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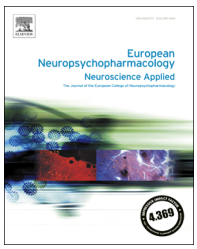

Emotion recognition and theory of mind are related to gray matter volume of the prefrontal cortex in schizophrenia

Arija Maat[a], Neeltje E.M. van Haren[b], Cali F. Bartholomeusz[c], René S. Kahn[b], Wiepke Cahn[b,*,1]

[a]*Department of Psychiatry, Waterland Ziekenhuis, Waterlandlaan 250, 1441 RN Purmerend, The Netherlands*
[b]*Department of Psychiatry, University Medical Center Utrecht – Brain Center Rudolf Magnus, Huispostnummer A 00.241, Postbus 85500, 3508 GA Utrecht, The Netherlands*
[c]*Melbourne Neuropsychiatry Center, Department of Psychiatry, The University of Melbourne and Melbourne Health, 161 Barry Street, Carlton South, Victoria 3053, Australia*

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Abstract
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 understood. 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. 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. 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

*Correspondence to: University Medical Center Utrecht – Brain Center Rudolf Magnus, Utrecht, The Netherlands. Tel.: +31 88 7556003; fax: +31 88 7555466.
E-mail address: w.cahn@umcutrecht.nl (W. Cahn).
[1]Postal address: Huispostnummer A 00.241, Postbus 85500, 3508 GA Utrecht, The Netