| Scatterplot of rostral middle PFC GMV for schizophrenia patients with poor or good hinting task performance. Group means are indicated by horizontal lines. PFC, Prefrontal Cortex; GMV, Gray Matter Volume.

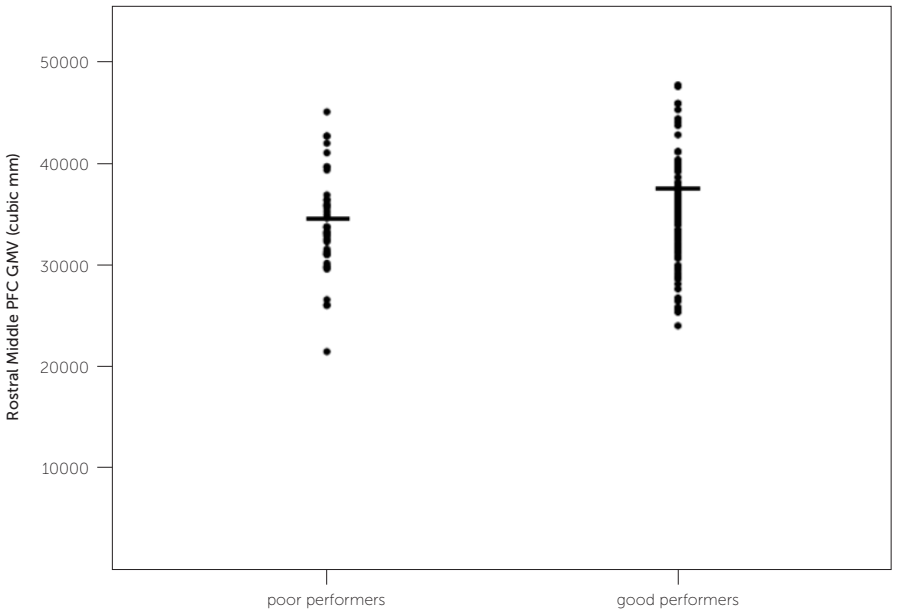


Table 1 | Demographic and clinical characteristics of schizophrenia patients and healthy controls, group differences on social cognitive tests and group differences on gray matter volume.

	Patients (n = 166)	Controls (n = 134)	Test statistic	p
Demographics				
Age, mean (SD)	26.73 (5.86)	27.06 (8.52)	t (298) = 0.39	0.70
Males, n (%)	129 (77.7)	64 (47.8)	χ^2 (1) = 28.99	<0.001
IQ, mean (SD)	93.81 (15.58)	111.24 (14.47)	t (298) = 9.95	<0.001
Duration of illness in years, mean (SD)	3.76 (3.60)			
PANSS positive, mean (SD)	16.09 (6.65)			
PANSS negative, mean (SD)	16.13 (6.62)			
PANSS Total, mean (SD)	6.13 (1.71)			
Right-handed, n (%)	148 (91.4)	118 (88.7)	χ^2 (2) = 2.57	0.28
Antipsychotic medication[a]				
Atypical, n (%)	114 (68.7)			
Typical, n (%)	24 (14.5)			
Not currently using, n (%)	2 (1.2)			
Data missing, n (%)	24 (14.5)			
Social cognition[b]				
DFAR happy, mean (SD)	86.14 (12.85)	87.60 (11.13)	F (1, 258) = 0.19	0.67
DFAR neutral, mean (SD)	77.16 (17.55)	83.30 (14.65)	F (1, 258) = 1.88	0.17
DFAR fear, mean (SD)	49.87 (20.10)	56.61 (17.33)	F (1, 258) = 0.62	0.43
DFAR anger, mean (SD)	62.63 (20.34)	73.16 (17.27)	F (1, 258) = 5.92	0.02
Benton, mean (SD)	22.46 (2.51)	22.92 (2.33)	t (282) = 1.57	0.12
Hints, mean (SD)	16.51 (3.21)	18.88 (1.25)	F (1, 277) = 11.35	0.001
Gray matter volume (mm^3)[c]				
Amygdala, mean (SD)	3229.43 (380.15)	3197.79 (377.20)	F (1, 291) = 5.35	0.02
Prefrontal cortex, mean (SD)	143592.31 (16095.13)	145721.59 (17901.41)	F (1, 295) = 25.91	<0.001
Superior frontal cortex, mean (SD)	47648.08 (5504.04)	48061.70 (6462.50)	F (1, 295) = 12.13	0.001
Middle frontal cortex, mean (SD)	47546.57 (6575.39)	48441.42 (6971.97)	F (1, 295) = 19.14	<0.001
- rostral, mean (SD)	34622.27 (4847.23)	35094.76 (5192.53)	F (1, 295) = 16.29	<0.001
- caudal, mean (SD)	12924.30 (2283.20)	13346.66 (2346.83)	F (1, 295) = 10.32	0.001

Inferior frontal cortex, mean (SD)	17799.34 (2401.57)	18517.68 (2740.65)	F (1, 295) = 18.50	<0.001
- triangularis, mean (SD)	8499.93 (1371.41)	8757.04 (1478.87)	F (1, 295) = 8.67	0.004
- operculum, mean (SD)	9299.40 (1334.72)	9760.64 (1529.72)	F (1, 295) = 20.02	<0.001
Orbitofrontal cortex, mean (SD)	30598.33 (3371.16)	30700.70 (3628.25)	F (1, 295) = 14.52	<0.001
- lateral , mean (SD)	15210.46 (1728.18)	15381.19 (1887.20)	F (1, 295) = 15.18	<0.001
- medial, mean (SD)	10226.76 (1324.10)	10128.43 (1283.61)	F (1, 295) = 3.56	0.06
- orbitalis, mean (SD)	5161.10 (746.65)	5191.08 (913.44)	F (1, 295) = 8.03	0.01

[a] Atypical antipsychotics include risperidone, olanzapine, quetiapine, clozapine and aripiprazole; typical antipsychotics include haloperidol, penfluridol, pimozide, zuclopentixol and perfenazine.

[b] Group differences on social cognitive tests and Benton adjusted for age, gender, IQ and face recognition ability (for DFAR only).

[c] Group differences on gray matter volume corrected for age, gender, and intracranial volume.

PANSS, Positive and Negative Syndrome Scale; PANSS Total, Total of the factorial means of PANSS sub-scores (PANSS positive, negative and general scale) allowing 30 % missing values; IQ, Wechsler Adult Intelligence Scale estimated Intelligence Quotient; DFAR, Degraded Facial Affect Recognition; Benton, Benton facial recognition task.

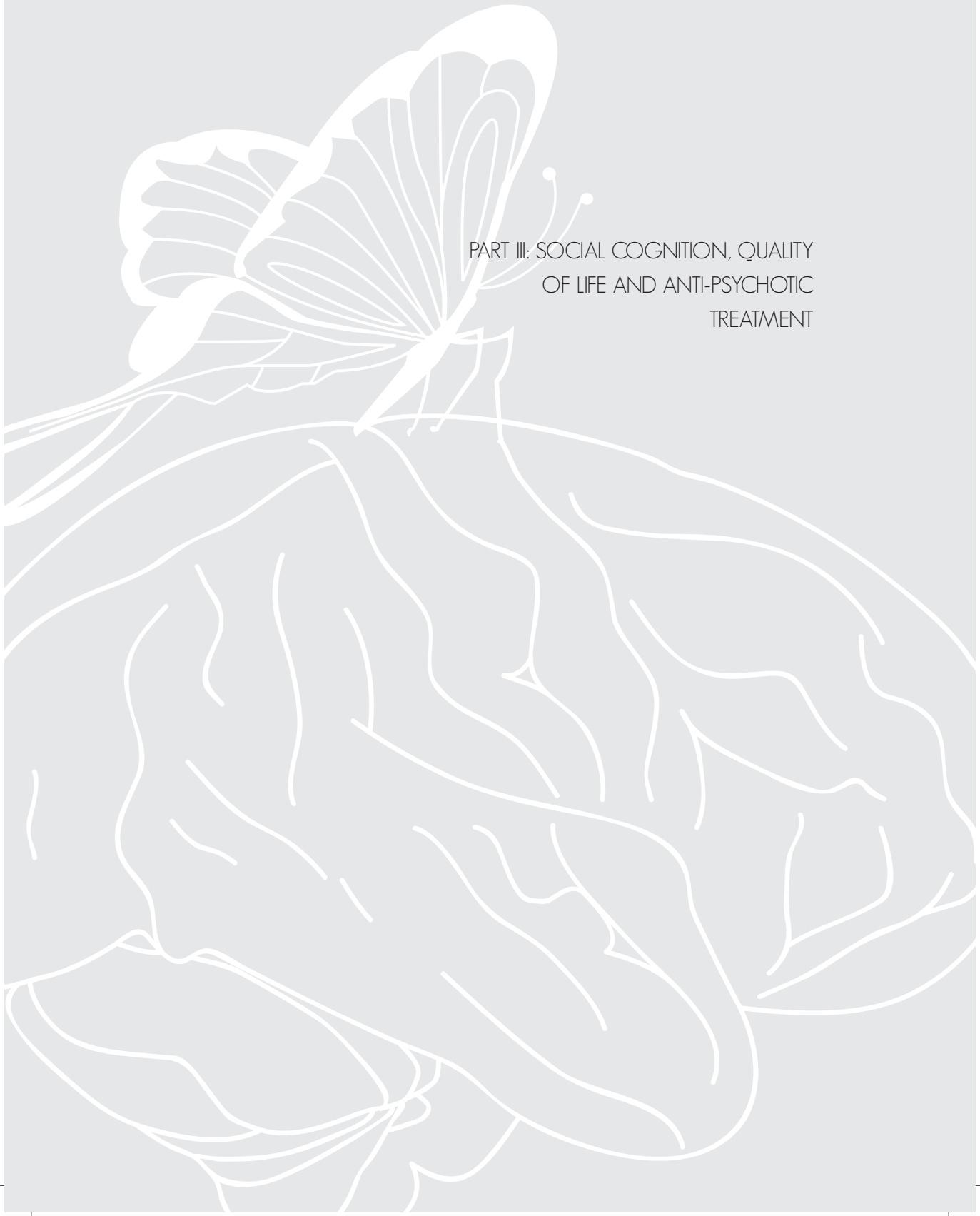
Table 2 | Demographic and clinical characteristics of schizophrenia patients with poor or good hinting task performance.

	Patients with poor performance (Score < 15) (n = 46)	Patients with good performance (Score 15-20) (n = 106)	Test-statistic	p
Demographics				
Hinting task, mean (SD)	12.59 (0.28)	18.22 (0.18)	F (1, 150) = 258.00	<0.001
Age, mean (SD)	25.04 (0.82)	27.55 (0.54)	F (1, 150) = 6.54	0.012
IQ, mean (SD)	84.09 (2.10)	98.86 (1.39)	F (1, 150) = 34.43	<0.001
Males, n (%)	38 (82.6)	82 (77.4)	χ^2 (1) = 0.53	0.47
Duration of illness in years, mean (SD)	3.19 (2.92)	4.20 (3.87)	F (1, 149) = 2.54	0.11
PANSS positive, mean (SD)	16.90 (8.17)	15.73 (6.15)	F (1, 139) = 0.88	0.35
PANSS negative, mean (SD)	18.95 (7.07)	15.45 (5.93)	F (1, 140) = 9.26	0.003
PANSS Total , mean	6.83 (1.80)	5.93 (1.66)	F (1, 143) = 2.91	0.004
Right-handed, n (%)	42 (93.3)	93 (89.4)	χ^2 (2) = 0.57	0.75
Antipsychotic medication[a]				
Atypical, n (%)	39 (84.8)	69 (65.1)	χ^2 (4) = 2.46	0.65
Typical, n (%)	7 (15.2)	17 (16.0)		
Not currently using, n (%)	0	2 (1.9)		
Data missing, n (%)	0	18 (17.0)		
Gray matter volume (mm3)[b]				
Amygdala, mean (SD)	3245.87 (341.77)	3251.13 (369.14)	F (1, 145) = 0.23	0.63
Prefrontal cortex, mean (SD)	142291.76 (15319.47)	144503.30 (16593.25)	F (1, 146) = 6.25	0.01
Superior frontal cortex, mean (SD)	47532.54 (5629.56)	47827.76 (5525.86)	F (1, 146) = 4.66	0.03
Middle frontal cortex, mean (SD)	46736.76 (6219.40)	47990.85 (6832.90)	F (1, 146) = 7.45	0.007
- rostral, mean (SD)	33853.28 (4724.74)	35013.75 (4921.11)	F (1, 146) = 11.38	0.001
- caudal, mean (SD)	12883.48 (2016.59)	12977.09 (2442.57)	F (1, 146) = 0.35	0.56
Inferior frontal cortex, mean (SD)	17622.13 (1936.13)	17849.27 (2506.58)	F (1, 146) = 0.17	0.69
Orbitofrontal cortex, mean (SD)	30400.33 (3435.56)	30835.42 (3412.58)	F (1, 146) = 2.55	0.11

[a] Atypical antipsychotics include risperidone, olanzapine, quetiapine, clozapine and aripiprazole; typical antipsychotics include haloperidol, penfluridol, pimozide, zuclopentixol and perfenazine.

[b] Group differences on gray matter volume corrected for age, gender, intracranial volume and IQ.

PANSS, Positive and Negative Syndrome Scale; PANSS Total, Total of the factorial means of PANSS sub-scores (PANSS positive, negative and general scale) allowing 30 % missing values; IQ, Wechsler Adult Intelligence Scale estimated Intelligence Quotient.



PART III: SOCIAL COGNITION, QUALITY OF LIFE AND ANTI-PSYCHOTIC TREATMENT

05

SOCIAL COGNITION AND QUALITY OF LIFE IN SCHIZOPHRENIA

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Schizophrenia Research 2012; 137(1-3): 212-8

ABSTRACT

Schizophrenia is associated with poor quality of life (QOL). Whereas the effects of neurocognitive deficits and psychopathology on QOL of schizophrenia patients have recently been elucidated, little is known about social cognitive deficits in this regard. This study investigated the influence of social cognition on QOL in schizophrenia. A sample of 1032 patients, 1011 of their siblings, and 552 healthy controls was recruited from the Dutch Genetic Risk and Outcome in Psychosis (GROUP) study. Participants completed a battery of cognitive tests, including social cognitive tests on theory of mind and emotion perception. To assess QOL the World Health Organization QOL Assessment-BREF (WHOQOL-BREF) was used. Schizophrenia symptoms were assessed with the Positive and Negative Syndrome Scale (PANSS). Social cognitive performance was significantly worse in patients compared to siblings and healthy controls. Patients had the poorest QOL, while QOL in healthy controls was better than in siblings. Theory of mind but not emotion perception or neurocognition was associated with QOL in patients, whereas neurocognition was the only significant predictor of QOL in siblings and healthy controls. There was a significant interaction between theory of mind and symptom severity with respect to QOL. Our study indicates that social cognition is associated with QOL in schizophrenia. Theory of mind rather than emotion perception is associated with QOL, and this association is moderated by schizophrenia symptoms. In particular, patients with relatively unimpaired theory of mind and more severe schizophrenia symptoms have poor QOL and could therefore benefit from therapeutic intervention.

KEYWORDS

Emotion Perception, Neurocognition, Schizophrenia, Social Cognition, Theory of Mind, Quality of Life

1. INTRODUCTION

Quality of life (QOL) in schizophrenia patients is impaired compared with that in the general population (Ruggeri *et al.*, 2005). Clinical factors, including schizophrenia symptoms and neurocognitive functioning, and socio-demographic variables have been suggested to contribute to the poor life satisfaction of patients with this disorder (Eack and Newhill, 2007; Fiszdon *et al.*, 2007; Pinikahana *et al.*, 2002). However, the associations between neurocognition and QOL are fairly modest and some studies indicate that the association is non-significant when illness severity is taken into account. (Heslegrave *et al.*, 1997; Hofer *et al.*, 2005; Matsui *et al.*, 2008; Wegener *et al.*, 2005). Furthermore, the predictive role of socio-demographic variables appears to be minor (Ruggeri *et al.*, 2005).

QOL and functional outcome in patients with schizophrenia are related (Brekke *et al.*, 2001). The latter scores community functioning, whereas QOL measures subjective life satisfaction (Brekke *et al.*, 2001). Evidence suggests that functional outcome in schizophrenia is more strongly related to social cognition than to neurocognition (Fett *et al.*, 2011; McGurk *et al.*, 2007; Pijnenborg *et al.*, 2009). This raises the possibility that social cognition may be a factor influencing QOL in schizophrenia. To the best of our knowledge, this issue has not been studied so far. Therefore, the aim of the current study was to examine the relation of QOL and social cognition using a large group of schizophrenia patients.

Social cognition is a multidimensional construct (Couture *et al.*, 2006). Theory of mind and emotion perception are important domains of social cognition based on the recent Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) recommendations (Green *et al.*, 2005). Theory of mind is the ability to infer the intentions and beliefs of others, sometimes also referred to as social intelligence (Baron-Cohen *et al.*, 2001). Emotion perception is the ability to infer emotional information from facial expressions (Couture *et al.*, 2006). In this

study, we focused on these two core domains of social cognition because they are impaired in schizophrenia and have previously been suggested to play a role in predicting outcome (Couture *et al*., 2006; Fett *et al*., 2011). Theory of mind is probably the most important domain in this regard, as it is more strongly associated with community functioning (r = 0.48), compared to other social cognitive domains including emotion perception (r = 0.22) (Fett *et al*., 2011).

Although neurocognition and social cognition are separable domains (van Hooren *et al*., 2008), it has been argued that social cognitive impairment in schizophrenia is non-specific and that any association with outcome may be due to confounding by neurocognitive impairment (Dickinson *et al*., 2008; Fiszdon and Johannesen, 2010; Kerr and Neale, 1993). Estimates of variance in social cognition accounted for by neurocognition range from 34 to 83 % (Sergi *et al*., 2007; Vauth *et al*., 2004). Importantly, most studies on the association of neurocognition and outcome do not report standardized measures of schizophrenia symptoms, thus neglecting the possibility that schizophrenia symptoms could moderate the relationship between cognition and outcome (Bora *et al*., 2009; Rassovsky *et al*., 2011; Ventura *et al*., 2009). Therefore, we included neurocognition and psychopathology in our analyses. In addition, we investigated the influence of social cognition and neurocognition on QOL of siblings of schizophrenia patients and of healthy controls to compare the effects of these factors on QOL between patients, their relatives and healthy individuals.

We hypothesized that social cognition of schizophrenia patients would predict their QOL. We expected that 1) the nature of the association would be positive, i.e., patients with a relatively unimpaired social cognition have a better QOL, and 2) theory of mind would more strongly predict QOL than emotion perception. To investigate an illness-related association, we explored a possible interaction between schizophrenia symptoms and social cognition in relation to QOL in patients.

2. METHOD

2.1. PROCEDURE AND SAMPLE

The data derives from baseline measures of the ongoing longitudinal multicenter study 'Genetic Risk and Outcome in Psychosis' (GROUP). The procedure of recruitment, informed consent, approval by the accredited Medical Ethics Review Committee (METC) and population characteristics have been described in a previous report on the GROUP study (N. Korver, P.J. Quee, H.B.M. Boos, C.J.P. Simons, GROUP, unpublished data, 2010). The full GROUP sample consisted of 1120 patients with a non-affective psychotic disorder, 1057 of their siblings, 919 of their parents and 590 unrelated healthy controls from the general population. In the present study, we only included siblings of schizophrenia patients, because unlike the parents, they were raised under the same environmental conditions. Also, only the participants for whom an IQ score was available were included, because our aim was to include neurocognition in the analyses.

Our inclusion criteria for patients, siblings and healthy controls were: (1) age between 16 and 60; (2) good command of the Dutch language and (3) ability and willingness to give informed consent. Patients had to meet the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (APA, 2000) criteria for a non-affective psychotic disorder, as assessed by the Comprehensive Assessment of Symptoms and History Interview (Andreasen *et al*., 1992). An additional inclusion criterion for the sibling group was the absence of a lifetime psychotic disorder. For the control group additional inclusion criteria were not having (1) a lifetime psychotic disorder and/or (2) a first degree family member with a lifetime psychotic disorder.

2.2. MEASURES

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

2.2.1 Measure of Quality of life

World Health Organization Quality Of Life Assessment-BREF (WHOQOL-BREF). This instrument is a 26-item self-report questionnaire assessing QOL (WHOQOL Group, 1998). It includes four domain scores (physical, psychological, social and environmental) and two individually scored items measuring a subject's overall perception of his QOL and satisfaction with his health. All items are rated on a five-point Likert scale. For all measures, higher scores reflect better QOL.

2.2.2. Measure of emotion perception

Degraded Facial Affect Recognition Task. The facial affect recognition task (van 't Wout *et al*., 2004) uses photographs of four different actors (two male, two female) depicting four emotions: angry, happy, fearful and neutral. The task comprises 64 trials consisting of 16 face presentations in each emotion category. The emotions were shown with 75% intensity in order to increase the difficulty of the task. Subjects were asked to indicate the emotional expression of each face with a button press and to respond as accurately as possible. Outcomes were the proportion of faces correctly recognized as neutral, happy, fearful and angry emotions.

2.2.3 Measure of theory of mind

Hinting Task. Theory of mind was assessed with the hinting task (Corcoran *et al*., 1995; Janssen *et al*., 2003; Versmissen *et al*., 2008). The task tests the ability of subjects to infer the real intentions behind indirect speech utterances. It comprises ten short passages presenting an interaction between two characters that end with one of the characters dropping a hint. The subject is then asked what the character really meant. Correctly identified hints are scored with two points. In case of an incorrect response a more obvious hint is added. A subsequent correct response is scored with one point; an incorrect response is scored as zero. The outcome range is 0-20.

2.2.4. Measures of neurocognition

Benton Facial Recognition Test. The short form of the Benton facial recognition test

(Benton *et al*., 1983), a measure of the ability to match unfamiliar faces, was used to assess whether deficits in facial affect recognition are not mediated by differences in general facial recognition ability.

Wechsler Adult Intelligence Scale (WAIS III). The Arithmetic (working memory), Digit Symbol-Coding (processing speed), Block Design (reasoning and problem solving) and Information subtests (verbal comprehension) of the WAIS III were administered as an indicator of IQ (Blyler *et al*., 2000; Wechsler, 1997). We are aware that neurocognition in schizophrenia is often represented in terms of separable dimensions of cognitive deficits. Hence, the grouping of neurocognition as a single construct (IQ) is somewhat artificial. We did so in the current study to reduce the complexity of the models, minimize the number of parameters, and maximize the robustness of the findings.

2.2.5. Symptom Assessment

The Positive and Negative Syndrome Scale (PANSS) (Kay *et al*., 1987). In the GROUP-project, current symptom severity was measured with the PANSS, which consists of 30 items. Each item is scored on a scale ranging from 1 (absent) to 7 (extreme), with item rating incorporating the behavioral effect of symptoms as well as their severity. Three domains are described for the PANSS, measuring positive, negative or general symptoms. Since the current study did not emphasize symptom dimensions but rather the concept of clinical symptoms in relation to social cognition and QOL, we decided to calculate the mean score for every domain, allowing 30 % missing values. The total of the mean sub-scores was used to assess the association between symptomatology and QOL in the current analyses.

2.3. ANALYSES

Statistical analyses were performed using SPSS version 15.0.

2.3.1. Sample characteristics

Differences in QOL between schizophrenia patients, their siblings and healthy controls were evaluated with ANOVA. Differences in social cognition between groups may be subject to confounding by general neurocognitive performance, age and gender. Therefore, we evaluated the differences in social cognitive impairments with ANCOVA adjusted for IQ, age and gender. Performance on the facial affect recognition task was also adjusted for general face recognition ability. A type-I error rate of .05 was used for the between group comparisons.

2.3.2. Principal component analysis

As the QOL questionnaire contains four domains and two individually scored items, we sought to reduce these data to a single factor to minimize multiple testing. To investigate the underlying structure of the questionnaire, the data was subjected to principal component analysis with varimax rotation. Prior to running the principal axis factoring, examination of the data on siblings and healthy controls indicated that the QOL-item measuring satisfaction with health was not perfectly normally distributed (skewness: -1.08). Given the robust nature of factor analysis, this deviation was not considered problematic.

2.3.3. Standard multiple regression

To determine whether social cognition was a predictor of QOL, we used standard multiple regression. For the patient group we also wanted to investigate the influence of illness severity on the analysis. Therefore, the total PANSS score (illness severity) was included as a predictor. In addition, we explored the interaction between illness severity and social cognition to examine possible interaction effects. All regression analyses were adjusted for the potentially confounding factors age, gender and IQ (for intercorrelations between IQ and the social cognitive tasks see Table 1). Prior

to interpreting the results of the regression analyses, several assumptions were evaluated. Inspection of the normal probability plot of standardized residuals as well as the scatter plot for standardized residuals against standardized predicted values indicated that the assumptions of normality, linearity and homoscedasticity of residuals were met.

3. RESULTS

The current study incorporated a subset of participants from the full GROUP sample. This subsample included 1032 schizophrenia patients, 1011 healthy siblings and 552 healthy controls. A total of 240 patients did not have a corresponding sibling included. The average number of siblings per patient that did have a relative included was 1.3. Sample characteristics are displayed in Table 2. Due to the family structure of the data, the data of patients and siblings was not statistically independent. We have tested whether this may possibly influence the results by calculating the correlations between patients and siblings for the main study-variables. The results of this analysis indicated that relatedness was not of major concern for a correct interpretation of the results, because the correlations were very weak ($r \approx .1$). Because the siblings of the schizophrenia patients did not significantly differ from the healthy controls in their performance on the hinting task and the facial affect recognition task, we considered them as one group in further analyses, but we allowed for potential differences by including status (i.e., control vs sibling) as a covariate in the multiple regression analyses. As shown in other studies examining differential responses to specific emotions (Phillips *et al*., 1999; Schneider *et al*., 1995; Walker *et al*., 1980), all groups recognized happy emotion best, followed by neutral, angry, and fearful emotion with the lowest rate of correct recognitions. Furthermore, in line with previous reports on affect recognition (Mandal *et al*., 1998), schizophrenia patients only differed from the siblings and healthy controls in recognizing the negative emotions anger and fear. We only included these emotions in further analyses because of their apparent specificity to schizophrenia patients.

3.1. PRINCIPAL COMPONENT ANALYSIS OF QOL

Data collected from patients (n = 930) and siblings and healthy controls (n = 1421) on QOL, were subjected to principal component analysis. In both groups, one factor (with Eigenvalue exceeding 1) was identified as underlying the 26 questionnaire items. In total, this factor accounted for around 60% of the variance in the questionnaire data in the patient group and for around 59% in the 'sibling and control' group.

3.2. STANDARD MULTIPLE REGRESSION 'PATIENTS'

For the data on the group of schizophrenia patients, two regression analyses were performed. The first model was adjusted for the severity of symptoms measured by total PANSS score. The variables in the model (age, gender, IQ, total PANSS score and social cognition) explained 17% of the variability in QOL in patients, ($F(7,805) = 24.16$, $p < .001$). The hinting task was a significant predictor of QOL in this model (ß = -.085, p = .02). The performance on the degraded facial affect recognition task did not significantly predict QOL. Importantly, contrary to the 'sibling and healthy control' group, IQ was not a significant predictor of QOL in schizophrenia patients (ß = -.025, p = .48). Post hoc analyses, in which we compared the effects of the separate PANSS scales in the regression, showed that all subscales had a negative effect on QOL, indicating that using the total PANSS score instead of separate scales was justified. Furthermore, because the sample consisted of recent-onset and chronic patients, a separate analysis was performed in which we included illness duration as a covariate. The results of this analysis were similar to those described above.

In our second model, we included an interaction effect of the hinting task and total PANSS score on QOL. We only included performance on the hinting task and not on the degraded affect recognition task, because the hinting task performance had a significant main-effect in our first model and affect recognition did not. Table 3 shows that the interaction between total PANSS score and performance on the hinting task significantly predicted the QOL of patients. For the interaction factor the regression coefficient (ß) was -.358. By Cohen's conventions, a combined effect of this

magnitude can be considered 'large' (f^2= -.256) (Cohen, 1988). The model explained 17 % of variance in QOL. We found that the total PANSS score was a moderator of the influence of the hinting task on QOL, as is graphically shown in Figure 1. The graph displays that in patients with a relatively low PANSS score, hinting task was not associated with QOL, while in patients with a mean or relatively high PANSS score a better performance on the hinting task was associated with a poor QOL.

3.3. STANDARD MULTIPLE REGRESSION 'SIBLINGS AND HEALTHY CONTROLS'

In siblings and healthy controls, variance in QOL could not be explained by performance on the hinting task or the degraded facial affect recognition task (see Table 4). IQ uniquely accounted for variance in QOL, but in combination with the other variables, the model explained only 2.4% of the variability in QOL.

4. DISCUSSION

This study investigated the relationship between social cognition and QOL in schizophrenia taking into account neurocognitive functioning and schizophrenia symptoms. We show that social cognition, rather than neurocognition, is associated with QOL in schizophrenia. Moreover, we found that theory of mind is a more important domain of social cognition than emotion perception in relation to QOL of schizophrenia patients. The inclusion of symptomatology in our analyses revealed an interaction effect between symptom severity and theory of mind with respect to QOL. Schizophrenia symptoms appear to moderate the influence of theory of mind on QOL in such a way that more severely ill patients with a relatively unimpaired theory of mind have a poorer QOL. This illness-related association is further emphasized by our finding that in siblings and healthy controls QOL is not related to social cognition but to neurocognition.

4.1. QUALITY OF LIFE AND SOCIAL COGNITION

In our study theory of mind but not neurocognition is significantly related to QOL of schizophrenia patients. This is in line with previous studies showing that social cognition is a stronger predictor of functional outcome in schizophrenia than neurocognition. However, whereas social cognition and functional outcome in schizophrenia are positively associated (Fett *et al*., 2011; McGurk *et al*., 2007; Pijnenborg *et al*., 2009) we found theory of mind to be negatively associated with QOL (this study). These different effects of social cognition may reflect the difference in outcome measures of QOL (subjective life satisfaction) and functional outcome (e.g., employment, housing and marital status). Apparently, whereas functional outcome in schizophrenia benefits from a higher social intelligence, QOL does not, probably because the patient realizes the impact of his illness on his social environment. The present findings are consistent with reports on relationships between QOL and 'insight' (Karow *et al*., 2008; Xiang *et al*., 2012) and 'social knowledge' (Matsui *et al*., 2008). These studies point out, that patients with better insight and social knowledge recognize their illness-related limitations, a recognition that is reflected in low QOL. Theory of mind and insight in psychosis are related constructs (Bora *et al*., 2007; Langdon *et al*., 2009; Quee *et al*., 2011), which may explain their similar effect on QOL in schizophrenia patients. This assumption needs to be addressed in future research.

4.2. THEORY OF MIND VERSUS EMOTION PERCEPTION

Our study reveals that emotion perception is a less important domain of social cognition with respect to QOL in schizophrenia. A possible explanation could be that a correct understanding of the thoughts and intentions behind emotions (= theory of mind) is more important than reading emotions in facial expression (= emotion perception). For example, if a patient is able to recognize that his friend is angry or scared, this will not affect his QOL. However, if he is capable of recognizing that his friend is angry at him or scared of him because of his paranoid behavior, this will increase his discomfort, resulting in impaired QOL.

4.3. QUALITY OF LIFE, THEORY OF MIND, AND SCHIZOPHRENIA SYMPTOMS

Intuitively, poor social cognition in schizophrenia patients should negatively impact QOL. Here, we find that poor theory of mind is inversely associated with QOL of a schizophrenia patient, on the condition that the patient has a relatively high total PANSS score. In other words, the relationship between social cognition and QOL is affected by the patient's psychiatric distress. A possible explanation for the interaction between theory of mind and symptom severity is that more severely ill patients with a relatively unimpaired theory of mind may be aware of the detrimental effects of their illness on their social environment. Therefore, it is important that the social environment is aware of the status of a patients' theory of mind, and understands that its interaction with the patient, can possibly negatively impact his well-being. Family coaching and education of peers could be helpful in this respect and help to improve QOL of schizophrenia patients.

4.4. STRENGTHS AND LIMITATIONS

The current study used a uniquely large sample to detect even delicate effects of the studied variables. The study was performed in the setting of daily psychiatric practice, which better reflects QOL in schizophrenia patients than clinical trials do. Also, as both a sibling and a healthy control group were added in the present study, we are certain that the association found between social cognition and QOL is specific to patients. Lastly, the inclusion of symptomatology in our analyses sheds light on the confounding effect of symptoms on the association between social cognition and QOL.

This study has limitations. First, the study is cross-sectional in design; hence, our findings do not imply causality. To identify causality, longitudinal research on symptoms, social cognitive functioning, and QOL in schizophrenia patients is needed. Second, our finding of a non-significant difference in performance on degraded facial affect recognition and hinting task between siblings and healthy controls is not in

line with previous studies, which demonstrated significant impairments in siblings as well (Anselmetti *et al*., 2009; Janssen *et al*., 2003). One explanation for this lack of difference could be self-selection bias, e.g., indicating that only the siblings with unimpaired social cognition were willing to participate in our study. However, a different outcome of our model was checked by using 'sibling group' or 'healthy control group' as a variable in standard multiple regression, and this did not change our findings. Furthermore, the lack of an association between social cognition and QOL in siblings and healthy controls, should be interpreted with caution because of the nature of the employed social cognitive task on theory of mind. The hinting task is specifically prone to ceiling effects and this may partly account for the fact that we did not find an association. Nevertheless, one could argue that all measures of theory of mind in non-psychotic siblings of schizophrenia patients and healthy controls will have this limitation, because there is by definition less variation in theory of mind among people without a psychotic disorder. Third, our assessment of neurocognition only tapped into certain domains. Therefore, the present conclusions do not necessarily generalize to all aspects of neurocognition. Fourth, we are aware that the non-uniformity of the characteristics of our patient sample with respect to patient status (clinically stable versus acutely ill) limits the findings of our study. However, in order to keep the analysis as parsimonious as possible, we limited our number of measures. Moreover, including duration of illness in our analyses did not change our main findings. Lastly, there is some debate regarding the capacity of people with a psychotic illness to make accurate assessments of QOL (Herrman *et al*., 2002). However, validation studies demonstrate that self-report measures of QOL are more accurate than clinician-report QOL measures, and that QOL can be rated accurately by patients (Voruganti *et al*., 1998).

The results of the present study indicate that schizophrenia patients with a relatively unimpaired theory of mind suffer from the impact of their disease on the environment and warrant family-coaching to improve patients' QOL.

REFERENCES

American Psychiatric Association, 2000. Diagnostic and Statistical Manual of Mental Disorders, fourth ed., text revision. American Psychiatric Association, Washington, DC.

Andreasen, N.C., Flaum, M., Arndt, S., 1992. The Comprehensive Assessment of Symptoms and History (CASH). An instrument for assessing diagnosis and psychopathology. Arch. Gen. Psychiatry 49 (8), 615-623.

Anselmetti, S., Bechi, M., Bosia, M., Quarticelli, C., Ermoli, E., Smeraldi, E., Cavallaro, R., 2009. 'Theory' of mind impairment in patients affected by schizophrenia and in their parents. Schizophr. Res. 115, 278-285.

Baron-Cohen, S., Wheelwright, S., Hill, J., Raste, Y., Plumb, I., 2001. The "Reading the Mind in the Eyes" Test revised version: a study with normal adults, and adults with Asperger syndrome or high-functioning autism. J. Child Psychol. Psychiatry 42, 241-51.

Benton, A.L., Sivan, A.B., Hamsher, K.D., Varney, N.R., Spreen, O., 1983. Benton's Test of Facial Recognition. Oxford University Press, New York, NY.

Blyler, C.R., Gold, J.M., Iannone, V.N., Buchanan, R.W., 2000. Short form of the WAIS-III for use with patients with schizophrenia. Schizophr. Res. 46, 209-215.

Bora E., Sehitoglu G., Aslier M., Atabay I., Veznedaroglu B., 2007. Theory of mind and unawareness of illness in schizophrenia: is poor insight a mentalizing deficit? Eur Arch Psychiatry Clin Neurosci. 257, 104–111.

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

Brekke, J.S., Kohrt, B., Green, M.F., 2001. Neuropsychological functioning as a moderator of the relationship between psychosocial functioning and the subjective experience of self and life in schizophrenia. Schizophr.
Bull. 27, 697-708.

Corcoran, R., Mercer, G., Frith, C.D., 1995. Schizophrenia, symptomatology and social inference: investigating "theory of mind" in people with schizophrenia. Schizophr. Res. 17, 5-13.

Cohen, J., 1988. Statistical power analysis for the behavioral sciences, second ed. Hillsdale, NJ: Erlbaum.

Couture, S.M., Penn, D.L., Roberts, D.L., 2006. The functional significance of social cognition in schizophrenia: a review. Schizophr. Bull. 32 (S1), S44-63.

Dickinson, D., Ragland, J.D., Gold, J.M., Gur, R.C., 2008. General and specific cognitive deficits in schizophrenia: Goliath defeats David? Biol. Psychiatry 64 (9), 823-827.

Eack, S.M., Newhill, C.E., 2007. Psychiatric symptoms and quality of life in schizophrenia: a meta-analysis. Schizophr. Bull. 33, 1225-37.

Fett, A.K., Viechtbauer, W., Dominguez, M.D., Penn, D.L., van Os, J., Krabbendam, L., 2011. The relationship between neurocognition and social cognition with functional outcomes in schizophrenia: a meta-analysis. Neurosci. Biobehav. Rev. 35 (3), 573-588.

Fiszdon, J.M., Choi, J., Goulet, J., Bell, M.D., 2007. Temporal relationship between change in cognition and change in functioning in schizophrenia. Schizophr. Res. 105, 105-113.

Fiszdon, J.M., Johannesen, J.K., 2010. Functional significance of preserved affect recognition in schizophrenia. Psychiatry Res. 176, 120-125.

Green, M.F., Olivier, B., Crawley, J.N., Penn, D.L., Silverstein, S., 2005. Social cognition in schizophrenia: recommendations from the measurement and treatment research to improve cognition in schizophrenia new approaches conference. Schizophr. Bull. 31, 882-887.

Herrman, H., Hawthorne, G., Thomas, R., 2002. Quality of life assessment in people living with psychosis. Soc. Psychiatry Psychiatr. Epidemiol. 37 (11), 510-518.

Heslegrave, R.J., Awad, A.G., Voruganti, L.N., 1997. The influence of neurocognitive deficits and symptoms on quality of life in schizophrenia. J. Psychiatry Neurosci. 22 (4), 235-243.

Hofer, A., Baumgartner, S., Edlinger, M., Hummer, M., Kemmler, G., Rettenbacher, M.A., Schweigkofler, H., Schwitzer, J., Fleischhacker, W.W., 2005. Patient outcomes in schizophrenia I: correlates with sociodemographic variables, psychopathology, and side effects. Eur. Psychiatry 20 (5-6), 386-394.

van Hooren, S., Versmissen, D., Janssen, I., Myin-Germeys, I., Campo, J., Mengelers, R., van Os, J., Krabbendam, L., 2008. Social cognition and neurocognition as independent domains in psychosis. Schizophr. Res. 103, 257-265.

Janssen, I., Krabbendam, L., Jolles, J., van Os, J., 2003. Alterations in theory of mind in patients with schizophrenia and non-psychotic relatives. Acta Psychiatr. Scand. 108 (2), 110-117.

Karow, A., Pajonk, F.G., Reimer, J., Hirdes, F., Osterwald, C., Naber, D., Moritz, S., 2008. The dilemma of insight into illness in schizophrenia: self- and expert-rated insight and quality of life. Eur. Arch. Psychiatry Clin. Neurosci. 258 (3), 152-159.

Kay, S.R., Fiszbein, A., Opler, L.A., 1987. The positive and negative syndrome scale (PANSS) for schizophrenia. Schizophr. Bull. 13, 261-276.
Kerr, S.L., Neale, J.M., 1993. Emotion perception in schizophrenia: specific deficit or further evidence of generalized poor performance? J. Abnorm. Psychol. 102 (2), 312-318.

Langdon R., Ward P., 2009. Taking the perspective of the other contributesto awareness of illness in schizophrenia. Schizophr Bull. 35, 1003–1011.

Mandal, M.K., Pandey, R., Prasad, A.B., 1998. Facial expressions of emotions and schizophrenia: a review. Schizophr. Bull. 24, 399-412.

Matsui, M., Sumiyoshi, T., Arai, H., Higuchi, Y., Kurachi, M., 2008. Cognitive functioning related to quality of life in schizophrenia. Prog. Neuropsychopharmacol. Biol. Psychiatry 32 (1), 280-287.

McGurk, S.R., Twamley, E.W., Sitzer, D.I., McHugo, G.J., Mueser, K.T., 2007. A meta-analysis of cognitive remediation in schizophrenia. Am. J. Psychiatry 164, 1791-1802.

Phillips, M., Williams, L., Senior, C., Bullmore, E., Brammer, M., Andrew, C., Williams, S., David, A., 1999. A differential neural response to threatening and non-threatening negative facial expressions in paranoid and non-paranoid schizophrenics. Psychiatry Res. Neuroimaging 92 (1), 11–31.

Pijnenborg, G.H., Withaar, F.K., Evans, J.J., van den Bosch, R.J., Timmerman, M.E., Brouwer, W.H., 2009. The predictive value of measures of social cognition for community functioning in schizophrenia: implications for neuropsychological assessment. J. Int. Neuropsychol. Soc. 15 (2), 239-247.

Pinikahana, J., Happell, B., Hope, J., Keks, N.A., 2002. Quality of life in schizophrenia: a review of the literature from 1995 to 2000. Int. J. Ment. Health Nurs. 11 (2), 103-111.

Quee P.J., van der Meer L., Bruggeman R., de Haan L., Krabbendam L., Cahn W., Mulder N.C., Wiersma D., Aleman A., 2011. Insight in psychosis: relationship with neurocognition, social cognition and clinical symptoms depends on phase of illness. Schizophr Bull. 37 (1), 29-37.

Rassovsky, Y., Horan, W.P., Lee, M.J., Sergi, M.J., Green, M.F., 2011. Pathways between early visual processing and functional outcome in schizophrenia. Psychol. Med. 41 (3), 487-97.

Ruggeri, M., Nose, M., Bonetto, C., Cristofalo, D., Lasalvia, A., Salvi, G., Stefani, B., Malchiodi, F., Tansella, M., 2005. Changes and predictors of change in objective and subjective quality of life: multiwave follow-up study in community psychiatric practice. Br. J. Psychiatry 187, 121-130.

Schneider, F., Gur, R.C., Gur, R.E., Shtasel, L., 1995. Emotional processing in schizophrenia--neurobehavioural probes in relation to psychopathology. Schizophr. Res. 17 (1), 67–75.

Sergi, M.J., Rassovsky, Y., Widmark, C., Reist, C., Erhart, S., Braff, D.L., Marder, S.R., Green, M.F., 2007. Social cognition in schizophrenia: relationships with neurocognition and negative symptoms. Schizophr Res. 90, 316-24.

Vauth, R., Rüsch, N., Wirtz, M., Corrigan, P.W., 2004. Does social cognition influence the relation between neurocognitive deficits and vocational functioning in schizophrenia? Psychiatry Res. 128 (2), 155-65

Ventura, J., Hellemann, G.S., Thames, A.D., Koellner, V., Nuechterlein, K.H., 2009. Symptoms as mediators of the relationship between neurocognition and functional outcome in schizophrenia: a meta-analysis. Schizophr. Res. 113, 189-99.

Versmissen, D., Janssen, I., Myin-Germeys, I., Mengelers, R., Campo, J.A., van Os, J., Krabbendam, L., 2008. Evidence for a relationship between mentalising deficits and paranoia over the psychosis continuum. Schizophr. Res. 99, 103-110.

Voruganti, L., Heslegrave, R., Awad, A.G., Seeman, M.V., 1998. Quality of life measurement in schizophrenia: reconciling the quest for subjectivity with the question of reliability. Psychol. Med. 28, 165-172.

Walker, E., Marwit, S., Emory, E., 1980. A cross-sectional study of emotion recognition in schizophrenics. J. Abnorm. Psychol. 89 (3), 428–436.

Wechsler, D., 1997. WAIS-III: Wechsler Adult Intelligence Scale, Administration and Scoring Manual, third ed. Psychological Corporation, San Antonio, TX.

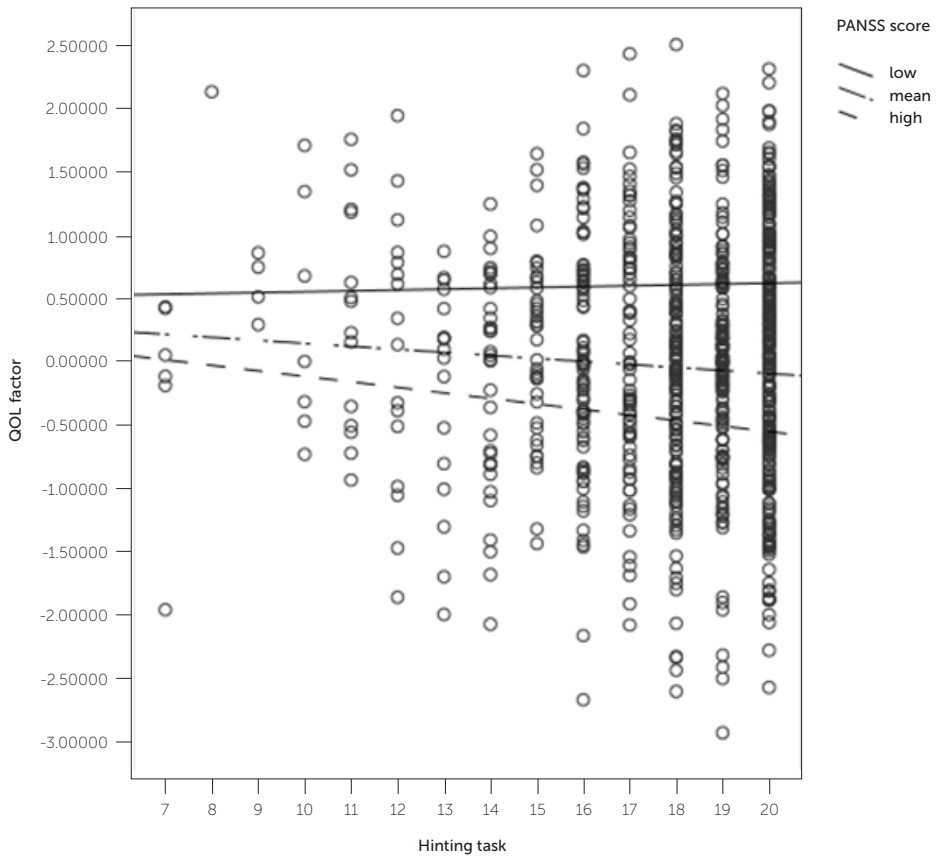
Wegener, S., Redoblado-Hodge, M.A., Lucas, S., Fitzgerald, D., Harris, A., Brennan, J., 2005. Relative contributions of psychiatric symptoms and neuropsychological functioning to quality of life in first-episode psychosis. Aust. N. Z. J. Psychiatry 39 (6), 487-492.

WHOQOL Group, 1998. Development of the World Health Organization WHOQOL-BREF quality of life assessment. Psychol. Med. 28, 551-558.

van 't Wout, M., Aleman, A., Kessels, R.P., Laroi, F., Kahn, R.S., 2004. Emotional processing in a non-clinical psychosis-prone sample. Schizophr. Res. 68, 271-281.

Xiang, Y.T., Wang, Y., Wang, C.Y., Chiu, H.F.K., Chen, Q., Chan, S.S.M., Lai, K.Y.C., Lee, E.H.M., Ungvari, G.S., 2012. Association of insight with sociodemographic and clinical factors, quality of life, and cognition in Chinese patients with schizophrenia. Compr. Psychiatry 53, 140-144.

Figure 1 | QOL in schizophrenia patients adjusted for total PANSS score (n = 887).



Description: The graph presents that in patients with a relatively low PANSS score, hinting task was not associated with QOL, while in patients with a mean or relatively high PANSS score a better performance on the hinting task was associated with a poor QOL. We divided the PANSS score in 'high' score (≥ mean +1 SD), 'mean' score (-1 SD > PANSS score < +1 SD) and 'low' score (≤ mean -1 SD) and plotted these three groups in a graph of QOL against the hinting task. Abbreviations: QOL= Quality of Life. QOL factor = standardized factor of Quality of Life. PANSS = Positive and Negative Syndrome Scale. low = PANSS score ≤ mean -1 SD. mean = -1 SD > PANSS score < +1 SD. high = PANSS score ≥ mean +1 SD.

Table 1 | Intercorrelations between the (social) cognitive tasks by group (Pearson's r)

	Controls			Siblings			Patients		
	Hinting task	DFAR fearful	DFAR angry	Hinting task	DFAR fearful	DFAR angry	Hinting task	DFAR fearful	DFAR angry
Hinting task		.030	.072		.045	.045		.172**	.169**
DFAR fearful	.030		.280**	.045		.325*	.172**		.335**
DFAR angry	.072	.280**		.045	.325**		.169**	.335**	
IQ	.157**	.114**	.018	.225**	.047	.017	.357**	.182**	.089**

DFAR= Degraded Facial Affect Recognition.** p < .001, * p < .05

Table 2 | Demographic and clinical sample characteristics, group differences on QOL and group differences on social cognitive tests.

	Controls n= 552 Mean (SD)	n	Siblings n= 1011 Mean (SD)	n	Patients n= 1032 Mean (SD)	n	Test statistic	p-value	Patients vs. Controls p-value	Sibs vs. Controls p-value	Patients vs. Sibs p-value
Age (yrs)	29.6 (10.2)	552	27.9 (8.2)	1011	27.3 (7.2)	1032	F (2,2592) = 14.84	< 0.001	< 0.001	< 0.001	.36
Male (%)	46		46		77		$\chi^2(2)=247.93$	< 0.001	< 0.001	.916	< 0.001
IQ	109.5 (15.0)		102.7 (15.5)		94.9 (16.0)		F (2,2592) = 165.68	< 0.001	< 0.001	< 0.001	< 0.001
Duration of illness (years)					4.3 (4.0)	983					
Psychotic episodes (number)					1.8 (1.1)	983					
Age of onset psychosis (years)					22.5 (6.8)	983					
Hinting task	19.1 (1.3)	546	18.8 (1.7)	1003	17.5 (2.8)	1008	F (2,2551) = 40.48	< 0.001	< 0.001	1.00	< 0.001
DFAR neutral	81.5 (15.0)	514	80.4(15)	935	77.8 (17.5)	927	F (2,2369) = 1.82	0.16	0.26	1.00	0.34
DFAR happy	87.3 (11.2)	514	88.2 (10.7)	935	86.8 (12.7)	927	F (2,2369) = 1.28	0.28	1.00	0.36	1.00
DFAR angry	70.4 (18.7)	514	68.8 (19.3)	935	62.5 (20.8)	927	F (2,2369) = 12.0	< 0.001	< 0.001	0.38	< 0.001
DFAR fearful	54.0 (18.2)	514	52.6(19.7)	935	47.6 (19.7)	927	F (2,2369) = 7.57	0.001	0.001	0.72	0.007
Benton	23.15(2.1)	548	23.18 (2.2)	997	22.8 (2.3)	998	F (2,2537) = 1.94	.145	1.00	.367	.279
PANSS positive					1.80 (0.76)	1002					
PANSS negative					2.00 (0.86)						
PANSS general					1.74 (0.52)						
PANSS total					5.54 (1.77)	1002					

Table 2 | continued

QOL	4.3 (0.6)	498	4.1 (0.7)	926	3.4 (1.0)	935	F (2,2356) = 260.40	< 0.001	< 0.001	<0.001	< 0.001
QOL health	4.1 (0.8)		4.0 (0.9)	927	3.4 (1.1)	931	F(2,2353) = 152.24	< 0.001	< 0.001	0.26	<0.001
QOL physical	4.2 (0.5)	498	4.1 (0.6)	927	3.4 (0.7)	934	F (2,2356) = 384.09	< 0.001	< 0.001	< 0.001	< 0.001
QOL psychological	4.0 (0.5)		3.8 (0.6)	926	3.3 (0.7)		F(2,2355) = 273.03	< 0.001	< 0.001	0.001	< 0.001
QOL social	4.0 (0.6)		3.9 (0.7)	926	3.2 (0.9)		F(2,2355) = 283.21	< 0.001	< 0.001	0.07	< 0.001
QOL environmental	4.1 (0.4)		4.0 (0.5)	926	3.5 (0.6)		F (2,2355) = 229.59	< 0.001	< 0.001	<0.001	< 0.001

QOL= Quality of Life. PANSS =Positive and Negative Syndrome Scale. DFAR= Degraded Facial Affect Recognition. Benton=Benton facial recognition task.
Note Group differences on social cognitive tests and Benton adjusted for IQ, gender, age and face recognition ability (for DFAR only).

Table 3 | Unstandardised (B) and standardised (ß) regression coefficients for each predictor in a regression model predicting QOL for patients including interaction variable (n = 812) (adjusted R^2 = .170).

Variable	B [95% CI]	ß
Age	-.010[-.018, -.002]*	-.076
Gender	-.038 [-.185, .110]	-.017
IQ	-.001 [-.006, .003]	-.025
DFAR Angry	-.001 [-.004, .002]	-.030
DFAR Fearful	-.003 [-.006, .001]	-.056
Hinting task	.040 [-.029, .108]	.115
Total PANSS	-.046 [-.227, .135]	-.085
(Total PANSS x Hinting task)	-.011 [-.022, -.001]*	-.358

QOL= Quality of Life. CI = confidence interval. DFAR= Degraded Facial Affect Recognition. PANSS = Positive and Negative Syndrome Scale.* p < .05.

Table 4 | Unstandardised (B) and standardised (ß) regression coefficients for each predictor in a regression model predicting QOL for siblings and controls (n = 1323) (adjusted R^2= .024).

Variable	B [95% CI]	ß
Age	.002 [-.004, .008]	.019
Gender	-.134 [-.237, -.031] *	-.072
IQ	.007 [.004, .011] **	.126
DFAR Angry	-9.37E-005 [-.003, .003]	-.002
DFAR Fearful	-.001 [-.004, .002]	-.018
Hinting task	.030 [-.005, .065]	.047

QOL= Quality of Life. CI = confidence interval. DFAR= Degraded Facial Affect Recognition.

Note Inclusion of 'group' ('sibling' or 'control') in the analysis did not change the main finding of IQ as a significant predictor of QOL. *p < .05. **p < .001.

06

OPEN, RANDOMIZED TRIAL OF THE EFECTS OF ARIPIPRAZOLE VERSUS RISPERIDONE ON SOCIAL COGNITION IN SCHIZOPHRENIA

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ABSTRACT

To date, only few studies have examined the impact of medication on social cognition and none have examined the effects of aripiprazole in this respect. The goal of this 8-week, randomized, multicenter, open-label study was to examine the effects of aripiprazole and risperidone on social cognition and neurocognition in individuals with schizophrenia. Eighty schizophrenia patients (DSM-IV-TR) aged 16-50 years were administered multiple computerized measures of social cognition and neurocognition including reaction times at baseline and the end of week 8. Social functioning was mapped with the Social Functioning scale and Quality of Life scale. The study ran from June 2005 to March 2011. Scores on social cognitive and neurocognitive tests improved with both treatments, as did reaction time. There were few differences between the two antipsychotics on (social) cognitive test-scores. The aripiprazole group performed better (more correct items) on symbol substitution ($p = .003$). Aripiprazole was also superior to risperidone on reaction time for emotional working memory and working memory ($p = .006$ and $p = .023$, respectively). Improvements on these tests were correlated with social functioning. In conclusion, aripiprazole and risperidone showed a similar impact on social cognitive test-scores. However, aripiprazole treatment produced a greater effect on patients' processing speed compared to risperidone, with these improvements being associated with concurrent improvements in social functioning. Further research on the long-term effects of aripiprazole on cognition is warranted.

KEYWORDS

Aripiprazole, Neurocognition, Risperidone, Schizophrenia, Social Cognition

1. INTRODUCTION

Impairments in social functioning are a core characteristic of schizophrenia, and have been shown to be most pronounced in persons with schizophrenia, compared to other clinical disorders, such as bipolar disorder (Penn *et al*., 1997; Wiersma *et al*., 2000). Deficits in social functioning are present throughout the course of the disorder (Addington and Addington, 2008). Indeed, they are even present before the onset of psychosis (Cannon *et al*., 2002; Davidson *et al*., 1999) and have been reported in relatives of schizophrenia patients (Hans *et al*., 2000).

The study of social cognition in schizophrenia examines the processes underlying social dysfunction (Penn *et al*., 1997; Pinkham *et al*., 2003). Social cognition has been defined as "a set of related processes applied to the recognition, understanding, accurate processing, and effective use of social cues and information in social situations (Penn *et al*., 1997)." Investigations of social cognition in schizophrenia, employing affect recognition tasks, social knowledge tasks, and theory-of-mind tasks have shown consistent impairments (Penn *et al*., 1997). A crucial finding is that performance on social cognition tasks predicts social functioning, and that this association cannot be accounted for by cognitive deficits (Couture *et al*., 2006; Fett *et al*., 2011).

Brain circuits underlying social cognition include the ventral striatum, the amygdala, the medial prefrontal and orbitofrontal cortex, the anterior cingulate, and the insula (Adolphs *et al*., 1998; Chemerinski *et al*., 2002; Hulshoff Pol *et al*., 2001; Phan *et al*., 2002). The importance of dopamine pathways in neural processing in these circuits is well established (Grace, 2000). Numerous investigations have revealed evidence that dopamine is involved in cognitive function such as attention, planning and working memory (Cools and Robbins, 2004; Veselinovic *et al*., 2013). Clinical studies in schizophrenia have suggested a negative correlation between neurocognitive performance and D2 receptor blockade (Sakurai *et al*., 2013; Uchida *et al*., 2009). So

far, antipsychotics have not been able to reverse the social deficits associated with schizophrenia (Mishara and Goldberg, 2004; Woodward *et al*., 2007), which might be due to their general antagonist activity at dopamine D2 receptors. We hypothesized that treatment with aripiprazole, because of the unique action of this drug as a partial dopamine agonist in brain circuits underlying social cognition (Burris *et al*., 2002), will lead to a significant improvement in social cognitive processing compared to other antipsychotics. To test this hypothesis we compared the effects of aripiprazole and the frequently prescribed atypical antipsychotic agent risperidone. Computerized behavioral tasks were used to measure social cognition and neurocognition and questionnaires were used to map social functioning.

2. METHODS

2.1 SAMPLE

Eligible patients were 16 to 50 years of age with a clinical diagnosis of schizophrenia (DSM-IV-TR criteria) and an adequate understanding of Dutch. Diagnosis was based on clinical interview, observational documentation and case note information. To improve the study's generalizability, patients with drug misuse were not excluded and there were no stability criteria. Exclusion criteria were: pregnancy, lactation, mental retardation and a history of severe cerebral injury. The study was conducted between June 2005 and March 2011 at three Dutch clinical sites. Institutional review boards of each of these sites approved the study, and all patients or their legal guardians provided written informed consent. The study was registered at Eudra-CT (identifier: 2008-003345-86).

The patients were randomly assigned in a 1:1 ratio to receive either aripiprazole or risperidone. A flexible dosage was used in the first week (i.e., start with 1 or 2 mg for risperidone and 7.5 or 15 mg for aripiprazole), and the dosage could be increased thereafter to a maximum of 6 mg for risperidone and 30 mg for aripiprazole,

according to the treating physician's judgment. Overlap in the administration of the antipsychotic agents that patients received before study entry was permitted for the first two weeks after randomization to allow gradual transition to study medication. Concomitant medication other than antipsychotics was permitted throughout the trial; the dosage was restricted to a maximum of 30 mg diazepam or equivalent, 120 mg propranolol, and 12 mg biperden or equivalent. Before they entered the trial, information on previous drug use was obtained with the Composite International Diagnostic Interview (CIDI) (Cottler *et al*., 1989). Symptom ratings were done at baseline and after 8 weeks of treatment with the Positive and Negative Syndrome Scale (PANSS) (Kay *et al*., 1987).

Computerized assessments of social cognitive and neurocognitive performance were conducted at baseline and after 8 weeks of treatment. Measures of social functioning were performed at baseline and endpoint. All measures used in the trial, were selected on the basis of established relevance and sensitivity to schizophrenia, as well as on their feasibility for use in a multisite study. As lengthy testing is not always acceptable to patients, the social cognitive and neurocognitive tests selected represent a compromise between the comprehensiveness of the tests and the desire to reduce the amount of missing data.

2.2 SOCIAL COGNITIVE ASSESSMENT

Facial affect recognition (van 't Wout *et al*., 2004): In this task 40 trials were presented, consisting of ten face presentations in each of four conditions: angry, fearful, happy or neutral. The faces had been passed through a filter that reduced visual contrast by 30% in order to increase the difficulty of the task. Subjects were asked to indicate the expression of each face.

Emotional working memory: In this task, a face of a man or a woman was shown on a computer screen, expressing a certain affective facial emotion, e.g. "fear". After two seconds the face was replaced with a word (e.g. "deer"). Subjects were asked to

indicate whether the facial emotion presented before rhymed with the word presented on the screen. This way, the task yields a measure of both emotion recognition and verbal working memory. There were 14 trials. A previous study in our center showed schizophrenia patients (n= 41) to perform worse on this task in comparison to healthy control subjects (n = 41), matched for gender and education (Scholten *et al*., 2007).

Emotional learning task (Exner *et al*., 2004): This task yields a measure of associative learning and memory. Pairs of faces and objects were presented over six learning and recall trials. In the learning trial, basic emotional facial expressions (joy, surprise, fear, anger, sadness, disgust) of the same woman paired with different objects, were successively presented. In the recall trial, that followed the learning trial immediately, an object was given and subjects had to match the correct emotion to each object. The experiment was discontinued if the subjects answered all six pairs correctly or after the completion of six learning and six recall trials.

Emotional memory: The stimuli used in this test were pictures derived from the International Affective Picture System (IAPS) database, depicting a variety of affective and non-affective scenes like a plane-crash, a field of flowers and a coffee cup (Lang *et al*., 1993). Emotional memory has been shown to be impaired in schizophrenia patients for tasks in which patients were required to remember IAPS pictures (Herbener, 2008). During the first session of the task, participants were shown 72 IAPS images (24 with neutral, 24 with positive and 24 with negative valence) in random order on a computer screen. After one hour, subjects were confronted with the same set of pictures again, but this time the pictures were presented among 45 pictures of comparable composition. Subjects were then asked to indicate whether the picture had been presented before, or whether the picture was new to them, by pressing a button. For baseline and endpoint measurements different scenes of equal emotional salience were used. The task was previously used for a study in our center, in which worse performance was observed for schizophrenia patients (n = 48) as compared to healthy control subjects (n = 48), matched for gender and education (Scholten *et al*., 2007).

2.3 NEUROCOGNITIVE ASSESSMENT

Digit Symbol Substitution Test (Wechsler, 1997): This test measures cognitive and perceptual-motor processing speed. The subject was given a code that pairs symbols with digits. The test consists of matching as many series of digits to their corresponding symbols as possible in 90 seconds.

Working memory: The conditions were the same as in the emotional working memory task; however, in this test, subjects were asked to solve a simple arithmetic problem presented on a screen (e.g., 1+2 =?) and were required to determine whether the answer (i.e., 3) rhymed or not with a subsequently presented word (e.g., "free").

Identity learning task (Exner *et al*., 2004): This task is the non-emotional version of the emotional learning task (see 2.2). Again, objects and faces were paired; but this time different human faces (three male and three female) showing neutral expressions were presented.

For all tests total number of correct answers and reaction time to completion of the test were the dependent measures. Alternative forms of the tests were used at baseline and endpoint to minimize practice effects.

2.4 ASSESSMENT OF SOCIAL FUNCTIONING

Social Functioning Scale (SFS) (Birchwood *et al*., 1990): The SFS measures skills and behavior relevant to the impairments and demography of schizophrenia patients. Higher scores on each domain of the SFS (i.e., self-care, independence, social behavior and recreational activities) reflect better social functioning; in our study scores were added to create a single measure of social functioning.

Quality of Life-Brief (QOL-Brief) (WHOQOL Group, 1998): This comprehensive short-form yields a profile of QOL and includes four domain scores: physical, psychological, social and environmental. Higher scores reflect better QOL; in our study scores the

four domains were added to create one measure of QOL.

2.5 STATISTICAL ANALYSIS

IBM SPSS Statistics 20.0 (IBM Corporation, Armonk, New York) was used for data analysis. Baseline characteristics for the patients who completed the trial were compared to drop-outs using χ^2 tests or t tests. Treatment groups were compared on these same parameters for the patients with week 8 data using χ^2 tests or t tests.

For consistency with other publications, the statistical analyses conducted in this study were similar to those from previous trials, e.g. the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE trial) (Keefe *et al*., 2007a; Penn *et al*., 2009). Our primary analyses compared treatment groups on social cognitive change scores from baseline to 8 weeks. Change scores were computed by subtracting the baseline scores from the scores at week 8. Separate analyses of covariance (ANCOVA) were performed with medication group as a fixed effect and baseline scores as covariates. One might argue that a MANCOVA-model, in which cognitive data is pooled together to reduce multiple testing, is more appropriate. However in our sample, inter-correlations between the social cognitive tests were low (r=.01 to r=.30) and importantly, they were not higher than the correlations between social cognitive and neurocognitive tests (r=.00 to r=.44).

Following Penn *et al*. (2009) we adjusted for multiple tests within each domain by dividing the alpha of .05 by the number of tests within that domain. Specifically, for the four social cognitive tests, significance level was set to .05/4=.0125. For reaction time analyses for the social cognitive tests significance level was set to .05/3=.0167 (for facial affect recognition there was no reaction time available). Significance levels for the secondary analyses (neurocognition, social functioning) were set in the same way. Effect sizes (d) were calculated using Cohen's formula (Cohen, 1988).

Exploratory correlational analyses examined the relationship between symptom

changes and changes in neuropsychological variables for both treatment groups together. To examine whether changes in cognitive performance were associated with concurrent changes in clinical outcome, correlational analyses were performed. In line with our hypothesis, this analysis was limited to the cognitive variables where either drug had differential effects.

3. RESULTS

3.1 SAMPLE CHARACTERISTICS

In total 48 participants (60 %) completed the trial. Drop-out rate between the two medication groups was not significantly different (χ^2 (1, n = 80) = 1.64, p = .20). Participants tested at baseline and week 8 were similar to patients who only completed the baseline assessment (Table 1). Participants at baseline had a mean positive PANSS score (range: 7 - 49) of M = 19, i.e., mildly symptomatic (Table 3). Reasons for discontinuation are listed in Figure 1. Participants who completed the trial were compared across treatment groups. No major differences were found for the important covariates (Table 2). Patients receiving treatment with either risperidone or aripiprazole showed a significant decrease in total, positive, and general PANSS scores from baseline. There were no differences in either baseline scores or magnitude of change scores between the two treatment groups (Table 3).

3.2 PRIMARY ANALYSES: SOCIAL COGNITIVE CHANGES

For the four social cognitive tests, change-scores were significantly different from zero, indicating enhanced performance after 8 weeks compared to baseline, irrespective of treatment (facial affect recognition: d = .29; emotional working memory: d = .50; emotional learning: d = .59; emotional memory: d = .34). However, there was no significant effect of medication-group on endpoint performance on any of the four social cognitive tests. The ANCOVA comparing reaction time between the two treatment groups revealed that for reaction time on emotional working memory

aripiprazole treatment was superior to risperidone ($F1,35 = 8.41$, $p < .01$). Table 4 presents mean and standard deviation of change in test-score, reaction-time and social functioning from baseline to week 8 by treatment.

3.3 SECONDARY ANALYSES: NEUROCOGNITIVE CHANGES AND CHANGES IN SOCIAL FUNCTIONING

Similar to social cognition, change-scores on neurocognition were significantly different from zero, indicating enhanced performance over time (symbol substitution: $d = .28$; working memory: $d = .28$; identity learning: $d = .34$). In addition, a treatment main effect was found, indicating that there was one neurocognitive domain, that is, symbol substitution ($F1,34 = 10.33$, $p < .01$), where aripiprazole was superior to risperidone. Moreover, reaction time on working memory improved significantly more in the aripiprazole-group compared to the risperidone-group ($F1,32 = 5.66$, $p < .05$). For social functioning as measured with the SFS and QOL-scale, scores improved significantly with time. However, there were no differences associated with treatment.

Furthermore, because more than half of the sample consisted of patients that were antipsychotic naive before baseline testing, the analyses were repeated with previous antipsychotic use included as a covariate. This did not produce results that differed significantly from the unadjusted analyses.

3.4 CORRELATIONAL ANALYSES

No correlations between changes in symptoms (PANSS positive, negative, general and total) and social cognitive test-score or reaction time reached significance. For neurocognitive tests, improvement of negative symptoms was significantly correlated with improvement on symbol substitution ($r = .35$, $p = .042$). Changes in reaction time on neurocognitive tests were not correlated with symptom change.

Pearson's correlations were calculated between changes on the total SFS and QOL

and the three neuropsychological variables that improved significantly more in the aripiprazole group compared to the risperidone group. Significant correlations were seen between scores on SFS and QOL and improvements on the symbol substitution test and reaction time on the working memory test (Figure 2).

Importantly, we also examined the effect of clinical change on the outcome measures, showing that improvement of positive symptoms was not significantly associated with improvement on the SFS or QOL-scale ($r = .18$, $p = .29$ and $r = .31$, $p = .09$, respectively). Due to overlap between QOL and SFS-domains and the PANSS negative and general psychopathology scales, the total PANSS, negative symptom, and general psychopathology score were not evaluated.

4. DISCUSSION

The primary goal of this 8-week, randomized, open-label study was to compare the effects of aripiprazole and risperidone on social cognition in individuals with schizophrenia. The assessment involved a relatively broad set of four social cognitive measures, of which three also examined reaction time. In addition to social cognition, neurocognition was assessed. The assessment consisted of three measures, of which two also examined reaction time. Finally social functioning was measured with two questionnaires.

We hypothesized that, because of aripiprazole's unique action as a partial dopamine agonist in brain circuits underlying social cognition, treatment with this drug would lead to a significant improvement in social cognitive processing compared to risperidone. However, although social cognitive performance did improve over time with both treatments, our results show that the two antipsychotics did not differ with regard to their effect on social cognitive test scores. These results parallel those of previous trials using risperidone, quetiapine, olanzapine, haloperidol, perphenazine

and ziprasidone, which reported social cognitive improvements relative to baseline, but no differences among treatment groups (Harvey *et al*., 2006; Penn *et al*., 2009; Sergi *et al*., 2007). Nevertheless, in our study there was a difference between the two treatments for reaction time on the social cognitive tests: i.e., aripiprazole was superior to risperidone on reaction time for emotional working memory. Perhaps the fact that aripiprazole is a partial dopamine agonist explains the larger improvements in social cognitive processing speed than observed with risperidone.

Performance on neurocognitive measures improved with both treatments. This finding is consistent with the CATIE- and EUFEST results (Davidson *et al*., 2009; Keefe *et al*., 2007a). In the present study, performance was significantly better in the aripiprazole-group for one of the tests, i.e., symbol substitution, which yields a measure of cognitive processing speed, as was reaction time in the aripiprazole-group for the working memory test. Importantly, the observed improvements on symbol substitution and reaction time for working memory, in both instances being superior to risperidone, were associated with concurrent improvements in QOL and social functioning. This is in line with previous research emphasizing the clinical importance of social cognition and neurocognition (Couture *et al*., 2006; Fett *et al*., 2011; Harvey *et al*., 2006).

One might argue that the greater improvements in reaction time observed in patients on aripiprazole could be due to less frequent extrapyramidal side-effects, particularly bradykinesia, in these individuals than in the patients treated with risperidone. However, the patients on risperidone did not report bradykinesia and the relatively low doses of risperidone in our sample render the occurrence of bradykinesia rather unlikely. Moreover, the greater improvement in reaction time for aripiprazole compared to risperidone was not observed across all tasks, suggesting selective improvement of information processing efficiency.

In line with previous research showing slight medication effects on cognition (Harvey

et al., 2006; Sergi *et al*., 2007), our study shows improvements on social cognition and neurocognition over time with both atypical antipsychotic treatments. The effect sizes for emotion perception in the CATIE trial were small for all treatment groups (olanzapine, quetiapine, risperidone and ziprasidone) and ranged from .04 to .18. The larger effect sizes reported in the present study compared with those of the CATIE study could be attributable to the younger age and less chronic medication use of the population examined in our study. Accordingly, the magnitude of the improvement observed in the present study (d = .28 to .59) is similar to that reported in the EUFEST-study (d = .33 to .56) and other studies of first-episode schizophrenia patients (Davidson *et al*., 2009; Harvey *et al*., 2005; Keefe *et al*., 2004; Keefe *et al*., 2007b).

The current study has limitations. First, a substantial percentage of subjects did not receive the follow-up assessment. However, the lack of baseline differences between cases with and those without follow-up data and the lack of difference in drop-out rate between the two treatment groups are reassuring and may imply that our results apply more broadly to patients with schizophrenia treated with aripiprazole or risperidone. Secondly, the short treatment duration may be a weakness of our study as medication-influenced changes in cognition may require more time. It has been argued, however, that the major part of cognitive improvement takes place in the first two months of antipsychotic treatment (Harvey and Keefe, 2001; Keefe *et al*., 2007a). Thirdly, the open-label design of this study and the possibility that the investigators may have been influenced by our hypothesis of potential beneficial effects of the dopaminergic properties of aripiprazole, may have led to an 'expectation bias'. However, the clinicians were typically unaware of this hypothesis and more importantly; all social cognitive tests were computerized, hence minimizing the possibility of expectation bias. Fourthly, learning effects caused by repeated administration of cognitive tests cannot be ruled out due to the absence of a control or placebo group. However, whenever possible, we used alternative forms of the tests at baseline and endpoint. The absence of a placebo control group also prevents confident conclusions that any

improvements were due specifically to use of medication. Lastly, our study did not assess all social cognitive areas such as, for example, social knowledge and theory of mind. Therefore, the present conclusions may not necessarily apply to all aspects of social cognition.

In summary, this study of the effects of aripiprazole versus risperidone on social cognition in schizophrenia did not reveal clear differences between both drugs in their impact on social cognitive performance. However, improvement was significantly greater for aripiprazole compared to risperidone in performance on one neurocognitive measure and in reaction time on one social cognitive and one neurocognitive test. These findings may warrant a more thorough investigation of putatively beneficial effects on social cognitive and neurocognitive performance. Additional studies are required to assess the long-term effects of aripiprazole on social cognition and neurocognition, taking into account motor side effects and preferably using a placebo control group. Whether a slight improvement in reaction times during social cognitive tasks has clinical implications also deserves further study.

REFERENCES

Addington, J., Addington, D., 2008. Social and cognitive functioning in psychosis. Schizophr. Res. 99 (1-3), 176-81.

Adolphs, R., Tranel, D., Damasio, A.R., 1998. The human amygdala in social judgment. Nature. 393 (6684), 470-474.

Birchwood, M., Smith, J., Cochrane, R., Wetton, S., Copestake, S., 1990. The Social Functioning Scale. The development and validation of a new scale of social adjustment for use in family intervention programmes with schizophrenic patients. Br. J. Psychiatry. 157, 853-9.

Burris, K.D., Molski, T.F., Xu, C., Ryan, E., Tottori, K., Kikuchi, T., Yocca, F.D., Molinoff, P.B., 2002. Aripiprazole, a novel antipsychotic, is a high-affinity partial agonist at human dopamine D2 receptors. J. Pharmacol. Exp. Ther. 302, 381–389.

Cannon, M., Caspi, A., Moffitt, T.E., Harrington, H., Taylor, A., Murray, R.M., Poulton, R., 2002. Evidence for early-childhood, pan-developmental impairment specific to schizophreniform disorder: results from a longitudinal birth cohort. Arch. Gen. Psychiatry. 59, 449–456.

Chemerinski, E., Nopoulos, P.C., Crespo-Facorro, B., Andreasen, N.C., Magnotta, V., 2002. Morphology of the ventral frontal cortex in schizophrenia: relationship with social dysfunction. Biol. Psychiatry. 52 (1), 1-8.

Cohen, J., 1988. Statistical Power Analysis for the Behavioral Sciences, second ed. Erlbaum, Hillsdale, NJ.

Cools, R., Robbins, T.W., 2004. Chemistry of the adaptive mind. Philos. Trans. Roy. Soc. A. 362, 2871–2888.

Cottler, L.B., Robins, L.N., Helzer, J.E., 1989. The reliability of the CIDI-SAM: a comprehensive substance abuse interview. Br. J. Addict. 84 (7), 801-814.

Couture, S.M., Penn, D.L., Roberts, D.L., 2006. The functional significance of social cognition in schizophrenia: a review. Schizophr. Bull. 32 (S1), S44–S63.

Davidson, M., Reichenberg, A., Rabinowitz, J., Weiser, M., Kaplan, Z., Mark, M., 1999. Behavioral and intellectual markers for schizophrenia in apparently healthy male adolescents. Am. J. Psychiatry. 156 (9), 1328-1335.

Davidson, M., Galderisi, S., Weiser, M., Werbeloff, N., Fleischhacker, W.W., Keefe, R.S., Boter, H., Keet, I.P., Prelipceanu, D., Rybakowski, J.K., Libiger, J., Hummer, M., Dollfus, S., López-Ibor, J.J., Hranov, L.G., Gaebel, W., Peuskens, J., Lindefors, N., Riecher-Rössler, A., Kahn, R.S., 2009. Cognitive effects of antipsychotic drugs in first-episode schizophrenia and schizophreniform disorder: a randomized, open-label clinical trial (EUFEST). Am. J. Psychiatry. 166 (6), 675-682.

Exner, C., Boucsein, K., Degner, D., Irle, E., Weniger, G. 2004. Impaired emotional learning and reduced amygdala size in schizophrenia: a 3-month follow-up. Schizophr. Res. 71 (2-3), 493-503.

Fett, A.K., Viechtbauer, W., Dominguez, M.D., Penn, D.L., van Os, J., Krabbendam, L., 2011. The relationship between neurocognition and social cognition with functional outcomes in schizophrenia: a meta-analysis. Neurosci. Biobehav. Rev. 35 (3), 573–588.

Grace, A.A., 2000. Gating of information flow within the limbic system and the pathophysiology of schizophrenia. Brain Res. Rev. 31 (2-3), 330-341.

Hans, S.L., Auerbach, J.G., Asarnow, J.R., Styr, B., Marcus, J., 2000. Social adjustment of adolescents at risk for schizophrenia: the Jerusalem Infant Development Study. J. Am. Acad. Child. Adolesc. Psychiatry. 39 (11), 1406-1414.

Harvey, P.D., Keefe, R.S., 2001. Studies of cognitive change in patients with schizophrenia following novel antipsychotic treatment. Am. J. Psychiatry. 158 (2), 176-184.

Harvey, P.D., Rabinowitz, J., Eerdekens, M., Davidson, M., 2005. Treatment of cognitive impairment in early psychosis: a comparison of risperidone and haloperidol in a large long-term trial. Am. J. Psychiatry. 162 (10), 1888–1895.

Harvey, P.D., Patterson, T.L., Potter, L.S., Zhong, K., Brecher, M., 2006. Improvement in social competence with short-term atypical antipsychotic treatment: a randomized, double-blind comparison of quetiapine versus risperidone for social competence, social cognition, and neuropsychological functioning. Am. J. Psychiatry. 163 (11), 1918-1925.

Herbener, E.S., 2008. Emotional memory in schizophrenia. Schizophr. Bull. 34, 875-887.

Hulshoff Pol, H.E., Schnack, H.G., Mandl, R.C., van Haren, N.E., Koning, H., Collins, D.L., Evans, A.C., Kahn, R.S., 2001. Focal gray matter density changes in schizophrenia. Arch. Gen. Psychiatry. 58 (12), 1118-1125.

Kay, S.R., Fiszbein, A., Opler, L.A., 1987. The positive and negative syndrome scale (PANSS) for schizophrenia. Schizophr. Bull. 13, 261–276.

Keefe, R.S., Seidman, L.J., Christensen, B.K., Hamer, R.M., Sharma, T., Sitskoorn, M.M., Lewine, R.R., Yurgelun-Todd, D.A., Gur, R.C., Tohen, M., Tollefson, G.D., Sanger, T.M., Lieberman, J.A., 2004. Comparative effect of atypical and conventional antipsychotic drugs on neurocognition in first-episode psychosis: a randomized, double-blind trial of olanzapine versus low doses of haloperidol. Am. J. Psychiatry. 161 (6), 985–995.

Keefe, R.S., Bilder, R.M., Davis, S.M., Harvey, P.D., Palmer, B.W., Gold, J.M., Meltzer, H.Y., Green, M.F., Capuano, G., Stroup, T.S., McEvoy, J.P., Swartz, M.S., Rosenheck, R.A., Perkins, D.O., Davis, C.E., Hsiao, J.K., Lieberman, J.A., CATIE Investigators, Neurocognitive Working Group, 2007a. Neurocognitive effects of antipsychotic medications in patients with chronic schizophrenia in the CATIE Trial. Arch. Gen. Psychiatry. 64 (6), 633-647.

Keefe, R.S., Sweeney, J.A., Gu, H., Hamer, R.M., Perkins, D.O., McEvoy, J.P., Lieberman, J.A., 2007b. Effects of olanzapine, quetiapine, and risperidone on neurocognitive function in early psychosis: a randomized, double-blind 52-week comparison. Am. J. Psychiatry. 164 (7), 1061–1071.

Lang, P.J., Greenwald, M.K., Bradley, M.M., Hamm, A.O., 1993. Looking at pictures: affective, facial, visceral, and behavioral reactions. Psychophysiology. 30 (3), 261-273.

Mishara, A.L., Goldberg, T.E., 2004. A meta-analysis and critical review of the effects of conventional neuroleptic treatment on cognition in schizophrenia: opening a closed book. Biol. Psychiatry. 55 (10), 1013–1022.

Penn, D.L., Corrigan, P.W., Bentall, R.P., Racenstein, J.M., Newman, L., 1997. Social cognition in schizophrenia. Psychol. Bull. 121 (1), 114-132.

Penn, D.L., Keefe, R.S., Davis, S.M., Meyer, P.S., Perkins, D.O., Losardo, D., Lieberman, J.A., 2009. The effects of antipsychotic medications on emotion perception in patients with chronic schizophrenia in the CATIE trial. Schizophr. Res. 115 (1), 17-23.

Phan, K.L., Wager, T., Taylor, S.F., Liberzon, I. 2002. Functional neuroanatomy of emotion: a meta-analysis of emotion activation studies in PET and fMRI. Neuroimage. 16 (2), 331-348.

Pinkham, A.E., Penn, D.L., Perkins, D.O., Lieberman, J., 2003. Implications for the neural basis of social cognition for the study of schizophrenia. Am. J. Psychiatry. 160 (5), 815-824.

Sakurai, H., Bies, R.R., Stroup, S.T., Keefe, R.S., Rajji, T.K., Suzuki, T., Mamo, D.C., Pollock, B.G., Watanabe, K., Mimura, M., Uchida, H., 2013. Dopamine D2 receptor occupancy and cognition in schizophrenia: analysis of the CATIE data. Schizophr. Bull. 39 (3), 564-74.

Scholten, M.R.M., 2007. Schizophrenia and sex differences in emotional processing. PhD thesis, University of Utrecht. Full text available at http://dspace.library.uu.nl/handle/1874/20970.

Sergi, M.J., Green, M.F., Widmark, C., Reist, C., Erhart, S., Braff, D.L., Kee, K.S., Marder, S.R., Mintz, J., 2007. Social cognition [corrected] and neurocognition: effects of risperidone, olanzapine, and haloperidol. Am. J. Psychiatry. 164 (10), 1585-1592.

Uchida, H., Rajji, T.K., Mulsant, B.H., Kapur, S., Pollock, B.G., Graff-Guerrero, A., Menon, M., Mamo, D.C., 2009. D2 receptor blockade by risperidone correlates with attention deficits in late-life schizophrenia. J. Clin. Psychopharmacol. 29 (6), 571–575.

Veselinovic, T., Schorn, H., Vernaleken, I.B., Hiemke, C., Zernig, G., Gur, R., Gründer, G., 2013. Effects of antipsychotic treatment on cognition in healthy subjects. J. Psychopharmacol. 27 (4), 374-85.

Wechsler, D., 1997. WAIS-III: Wechsler Adult Intelligence Scale, Administration and
Scoring Manual, third ed. Psychological Corporation, San Antonio, TX.

WHOQOL Group, 1998. Development of the World Health Organization WHOQOLBREF
quality of life assessment. Psychol. Med. 28, 551–558.

Wiersma, D., Wanderling, J., Dragomirecka, E., Ganev, K., Harrison, G., An Der Heiden, W., Nienhuis, F.J., Walsh, D., 2000. Social disability in schizophrenia: its development and prediction over 15 years in incidence cohorts in six European centres. Psychol. Med. 30, 1155–1167.

Woodward, N.D., Purdon, S.E., Meltzer, H.Y., Zald, D.H., 2007. A meta-analysis of cognitive change with haloperidol in clinical trials of atypical antipsychotics: dose effects and comparison to practice effects. Schizophr. Res. 89 (1-3), 211–224.

van 't Wout, M., Aleman, A., Kessels, R.P., Laroi, F., Kahn, R.S., 2004. Emotional processing in a non-clinical psychosis-prone sample. Schizophr. Res. 68, 271–281.

Table 1 | Demographic and clinical characteristics of schizophrenia patients randomly assigned to 8 weeks of treatment with aripiprazole or risperidone

	BL data and week 8 data available (n = 48)	BL data available but week 8 data not available (n = 32)	p-value for comparing patients with week 8 data vs. without	
Variable	Mean (SD) or n (%)	Mean (SD) or n (%)	t or χ^2 statistic	p-value
Age (years) (Range: 16-50)	25.48 (6.01)	26.91 (7.29)	.77	.38
Level of education (highest attended)				
Academic	7 (14.6%)	5 (15.6%)	.07	.97
High school	39 (81.2%)	26 (81.2%)		
Lower	2 (4.2%)	1(3.1%)		
Gender				
Male	39 (81.2%)	25 (78.1%)	.12	.47
Female	9 (18.8%)	7 (21.9%)		
Ethnicity				
Caucasian	35 (72.9%)	19 (59.4%)	10.93	.14
Moroccan	2 (4.2%)	4 (12.5%)		
Surinamese	5 (10.4%)	2 (6.2%)		
Turkish	0 (0.0%)	4 (12.5%)		
Other	6 (12.6%)	3 (9.3%)		
Hospital				
UMCU	32 (66.7%)	25 (78.1%)	1.25	.54
Delta	11 (22.9%)	5 (15.6%)		
GGZ Nijmegen	5 (10.4%)	2 (6.2%)		

Table 1 | continued

Baseline antipsychotic medication				
Drug-naive	28 (58.3%)	18 (56.2%)	4.48	.48
Typical	9 (18.8%)	7 (21.9%)		
Olanzapine	7 (14.6%)	6 (18.8%)		
Quetiapine	3 (6.2%)	0 (0.0%)		
Sulpiride	1 (2.1%)	0 (0.0%)		
Unknown	0 (0.0%)	1 (3.1%)		
Baseline drug abuse				
Nicotine	35 (72.9%)	20 (66.7%)	.34	.37
Alcohol	32 (68.1%)	18 (60.0%)	.53	.31
Cannabis	27 (56.2%)	13 (43.3%)	1.23	.19
Cocaine	4 (8.3%)	3 (10%)	.06	.55
PANSS (total score)	71.52 (13.31)	75.39 (20.81)	.98	.33

Abbreviations: BL = Baseline; UMCU = University Medical Center Utrecht, the Netherlands; Delta = DeltaBouman Psychiatric Teaching Hospital, Poortugaal, The Netherlands; GGZ Nijmegen = Mental Health Institute, Nijmegen, The Netherlands; PANSS = Positive and Negative Syndrome Scale.

Table 2 | Baseline characteristics of 48 schizophrenia patients by randomly assigned treatment arm

	Aripiprazole (n = 20)	Risperidone (n = 28)	p-value for comparing patients with week 8 data between treatment groups	
Variable	Mean (SD) or n (%)	Mean (SD) or n (%)	t or χ^2 statistic	p-value
Age (years) (Range: 16-50)	26.40 (7.21)	24.82 (5.03)	.90	.38
Level of education (highest attended)				
Academic	3 (15.0%)	4 (14.3%)	-1.43	.16
High school	17 (85.0%)	23 (82.1%)		
Lower	0 (0%)	1(3.6%)		
Gender				
Male	17 (85.0%)	22 (78.6%)	.32	.57
Female	3 (15.0%)	6 (21.4%)		
Ethnicity				
Caucasian	17 (85.0%)	18 (64.3%)	4.62	.59
Other	3 (15.0%)	10 (35.7%)		
Hospital				
UMCU	13 (65.0%)	19 (67.9%)	.09	.96
Delta	5 (25.0%)	6 (21.4%)		
GGZ Nijmegen	2 (10.0%)	3 (10.7%)		
Baseline antipsychotic medication				
Drug-naive	12 (60.0%)	16 (57.1%)	2.02	.73
Typical	5 (25.0%)	4 (14.3%)		
Olanzapine	2 (10.0%)	5 (17.9%)		

Table 2 | continued

Quetiapine	1 (5.0%)	2 (7.1%)		
Sulpiride	0 (0.0%)	1 (3.6%)		
Baseline drug abuse				
Nicotine	15 (75.0%)	20 (71.4%)	.08	.78
Alcohol	16 (80.0%)	16 (59.3%)	2.28	.13
Cannabis	11 (55.0%)	16 (57.1%)	.02	.88
Cocaine	2 (10.0%)	2 (7.1%)	.13	.72
Medication dose (mg)	17.00 (6.21)	3.55 (1.12)		
	Range: 7.5- 30	Range: 1- 6		

Abbreviations: UMCU = University Medical Center Utrecht, the Netherlands; Delta = DeltaBouman Psychiatric Teaching Hospital, Poortugaal, The Netherlands; GGZ Nijmegen = Mental Health Institute, Nijmegen, The Netherlands.

Table 3 | PANSS changes in schizophrenia patients randomly assigned to 8 weeks of treatment with aripiprazole or risperidone[a]

	Aripiprazole (n = 17)		Risperidone (n = 27)	
Variable	Mean	SD	Mean	SD
Positive symptom subscale				
Baseline	18.65	4.65	19.56	4.05
Change	- 7.00	5.40	- 6.00	4.91
Negative symptom subscale				
Baseline	18.29	5.96	17.26	5.93
Change	- 2.35	5.53	- 1.26	7.20
General Symptom subscale				
Baseline	35.65	8.49	34.63	7.59
Change	- 7.82	8.85	- 5.59	9.83
Total				
Baseline	72.59	14.33	71.44	13.20
Change	- 17.24	15.89	- 12.85	17.58

Abbreviation: PANSS = Positive and Negative Syndrome Scale.
[a] Lower scores on the PANSS are indicative of clinical improvement.

Table 4 | Change from baseline to week 8 on test-score and reaction time for social cognition and neurocognition and change from baseline to week 8 on outcome measures by treatment [a]

	Aripiprazole		Risperidone		p-value for comparing treatment groups[b]	
Variable	Mean (SD)	n	Mean (SD)	n	F-statistic	p-value
Social cognition						
Facial affect recognition						
Baseline	49.28 (4.99)	18	47.04 (8.18)	24	F1,39 = .01	.93
Change	1.11 (7.58)		2.63 (8.84)			
Emotional working memory						
Baseline	11.44 (1.93)	16	10.18 (2.95)	22	F1,35 = .79	.38
Change	.94 (1.91)		1.32 (3.17)			
Baseline RT	141.09 (39.32)		140.80 (31.90)		F 1,35 = 8.41	.006
Change RT	-24.10 (31.57)		-1.62 (24.20)			
Emotional learning task						
Baseline	19.58 (8.12)	12	17.58 (9.95)	19	F1,28 = .39	..54
Change	3.50 (7.10)		6.11 (8.86)			
Baseline RT	587.58 (99.13)		624.58 (243.87)		F1,28 = 3.90	.06
Change RT	-134.81 (175.41)		-13.42 (220.34)			
Emotional memory						
Baseline	63.29 (8.97)	14	61.29 (8.22)	21	F1,32 = 1.32	.26
Change	2.93 (7.36)		2.24 (9.23)			
Baseline RT	142.84 (36.62)		156.42 (43.00)		F1,32 = .02	.88
Change RT	-18.70 (28.52)		-26.89 (34.85)			
Neurocognition						
Digit symbol substitution						
Baseline	50.11 (14.97)	19	37.61 (9.99)	18	F1,34 = 10.33	.003
Change	4.26 (5.93)		3.17 (4.53)			
Working memory						
Baseline	12.06 (1.82)	17	11.57 (2.64)	21	F1,35 = .87	.36
Change	.82 (2.51)		.48 (1.91)			
Baseline RT	121.12 (32.60)		134.93 (36.89)		F1,32 = 5.66	.023
Change RT	-17.20 (24.53)		-8.62 (30.09)			

Table 4 | continued

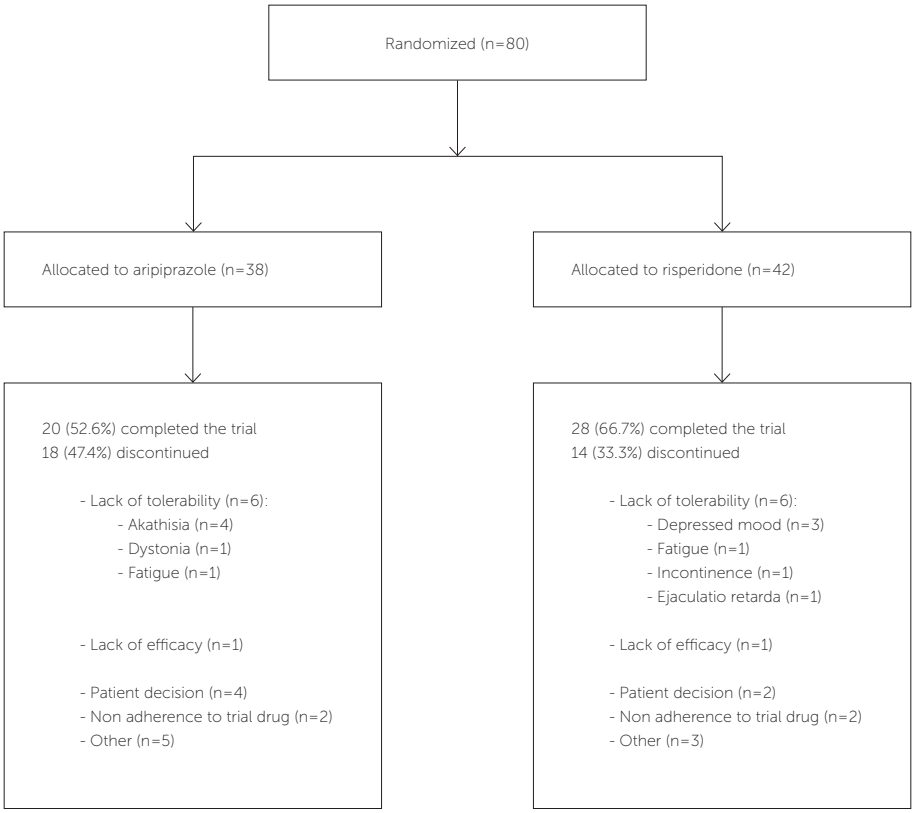
Identity learning						
Baseline	21.17 (9.81)	12	20.32 (9.87)	22	F1,31 = 1.04	.32
Change	.83 (11.67)		4.77 (10.38)			
Baseline RT	530.47 (138.97)		566.96 (180.30)		F1,31 = .06	.80
Change RT	-78.40 (230.66)		-95.03 (179.25)			
Outcome measures						
QOL						
Baseline	76.38 (7.91)	16	77.47 (16.62)	17	F1,30 = .85	.37
Change	4.88 (9.41)		6.47 (13.73)			
SFS						
Baseline	87.50 (16.07)	18	94.83 (13.73)	24	F1,39 = .89	.35
Change	4.94 (17.55)		-3.25 (17.14)			

Abbreviations: RT = reaction time seconds; QOL = Quality of Life; SFS = Social Functioning Scale.

[a] For test-score and outcome measures higher scores are indicative of better performance and for reaction time lower scores are indicative of better performance.

[b] F and p-values are for the treatment group comparison from an ANCOVA with Nbaseline score as covariate.

Figure 1 | Flowchart of schizophrenia patients randomly assigned to 8 weeks of treatment with aripiprazole or risperidone



07

DISCUSSION

7. DISCUSSION

7.1 OBJECTIVES

The aims of the research presented in this thesis were; 1) to examine whether social cognitive impairment in schizophrenia should be considered a trait and/or a state characteristic (Part I, Chapters 2 and 3), 2) to identify eventual structural abnormalities of for social cognition relevant brain structures in patients with the disease (Part II, Chapter 4), and 3) to explore the impact of social cognitive deficits on quality of life (QOL) as well as the effect of anti-psychotic medication on social cognition in schizophrenia (Part III, Chapters 5 and 6). Both cross-sectional and longitudinal epidemiological methods, neuroimaging, and a randomized clinical trial were applied as a means.

7.2 MAIN FINDINGS

Part I

In Chapter 2 we used a genetically sensitive cross-trait cross-sibling design to investigate the nature of the association between schizophrenia symptoms and social cognition. First, in line with previous studies (Chan *et al*., 2010; Kohler *et al*., 2010; Marwick and Hall, 2008; Penn *et al*., 2008), our findings showed impaired social cognitive functioning, i.e., emotion recognition and Theory of Mind (ToM), in schizophrenia patients compared to healthy controls. Second, social cognitive impairment was found to be associated with schizophrenia symptoms in patients and with subclinical symptoms in siblings. Third, social cognitive functioning appeared to cluster between siblings. Fourth, the associations between patients' emotion recognition and subclinical symptoms in siblings appeared to be significant, whereas those between patients' ToM and subclinical symptoms in siblings were not.

In Chapter 3, emotion recognition deficits in the same cohort of schizophrenia patients were explored in a longitudinal manner. More specifically, we investigated whether

emotion recognition deficits in schizophrenia are present primarily during psychosis (i.e., state dependent) and/or are associated with the disorder (i.e., trait dependent). Emotion recognition performance was compared between schizophrenia patients across different stages of illness, i.e., remission versus non-remission, at baseline and after three years follow-up. In line with the results from previous studies (Green *et al*., 2012; Pinkham *et al*., 2007), we demonstrated that emotion recognition impairments are present in non-acute stages of the illness (i.e., remission state). The study also showed further deterioration of emotion recognition deficits during the acute phase of the disorder (i.e., non-remission state).

Part II

In Chapter 4 the relationship of emotion recognition and ToM with gray matter volumes of the amygdala and prefrontal cortex (PFC) in schizophrenia patients and healthy controls was investigated. Schizophrenia patients showed poorer recognition of angry faces and impaired ToM performance, as well as decreased amygdala and PFC gray matter volumes, compared to healthy controls. PFC, but not amygdala gray matter volume was related to emotion recognition and ToM performance in schizophrenia. Specifically, a reduction of pars triangularis gray matter volume was related to poorer emotion recognition, while a reduction of middle PFC gray matter volume was related to poorer ToM skills.

Part III

Chapter 5 examined the impact of social cognitive deficits on QOL in schizophrenia. The results of this study showed that ToM, but not emotion recognition, is a significant predictor of QOL in schizophrenia. Unexpectedly, and in contrast to previous findings suggesting that lower social cognition is associated with poor outcome (Fett *et al*., 2011), lower ToM was associated with better QOL. The findings further indicated an interaction between ToM and symptoms, showing that QOL was the lowest in those with high symptom levels and relatively unimpaired ToM.

In Chapter 6 we compared the effects of aripiprazole versus risperidone on social cognition in individuals with schizophrenia. The results showed that social cognitive performance did improve over time with both treatments, but the two anti-psychotics did not differ with regard to their effect on social cognitive test scores. However, aripiprazole treatment produced a greater effect on patients' processing speed compared to risperidone, with these improvements being associated with concurrent improvements in social functioning.

How may the findings described above advance our understanding of social cognition in schizophrenia and what are the implications for clinical practice and future research? The following paragraphs aim to put our main findings into a broader perspective.

7.3 SOCIAL COGNITION, STATE OR TRAIT?

Emotion recognition and ToM performance showed significant familial clustering (Chapter 2). Since siblings of patients with schizophrenia share on average 50% of their genes with their affected ill brothers and sisters, this familial clustering may reflect the expression of shared susceptibility genes for schizophrenia (Tsuang *et al*., 2001). Obviously, impairment of emotion recognition and ToM may also have been acquired in a shared environment (e.g., parental neglect).

In line with previous reports (Shean *et al*., 2005; Ventura *et al*., 2013), the study described in Chapter 2 showed that significant associations were present between symptoms and social cognitive performance, i.e., ToM and emotion recognition, within the patients. These associations were also present, albeit to a lesser extent, within their siblings. In a cross-trait cross-sibling design, the associations between patients' ToM and subclinical symptoms in siblings appeared to be non-significant, suggesting that their overlap within patients is due to individual rather than shared familial factors. Indicative of a shared etiology, familial co-variation was present between patients' emotion recognition ability and subclinical symptoms in siblings.

The study described in Chapter 3 demonstrated that emotion recognition impairments are present in non-acute stages of the illness (i.e., remission state). However, the study also showed further deterioration of emotion recognition deficits during acute phases of the disorder (i.e., non-remission state). This finding is in agreement with the findings from Chapter 2 and other reports showing that emotion recognition performance is significantly related to symptom severity (Edwards *et al*., 2002; Kohler *et al*., 2000; Laroi *et al*., 2010; Marwick and Hall, 2008; Tseng *et al*., 2013). Hence, emotion recognition in schizophrenia patients is not only trait dependent, but also state dependent. Therefore, improving the symptomatic course of schizophrenia may impact on social cognitive ability and by consequence social functioning of the patient.

7.4 THE DISRUPTED SOCIAL BRAIN

The study described in Chapter 4 showed that PFC, but not amygdala gray matter volume is related to emotion recognition and ToM performance in schizophrenia. The PFC, which constitutes one third of the neocortex, is one of the last parts of the cortex to develop in the human brain (Fuster, 2001; Fuster, 2002). The late maturation of this region is consistent with behavioral evidence that the PFC is critical for those higher cognitive functions that develop later in life, like complex linguistics and mentalizing skills, such as ToM (Venkatasubramanian *et al*., 2008). Also, the phylogenetic recentness of the PFC supports the observation that this region is crucial in complex social cognitive functions, a faculty in which humans are considered to be more specialized than most other primates (Povinelli and Preuss, 1995; Semendeferi, 2012).

Although functional neuroimaging studies in schizophrenia patients have consistently demonstrated abnormal activity of the amygdala during social cognitive processing (Aleman and Kahn, 2005; Pessoa, 2008), we did not demonstrate an association between amygdala volume and either measure of social cognition. Neuroimaging studies examining functional brain connectivity show that the amygdalae are strongly connected to prefrontal areas (Aleman and Kahn, 2005; Iidaka *et al*., 2001; Kim

et al., 2011; Mukherjee *et al.*, 2014; Stein *et al.*,2007). Two fMRI studies examining frontolimbal connectivity during social cognitive tasks demonstrated significantly weaker amygdala-prefrontal cortical coupling in schizophrenia patients than in healthy controls (Anticevic *et al.*, 2012; Das *et al.*, 2007). The volumetric reduction of the PFC in schizophrenia patients observed in our study might be associated with a reduced connectivity between the PFC and the amygdala, and consequently induce altered functional processing in the amygdala during social cognitive tests, as shown in previous functional MRI research (Aleman and Kahn, 2005).

7.5 QUALITY OF LIFE AND SOCIAL COGNITION

Our finding of ToM but not neurocognition being significantly related to QOL of schizophrenia patients, as described in Chapter 5, is in line with previous studies showing that social cognition is a stronger predictor of functional outcome in schizophrenia than neurocognition. Whereas social cognition and functional outcome in schizophrenia are positively associated (Fett *et al*., 2011; McGurk *et al*., 2007; Pijnenborg *et al*., 2009), we found ToM to be negatively associated with QOL. These different effects of social cognition may reflect the difference in outcome measures of QOL (subjective life satisfaction) and functional outcome (e.g., employment, housing and marital status). Apparently, whereas functional outcome in schizophrenia benefits from a higher social intelligence, QOL does not, probably because the patient realizes the impact of his illness on his social environment. The present findings are consistent with reports on relationships between QOL and 'insight' (Karow *et al*., 2008; Xiang *et al*., 2012). These studies point out, that patients with better insight recognize their illness-related limitations, a recognition that is reflected in low QOL. ToM and 'insight' in psychosis are related constructs (Bora *et al*., 2007; Langdon *et al*., 2009; Quee *et al*., 2011), which may explain their similar effect on QOL in schizophrenia patients. Therefore, it is important that the social environment is aware of the status of a patient's ToM, and understands that its interaction with the patient can possibly negatively impact his well-being. Family coaching and education of peers could be helpful in this respect and help to improve

QOL of schizophrenia patients.

7.6 EFFECTS OF ANTI-PSYCHOTIC TREATMENT ON SOCIAL COGNITION

The study described in chapter 6 of this thesis showed improvements on cognition over time with both aripiprazole and risperidone. The two anti-psychotics did not differ with regard to their effects on social cognitive test scores. These results parallel those of previous trials using risperidone, quetiapine, olanzapine, haloperidol, perphenazine and ziprasidone, which reported social cognitive improvements relative to baseline, but no differences among treatment groups (Harvey *et al*., 2006; Penn *et al*., 2009; Sergi *et al*., 2007). In our study there was a difference between the two treatments for reaction time on two cognitive tests: i.e., aripiprazole was superior to risperidone for reaction time on emotional working memory and working memory. Also, performance was significantly better in the aripiprazole group for symbol substitution, which yields a measure of cognitive processing speed. Perhaps, the fact that aripiprazole is a partial dopamine agonist explains the larger improvements in cognitive processing speed than observed with risperidone. However, the absence of a placebo control group prevents confident conclusions that any improvements were due specifically to the use of medication. Moreover, one might argue that the greater improvements in reaction time observed in patients on aripiprazole could be due to less severe extrapyramidal side effects, particularly bradykinesia, in these individuals than in the patients treated with risperidone. Our findings warrant a more thorough investigation of putatively beneficial effects of aripiprazole on cognitive performance. Additional studies are required to assess the long-term effects of aripiprazole on cognition, taking into account motor side effects and preferably using a placebo control group.

7.7 POSSIBLE IMPLICATIONS FOR CLINICAL PRACTICE AND FUTURE RESEARCH

The results of this thesis could have implications for clinical practice. The findings

from Chapters 2 and 3 indicate that social cognition is clinically relevant because of the significant association with schizophrenia symptoms. Therefore, improving the symptoms of schizophrenia may impact on social cognitive ability. Conversely, improvement of social cognition may contribute to the reduction and prevention of the symptoms of the illness. The latter is of specific interest with respect to patients who present for the first time with psychosis and for high-risk individuals.

Unfortunately, social cognitive impairment in schizophrenia is only marginally influenced by the currently available anti-psychotic medications (Harvey *et al*., 2006; Penn *et al*., 2009; Sergi *et al*., 2007; Chapter 6). In addition, social cognitive dysfunction is present also in the absence of acute symptoms of the disease (Chapters 2 and 3). Therefore, new medications and cognitive therapies to improve social cognition in schizophrenia as add-ons to anti-psychotic treatment are necessary (Van Os and Kapur, 2009). However, although better social cognitive functioning appears to be associated with better functional outcome in schizophrenia (Irani *et al*., 2012), one should take into account that improvement of certain social cognitive skills might be counterproductive as for QOL, particularly in severely ill patients (Chapter 5).

Much remains to be understood regarding social cognition in schizophrenia. An important point concerning the measurement of social cognition is highlighted below. Social cognition comprises a wide variety of psychological constructs, e.g., ToM, emotion recognition, empathy and social knowledge. The present thesis did not assess all social cognitive areas and therefore the conclusions of this thesis may not necessarily apply to all aspects of social cognition. Moreover, the tasks used to measure social cognition were not the same ones in all our studies complicating the comparability of the data. Unfortunately, all research on social cognition in schizophrenia to date suffers from this non-uniformity (Green *et al*., 2013). Standardized measures to assess social cognition are needed, not only for use in the search of the etiology of schizophrenia, but also to serve as reliable and valid endpoints to evaluate treatment response in clinical trials. The "Social Cognition and

Functioning in Schizophrenia" study (SCAF), now attempts to address this issue by selecting paradigms from social neuroscience that could be adapted for use as social cognitive measurements in schizophrenia (Green *et al*., 2013).

7.8 CONCLUSION

Taken together, this thesis contributes to the knowledge on social cognition and its structural brain correlates in schizophrenia and elucidates associations between social cognitive performance and both QOL and anti-psychotic drug therapy. The current findings show that social cognition in schizophrenia is a relevant construct for basic science as well as clinical practice and, therefore, deserves attention of future research.

Conclusions:

1. Schizophrenia is associated with impairments in emotion recognition and ToM. These impairments are related to schizophrenia symptoms.
2. Suggestive of a common familial basis, social cognitive functioning clusters between schizophrenia patients and their siblings.
3. The associations between ToM and symptoms observed in schizophrenia patients are due to individual factors.
4. Emotion recognition in schizophrenia patients is not only trait dependent, but also state dependent.
5. Reduced prefrontal cortex, but not amygdala gray matter volume is associated with social cognitive deficits in schizophrenia.
6. ToM rather than emotion recognition is associated with QOL, and this association is moderated by schizophrenia symptoms.
7. Patients with relatively unimpaired ToM and more severe schizophrenia symptoms have poor QOL.
8. Aripiprazole and risperidone have similar impact on social cognitive performance in schizophrenia.
9. Aripiprazole treatment has a greater effect on schizophrenia patients' processing speed compared to treatment with risperidone.

REFERENCES

Aleman, A., Kahn, R.S., 2005. Strange feelings: Do amygdala abnormalities dysregulate the emotional brain in schizophrenia? Prog. Neurobiology 77, 283 - 298.

Anticevic A., Repovs G., Barch D.M., 2012. Emotion Effects on Attention, Amygdala Activation, and Functional Connectivity in Schizophrenia. Schizophrenia Bulletin 38 (5), 967–980.

Bora E., Sehitoglu G., Aslier M., Atabay I., Veznedaroglu B., 2007. Theory of mind and unawareness of illness in schizophrenia: is poor insight a mentalizing deficit? Eur Arch Psychiatry Clin Neurosci. 257, 104–111.

Chan, R.C.K., Li, H., Cheung, E.F.C., Gong, Q., 2010. Impaired facial emotion perception in Schizophrenia. Psych. Res. 178, 381 – 390.

Das P., Kemp A.H., Flynn G., Harris A.W.F., Liddell B.J., Whitford T.J., Peduto A., Gordon E., Williams L.M., 2007. Functional disconnections in the direct and indirect amygdala pathways for fear processing in schizophrenia. Schizophrenia Research 90, 284-294.

Edwards, J., Jackson, H.J., Pattison, P.E., 2002. Emotion recognition via facial expression and affective prosody in schizophrenia: a methodological review. Clin. Psychol. Rev. 22, 789 – 832.

Fett, A.K., Viechtbauer, W., Dominguez, M.D., Penn, D.L., van Os, J., Krabbendam, L., 2011. The relationship between neurocognition and social cognition with functional outcomes in schizophrenia: a meta-analysis. Neurosci. Biobehav. Rev. 35 (3), 573-588.

Fuster J.M., 2002. Frontal lobe and cognitive development. Journal of Neurocytology 31 (3-5), 373-85.

Fuster J.M., 2001. The prefrontal cortex--an update: time is of the essence. Neuron 30 (2), 319-33.

Green, M.F., Bearden, C.E., Cannon, T.D., Fiske, A.P., Hellemann, G.S., Horan, W.P., Kee, K., Kern, R.S., Lee, J., Sergi, M.J., Subotnik, K.L., Sugar, C.A., Ventura, J., Yee, C.M., Nuechterlein, K.H., 2012. Social cognition in schizophrenia, part 1: performance across phase of illness. Schizophr. Bull. 38, 845 – 864.

Green, M., Junghee, L., Ochsner, K.N., 2013. Adapting Social Neuroscience Measures for Schizophrenia Clinical Trials, Part 1: Ferrying Paradigms Across Perilous Waters. Schizophrenia Bulletin vol. 39 no. 6 pp. 1192–1200.

Harvey, P.D., Patterson, T.L., Potter, L.S., Zhong, K., Brecher, M., 2006. Improvement in social competence with short-term atypical antipsychotic treatment: a randomized, double-blind comparison of quetiapine versus risperidone for social competence, social cognition, and neuropsychological functioning. Am. J. Psychiatry. 163 (11), 1918-1925.

Iidaka T., Omori M., Murata T., Kosaka H., Yonekura Y., Okada T., Sadato N., 2001. Neural interaction of the amygdala with the prefrontal and temporal cortices in the processing of facial expressions as revealed by fMRI. Journal of Cognitive Neuroscience 13, 1035–1047.

Irani, F., Seligman, S., Kamath, V., Kohler, C., Gur, R.C., 2012. A meta-analysis of emotion perception and functional outcomes in schizophrenia. Schizophr Res. 137(1-3):203-11.

Karow, A., Pajonk, F.G., Reimer, J., Hirdes, F., Osterwald, C., Naber, D., Moritz, S., 2008. The dilemma of insight into illness in schizophrenia: self- and expert-rated insight and quality of life. Eur. Arch. Psychiatry Clin. Neurosci. 258 (3), 152-159.

Kim M.J., Loucks R.A., Palmer A.L., Brown A.C., Solomon K.M., Marchante A.N., Whalen P.J., 2011. The structural and functional connectivity of the amygdala: from normal emotion to pathological anxiety. Behavioural brain research 223, 403–410.

Kohler, C.G., Bilker, W., Hagendoorn, M., Gur, R.E., Gur, R.C., 2000. Emotion recognition deficit in schizophrenia: association with symptomatology and cognition. Soc. Biol. Psych. 48, 127 – 136.

Kohler, C.G., Walker, J.B., Martin, E.A., Healey, K.M., Mober, P.J., 2010. Facial emotion perception in schizophrenia. Schizophr. Bull. 36, 1009 – 1019.

Langdon R., Ward P., 2009. Taking the perspective of the other contributesto awareness of illness in schizophrenia. Schizophr Bull. 35, 1003–1011.

Laroi, F., Fonteneau, B., Mourad, H. & Raballo, A., 2010. Basic emotion recognition and psychopathology in schizophrenia. J. Of Nerv. And Ment. Disease 198, 79 – 81.

Marwick, K., Hall, J., 2008. Social cognition in schizophrenia: a review of face processing. Brit. Med. Bull. 88, 43 – 58.

McGurk, S.R., Twamley, E.W., Sitzer, D.I., McHugo, G.J., Mueser, K.T., 2007. A meta-analysis of cognitive remediation in schizophrenia. Am. J. Psychiatry 164, 1791-1802.

Mukherjee P, Whalley HC, McKirdy JW, Sprengelmeyer R, Young AW, McIntosh AM, Lawrie SM, Hall J, 2014. Altered Amygdala Connectivity Within the Social Brain in Schizophrenia. Schizophrenia Bulletin 40 (1), 152-60.

Penn, D.L., Sanna, L.J., Roberts, D.L., 2008. Social cognition in schizophrenia: an overview. Schizophr. Bull. 34, 408 – 411.

Penn, D.L., Keefe, R.S., Davis, S.M., Meyer, P.S., Perkins, D.O., Losardo, D., Lieberman, J.A., 2009. The effects of antipsychotic medications on emotion perception in patients with chronic schizophrenia in the CATIE trial. Schizophr. Res. 115 (1), 17-23.

Pijnenborg, G.H., Withaar, F.K., Evans, J.J., van den Bosch, R.J., Timmerman, M.E., Brouwer, W.H., 2009. The predictive value of measures of social cognition for community functioning in schizophrenia: implications for neuropsychological assessment. J. Int. Neuropsychol. Soc. 15 (2), 239-247.

Pinkham, A.E., Penn, D.L., Perkins, D.O., Graham, K.A., Siegel, M., 2007. Emotion perception and social skill over the course of psychosis: a comparison of individuals at risk for psychosis and individuals with early and chronic schizophrenia. Cogn. Neuropsych. 12 (3), 198 – 212.

Povinelli D.J., Preuss T.M., 1995. Theory of mind: evolutionary history of a cognitive specialization. Trends in Neuroscience 18 (9), 418-24.

Quee P.J., van der Meer L., Bruggeman R., de Haan L., Krabbendam L., Cahn W., Mulder N.C., Wiersma D., Aleman A., 2011. Insight in psychosis: relationship with neurocognition, social cognition and clinical symptoms depends on phase of illness. Schizophr Bull. 37 (1), 29-37.

Semendeferi K., 2012. Human prefrontal cortex: evolution, development, and pathology. Progress in Brain Research 195, 191-218.

Sergi, M.J., Green, M.F., Widmark, C., Reist, C., Erhart, S., Braff, D.L., Kee, K.S., Marder, S.R., Mintz, J., 2007. Social cognition [corrected] and neurocognition: effects of risperidone, olanzapine, and haloperidol. Am. J. Psychiatry. 164 (10), 1585-1592.

Shean, G., Murphy, A., Meyer, J., 2005. Social Cognition and Symptom Dimensions. The Journal of Nervous and Mental Disease 193: p. 751-755.

Stein J.L., Wiedholz L.M., Bassett D.S., Weinberger D.R., Zink C.F., Mattay V.S., Meyer-Lindenberg A., 2007. A validated network of effective amygdala connectivity. Neuroimage 36, 736–745.

Tseng, H.H., Chen, S.H., Liu, C.M., Howes, O., Huang, Y.L., Hsieh, M.H., Liu, C.C., Shan, J.C., Lin, Y.T, Hwu, H.G., 2013. Facial and prosodic recognition deficits associate with specific clusters of psychotic symptoms in schizophrenia. Plos One 8, 1 – 7.

Tsuang, M.T., Stone, W.S., Faraone, S.V., 2001. Genes, environment and schizophrenia. Br J Psychiatry Suppl. 40:s18-24.

Van Os, J. and Kapur, S., 2009. Schizophrenia. Lancet. 374 :635-45.

Venkatasubramanian G., Jayakumar P.N., Keshavan M.S., 2008. Automated MRI parcellation study of regional volume and thickness of prefrontal cortex (PFC) in antipsychotic-naïve schizophrenia. Acta psychiatrica Scandinavica 117 (6), 420-31.

Ventura, J., Wood, R.D., Helleman, G.S., 2013. Symptom domains and neurocognitive functioning can help differentiate social cognitive processes in schizophrenia: A meta-analysis. Schiz Bull 39(1):102-11

Xiang, Y.T., Wang, Y., Wang, C.Y., Chiu, H.F.K., Chen, Q., Chan, S.S.M., Lai, K.Y.C., Lee, E.H.M., Ungvari, G.S., 2012. Association of insight with sociodemographic and clinical factors, quality of life, and cognition in Chinese patients with schizophrenia. Compr. Psychiatry 53, 140-144.

SUMMARY

SUMMARY

The research presented in this thesis entitled 'Social cognition in schizophrenia' had three main objectives. The first objective was to further characterize the relation between social cognition and schizophrenia symptoms (Part I, Chapters 2 and 3). Second, we sought to identify possible neural substrates of social cognitive impairment in schizophrenia (Part II, Chapter 4). Third, the impact of social cognitive deficits on quality of life (QOL) as well as the effect of anti-psychotic medication on social cognition in schizophrenia were explored (Part III, Chapters 5 and 6).

In Chapter I the etiology, symptomatology and effectiveness of antipsychotic treatment are discussed. Next, an introduction to the relation of social cognition and schizophrenia is provided. Schizophrenia is known to be associated with social cognitive impairments. In particular, emotion recognition, i.e., the ability to infer emotional information from facial expressions, and theory of mind (ToM), i.e., the ability to infer the intentions and beliefs of other individuals appear to be for schizophrenia important domains of social cognition, because they are valid predictors of social functioning of the patients. To date, it remains undetermined whether social cognitive deficits should be considered state or trait characteristics of the disorder. Finally, current notions on possible neural substrates of social cognitive impairment in schizophrenia are discussed.

Part I: Social cognition and symptomatology

Chapter 2 describes a study of the association between social cognitive impairments and symptoms in schizophrenia. The study used a genetically sensitive cross-trait cross-sibling design to investigate the nature of the overlap between symptoms and social cognitive deficits. A sample of 1032 patients, 1017 of their healthy siblings and 579 control subjects were recruited within the Dutch Genetic Risk and Outcome in Psychosis (GROUP) study. Participants completed a battery of cognitive tests, including two social cognitive tests on ToM (hinting task) and emotion recognition (Degraded

Facial Affect Recognition Task). Within siblings, symptoms were assessed with the Structured Interview for Schizotypy-Revised. The 'Positive and Negative Syndrome Scale' (PANSS) was used to assess patients' symptoms. There were significant associations between social cognitive performance and disorganized and, albeit to a lesser degree, negative symptoms. The associations between positive symptoms and social cognition were significant but smaller. Suggestive of a shared etiology, both emotion recognition and ToM clustered within families. The associations between patients' ToM and subclinical symptoms in siblings were not significant, showing that the overlap within patients is due to individual rather than shared familial factors. However, suggestive of a common familial substrate emotion recognition impairment overlapped significantly with disorganized and positive symptoms of siblings.

Chapter 3 examines whether social cognitive deficits in patients are present primarily during psychosis (i.e., state dependent) or form an integral part of the disorder (i.e., trait dependent). The same sample of patients was used as in Chapter 2 (GROUP study), but this time a longitudinal design was applied. Emotion recognition was assessed with the Degraded Facial Affect Recognition Task in 521 schizophrenia patients and 312 healthy controls at baseline (T1) and after three years follow-up (T2). Symptomatic remission was assessed with the 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). First, as expected, schizophrenia patients performed worse than healthy controls on emotion recognition at T1. Second, patients who stayed in remission for three years (RR) improved on emotion recognition performance over time, whereas patients, who returned to a non-remission state after three years (RN), performed worse at follow-up compared to baseline. Third, we showed that the patient group in remission at baseline and in non-remission at follow-up (RN) had a worse 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 emotion recognition performance over time. Together, our findings indicate that emotion

recognition in schizophrenia patients is associated with symptomatic remission. The results provide support for the hypothesis that emotion recognition deficits in schizophrenia are both state and trait dependent.

Part II: The disrupted social brain

Chapter 4 describes a structural imaging investigation of the relationship between social cognition and brain abnormalities of the amygdala and the prefrontal cortex (PFC) in schizophrenia patients. The sample was recruited within the GROUP study and consisted of 166 patients with schizophrenia and 134 healthy controls. The same measures of facial emotion recognition and ToM were applied and, in addition, MRI brain scans were acquired. Automated parcellation of the brain to determine gray matter volume of the amygdala and the superior, middle, inferior and orbital PFC was performed. Schizophrenia patients showed poorer recognition of angry faces and impaired ToM performance, as well as decreased amygdala and PFC gray matter volumes, compared to healthy controls. PFC but not amygdala gray matter volume was related to emotion recognition and ToM performance in schizophrenia. Specifically, a reduction of pars triangularis gray matter volume was related to poorer emotion recognition, while a reduction of middle PFC gray matter volume was related to poorer ToM skills. The association between PFC gray matter volume and these aspects of social cognition was not present in healthy controls. Our findings suggest that the reduced amygdala activity observed in schizophrenia during social cognitive tasks is not the result of reduced amygdala gray matter volume, but may be explained by the loss of PFC gray matter volume.

Part III: Social cognition, quality of life and anti-psychotic treatment

In Chapter 5 a study is described of the association between social cognitive functioning and quality of life (QOL) in schizophrenia. The sample consisted of 1032 patients, 1011 of their siblings, and 552 healthy controls (GROUP study). Again, social cognition was assessed with the hinting task (ToM) and the Degraded Facial Affect Recognition Task (emotion recognition). QOL was assessed with the World Health

Organization QOL Assessment-BREF (WHOQOL-BREF). Schizophrenia symptoms were assessed with the PANSS. Social cognitive performance was significantly worse in patients compared to siblings and healthy controls. Patients had the poorest QOL, while QOL in healthy controls was better than in siblings. ToM but not emotion recognition or neurocognition was associated with QOL in patients, whereas neurocognition was the only significant predictor of QOL in siblings and healthy controls. In contrast to the expectations, patients' ToM was negatively associated with QOL. In addition, there was a significant interaction between ToM and symptom severity, showing that higher symptoms were associated with a worse QOL in those with better ToM. Insight could be a possible explanation for the findings, i.e., more severely ill patients with relatively unimpaired ToM may be more aware of the effects of their illness on their social environment.

Chapter 6 examines the impact of medication on social cognition. An 8-week, randomized, multicenter, open-label study was used to examine the effects of aripiprazole and risperidone on social cognition in individuals with schizophrenia. Eighty schizophrenia patients, aged 16-50 years, were administered multiple computerized measures of social cognition and neurocognition including reaction times at baseline and the end of week 8. Social functioning was mapped with the Social Functioning Scale and WHOQOL-BREF. Scores on social cognitive and neurocognitive tests improved with both treatments, as did reaction time. There were few differences between the two antipsychotics on social cognitive test-scores. However, performance was significantly better in the aripiprazole-group for one of the tests, i.e., symbol substitution, which yields a measure of cognitive processing speed. Aripiprazole was also superior to risperidone on reaction time for emotional working memory and working memory. Importantly, the observed improvements were associated with concurrent improvements in QOL and social functioning. The results indicate that further research on the long-term effects of aripiprazole on cognition is warranted.

Chapter 7 is an integrative summary and discussion of the main findings presented in Chapters 2 to 6. Clinical implications are discussed and directions for future research are given.

NEDERLANDSE SAMENVATTING

Dit proefschrift getiteld 'Social Cognition in Schizophrenia' bevat de resultaten van een aantal onderzoeken naar sociale cognitie bij patiënten met schizofrenie. Het eerste deel beschrijft de resultaten van onderzoek naar het verband tussen stoornissen in sociale cognitie en de symptomen van schizofrenie (Deel I, Hoofdstuk 2 en 3). In Deel II (Hoofdstuk 4) wordt een onderzoek beschreven waarin nagegaan wordt of hersenstructuren, die relevant zijn voor sociale cognitie, afwijkend zijn bij patiënten met schizofrenie. Het derde en laatste deel beschrijft de resultaten van onderzoek naar het effect van beperkingen in sociale cognitie op kwaliteit van leven alsmede het effect van anti-psychotica op sociale cognitie bij schizofrenie (Hoofdstuk 5 en 6).

Hoofdstuk 1 geeft een algemene introductie over schizofrenie. De symptomen en de etiologie van de ziekte worden besproken. Schizofrenie is een chronische psychiatrische aandoening, die wordt gekenmerkt door zogenaamde positieve symptomen, onder andere hallucinaties en wanen, en negatieve symptomen, waaronder apathie. Met name de postieve symptomen van de ziekte zijn niet altijd aanwezig en kunnen in ernst fluctueren in de tijd. Het ontstaan van de ziekte schizofrenie hangt samen met een wisselwerking tussen genetische factoren en omgevingsfactoren, zoals bijvoorbeeld trauma, stress en cannabisgebruik. Voorts wordt in Hoofdstuk 1 de term 'sociale cognitie' geïntroduceerd. Sociale cognitie kan worden beschouwd als het geheel van denkprocessen, die ten grondslag liggen aan het verwerken van emotionele en sociale informatie. Schizofrenie gaat gepaard met beperkingen in de sociale cognitie. Schizofrenie patiënten zijn met name beperkt voor wat betreft het herkennen van emoties op gezichten en het interpreteren van de intenties van anderen, respectievelijk emotieherkenning en theory of mind (ToM) genoemd. Emotieherkenning en ToM zijn belangrijke aspecten van sociale cognitie bij schizofrenie, omdat zij het sociale functioneren van patiënten beïnvloeden.

Deel I: Sociale cognitie en symptomen

Hoofdstuk 2 beschrijft onderzoek naar de associatie tussen sociale cognitie en de symptomen van schizofrenie. Het onderzoek maakte gebruik van een 'cross-trait cross-sibling' design om de aard van de overlap tussen de symptomen van de ziekte en sociaal cognitieve beperkingen nader te analyseren. In totaal 1032 patiënten, 1017 gezonde broers en zusters van deze patiënten en 579 gezonde personen werden gerecruteerd binnen de Dutch Genetic Risk and Outcome in Psychosis studie (GROUP studie). Deelnemers voltooiden een reeks cognitieve testen, waaronder de 'Degraded Facial Affect Recognition Task' en de 'hinting task'. De 'Degraded Facial Affect Recognition Task' is een sociaal cognitieve test voor emotieherkenning, de 'hinting task' is een test gericht op ToM. Bij de familieleden werden subklinische symptomen vastgesteld aan de hand van een gestructureerde vragenlijst gericht op schizotypische symptomen (de 'Structured Interview for Schizotypy-Revised'). De symptomen van patiënten werden gemeten met de 'Positive and Negative Syndrome Scale' (PANSS). Patiënten hadden een slechtere sociale cognitie dan hun broers en zusters en gezonde proefpersonen. Bij de patiënten werd een significant verband gevonden tussen sociale cognitie en symptomen. Ook bij de broers en zusters van patiënten bestond een verband tussen sociale cognitie en, in dit geval, subklinische symptomen. Het sociaal cognitief functioneren van patiënten hield onderling verband met dat van hun familieleden, hetgeen suggereert dat er sprake is van gedeelde familiare etiologie, ook wel een 'trait effect' genoemd. De associatie tussen ToM van patiënten en subklinische symptomen bij hun broers en zussen was niet significant. Dit impliceert dat de overlap tussen ToM en symptomen binnen de patiënten het gevolg is van individuele factoren, en niet van gedeelde familiaire factoren. Emotieherkenning van patiënten vertoonde wel overlap met sub-klinische symptomen van familieleden. Dit suggereert dat de overlap tussen deze twee domeinen wel familiair is.

Hoofdstuk 3 onderzoekt of stoornissen in social cognitie met name aanwezig zijn in symptomatische patiënten, of dat zij ook aanwezig zijn als patiënten geen of weinig symptomen hebben. Dezelfde groep patiënten werd gebruikt als in Hoofdstuk 2,

maar deze keer werd een longitudinale analyse toegepast. Sociale cognitie werd gemeten op T1 en drie jaar later op T2. Emotieherkenning werd op dezelfde manier gemeten als in Hoofdstuk 2 in een sub-groep van de GROUP studie bestaande uit 521 schizofrenie patiënten en 312 gezonde deelnemers. Symptomatische remissie werd bepaald met de 'PANSS remission tool'. Patiënten werden in vier groepen verdeeld: remissie T1 en remissie T2 (RR); remissie T1 en non-remissie T2 (RN); non-remissie T1 en non-remissie T2 (NN) en non-remissie T1 en remissie T2 (NR). De resultaten van de studie lieten ten eerste zien dat de patiënten, zoals verwacht, slechter presteerden op emotieherkenning dan de gezonde proefpersonen. Ten tweede was de emotieherkenning van patiënten die in remissie bleven (RR) na drie jaar verbeterd, terwijl emotieherkenning van patiënten die van remissie naar non-remissie gingen (RN) na drie jaar juist was verslechterd. Tot slot was de emotieherkenning van de patiëntengroep die in remissie was op T1 en in non-remissie op T2 (RN) verslechterd met de tijd, terwijl de patiëntengroep die in non-remissie was op T1 en in remissie op T2 (NR) juist was verbeterd met de tijd. De resultaten van Deel I tonen aan dat defecten in emotieherkenning niet alleen geassocieerd zijn met het kwetsbaar zijn voor de ziekte (een zogenaamde 'trait' marker), maar óók met het wel of niet in symptomatische remissie zijn tijdens de ziekte (een zogenaamde 'state' marker).

Deel II: Het non-sociale brein

Door middel van functioneel MRI onderzoek, waarbij hersenactiviteit wordt gemeten tijdens het maken van cognitieve testen, is vastgesteld dat de amygdala en de prefrontale cortex (PFC) belangrijke hersenstructuren zijn voor sociale cognitie. Hoofdstuk 4 beschrijft een MRI onderzoek waarin wordt nagegaan of de defecten in social cognitie bij schizofrenie patiënten geassocieerd zijn met structurele afwijkingen van deze hersenstructuren. De onderzochte groep bestond uit 166 schizofrenie patiënten en 134 gezonde proefpersonen, die binnen de GROUP studie waren gerecruteerd. Dezelfe maten voor emotieherkenning en ToM werden gebruikt als in Hoofdstuk 2 en 3. De grijze stof volumes van de amygdala en het pars superior, medialis, inferior en orbitalis van de PFC werden verkregen met een

automatisch parcellatie programma voor structurele MRI hersencans. Schizofrenie patiënten scoorden slechter op het herkennen van boze gezichten in vergelijking met gezonde proefpersonen, en patiënten scoorden ook slechter op ToM. Het grijze stof volume van alle gemeten hersenstructuren was kleiner in patiënten in vergelijking tot gezonde proefpersonen. Het volume van de PFC was significant geassocieerd met prestaties op de testen voor emotieherkenning en ToM bij de schizofrenie patiënten, het volume van de amygdala was dat niet. Meer specifiek was een afname van het volume van het pars triangularis van de PFC gerelateerd aan een lagere score op emotieherkenning, en een afname van volume van het pars medialis van de PFC aan een lagere score op ToM. De genoemde associaties werden niet gevonden bij de gezonde proefpersonen. Een mogelijke verklaring voor de resultaten is dat een veranderde functie van de amygdala bij schizofrenie patiënten, zoals gemeten met functionele MRI tijdens sociaal cognitieve tests, niet berust op stucturele afwijkingen van de amygdala, maar juist op een structurele afwijkingen van de PFC. Studies met betrekking tot de connectiviteit tussen de amygdala en de PFC zouden deze hypothese verder kunnen onderzoeken.

Deel III: Sociale cognitie, kwaliteit van leven en anti-psychotica

Hoofdstuk 5 beschrijft een onderzoek naar de relatie tussen sociale cognitie en kwaliteit van leven van schizofrenie patiënten. Een groep van 1032 patiënten, 1011 van hun broers en zusters, en 552 gezonde proefpersonen werd geïncludeerd binnen de GROUP studie. De deelnemers maakten een reeks cognitieve testen, waaronder twee sociale cognitie testen voor emotieherkenning en ToM. Om kwaliteit van leven te meten werd de 'World Health Organization QOL Assessment-BREF (WHOQOL-BREF)' gebruikt en om schizofrenie symptomen te meten werd de PANSS gebruikt. Patiënten scoorden slechter op de sociale cognitie testen in vergelijking tot hun familieleden en gezonde proefpersonen. Bij patiënten werd de slechtste kwaliteit van leven gemeten, daarna bij de broers en zusters. Bij de gezonde deelnemers werd de beste kwaliteit van leven gemeten. ToM was significant en negatief geassocieerd met de kwaliteit van leven van schizofrenie patiënten, maar er werd geen associatie

gevonden met emotieherkenning of neurocognitie. De associatie tussen ToM en kwaliteit van leven werd beïnvloed door de ernst van de schizofrenie symptomen, waarbij ernstiger symptomen en een betere ToM leidden tot een slechtere kwaliteit van leven. Met name bij patiënten met een relatief intacte ToM en bij wie tegelijk ernstige symptomen bestonden, was de kwaliteit van leven slecht. Inzicht zou hier mogelijk een rol in kunnen spelen. Een verklaring voor het negatieve verband zou kunnen zijn dat ernstig zieke patiënten met een relatief onaangetaste ToM zich meer bewust zijn van hun ziekte en van de negatieve invloed van de ziekte op hun omgeving.

Hoofdstuk 6 beschrijft de bevindingen van een onderzoek naar de invloed van anti-psychotische medicatie op sociale cognitie bij schizofrenie patiënten. Een gerandomiseerd, open-label onderzoek werd uitgevoerd in drie psychiatrische ziekenhuizen in Nederland om de effecten van aripiprazole en risperidone op sociale cognitie te onderzoeken. Tachtig schizofrenie patiënten maakten een aantal computertesten, die sociale cognitie en neurocognitie meten op T1 en na acht weken (T2). Het niveau van sociaal functioneren werd vastgesteld met de Social Functioning Scale en de WHOQOL-BREF. Het sociaal cognitief en neurocognitief functioneren verbeterde zowel in de aripiprazole als in de risperidone groep. Ook de reactietijden op de tests verbeterden in beide groepen. Er waren nauwelijks verschillen tussen de twee anti-psychotica op de test scores. De aripiprazole groep, echter, presteerde na acht weken beter dan de risperidone groep op één van de neurocognitieve testen, namelijk op de test, die de snelheid van het denken meet. Bovendien waren de reactietijden van de testen op werkgeheugen en emotioneel werk geheugen bij de patiënten uit de aripiprazole groep op T2 ook significant beter dan de reactietijden van de patiënten uit de risperidone groep. De prestaties op deze testen waren significant geassocieerd met verbeteringen in sociaal functioneren.

Hoofdstuk 7 presenteert een samenvatting en discussie van de bevindingen van de Hoofdstukken 2 tot en met 6. Het hoofdstuk besluit met klinische implicaties en suggesties voor toekomstig onderzoek.

PUBLICATIONS

Cocaine is a major risk factor for antipsychotic induced akathisia, parkinsonism and dyskinesia.
Maat, A., Fouwels, A., de Haan, L. Psychopharmacol. Bull. 2008; 41(3), 5-10.

Social cognitive impairments and psychotic symptoms: what is the nature of their association?
Fett, A.K., Maat, A.; GROUP Investigators. Schizophr. Bull. 2013; 39(1), 77-85.

Social cognition and quality of life in schizophrenia.
Maat, A., Fett, A.K., Derks, E.M.; GROUP Investigators. Schizophr. Res. 2012; 137(1-3), 212-8.

Open, randomized trial of the effects of aripiprazole versus risperidone on social cognition in schizophrenia.
Maat, A., Cahn, W., Hovens, J.E., Gijsman, H.J., Kahn, R.S., Aleman, A. Eur Neuropsychopharmacol. 2014; 24(4), 575-84.

Emotion processing in schizophrenia is state and trait dependent.
Maat, A., van Montfort, S.J.T., de Nijs, J., Derks, E.M.; GROUP investigators. Submitted.

Emotion recognition and theory of mind are related to gray matter volume of the prefrontal cortex in schizophrenia.
Maat, A., van Haren, N.E., Bartholomeusz, C.F., Kahn, R.S., Cahn, W. Submitted

PUBLISHED ABSTRACTS AND PRESENTATIONS

Social cognition and quality of life in schizophrenia.
Maat, A., Fett, A.K., Derks, E.M.; GROUP Investigators. SIRS, Florence, Italy, April 2012.

Open, randomized trial of the effects of aripiprazole versus risperidone on social cognition in schizophrenia.
Maat, A., Cahn, W., Hovens, J.E., Gijsman, H.J., Kahn, R.S., Aleman, A. ICOSR, Orlando, U.S.A, April 2013.

Open, randomized trial of the effects of aripiprazole versus risperidone on social cognition in schizophrenia.
Maat, A., Cahn, W., Hovens, J.E., Gijsman, H.J., Kahn, R.S., Aleman, A. ECNP, Barcelona, Spain, October 2013.

Social cognition and quality of life in schizophrenia.
Maat, A., Fett, A.K., Derks, E.M.; GROUP Investigators. Phrenos, Zwolle, The Netherlands, October 2013.

Open, randomized trial of the effects of aripiprazole versus risperidone on social cognition in schizophrenia.
Maat, A., Cahn, W., Hovens, J.E., Gijsman, H.J., Kahn, R.S., Aleman, A. SAP-dag NVVP, Amersfoort, the Netherlands, November 2013.

Emotion recognition and theory of mind are related to gray matter volume of the prefrontal cortex in schizophrenia.
Maat, A., van Haren, N.E., Bartholomeusz, C.F., Kahn, R.S., Cahn, W. ECNP, Nice, France, March 2014.

Emotion recognition and theory of mind are related to gray matter volume of the prefrontal cortex in schizophrenia.
Maat, A., van Haren, N.E., Bartholomeusz, C.F., Kahn, R.S., Cahn, W. SIRS, Florence, Italy, April 2014.

Emotion recognition and theory of mind are related to gray matter volume of the prefrontal cortex in schizophrenia.
Maat, A., van Haren, N.E., Bartholomeusz, C.F., Kahn, R.S., Cahn, W. SOBP, New York, U.S.A., May 2014.

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CURRICULUM VITAE

De schrijfster van dit proefschrift werd geboren op 21 december 1981 te Gouda. Zij volgde basisonderwijs op de Sunshine School te Koeweit en de Oudenhof Bokkesprong School te Oegstgeest. In 2000 behaalde zij cum laude het eindexamen gymnasium aan het Stedelijk Gymnasium te Leiden. Aansluitend ving zij de studie Geneeskunde aan bij de Universiteit van Amsterdam. Het doctoraalexamen werd afgelegd in 2006, het artsexamen in 2008. Gedurende de doctoraal fase verrichtte zij wetenschappelijk onderzoek bij het Psychiatrisch Centrum Suriname te Paramaribo, Suriname, onder supervisie van prof.dr. L. de Haan. In 2007 volgde zij een keuze co-schap op de afdeling Kindergeneeskunde van het Paarl Hospital te Paarl, Zuid-Afrika. Na haar Geneeskunde opleiding werkte zij als basisarts op de afdeling Neurologie van het Onze Lieve Vrouwe Gasthuis te Amsterdam onder supervisie van prof.dr. P. Portegies. In 2009 startte zij haar opleiding tot psychiater aan de Universiteit Utrecht met als opleiders prof.dr. R.S. Kahn en dr. J. Wijkstra. In 2010 werd een aanvang gemaakt met het onderzoek, dat in dit proefschrift beschreven is. In het kader van dit onderzoek was zij in 2012 een half jaar werkzaam bij het Melbourne Neuropsychiatry Centre, University of Melbourne and Melbourne Health, Australië (hoofd: prof.dr. C. Pantelis). Op 18 oktober 2014 zal zij de opleiding Psychiatrie afronden, waarna zij zal gaan werken als psychiater op de afdeling Psychiatrie (hoofd: prof.dr. D.A.J.P. Denys) van het Academisch Medisch Centrum te Amsterdam.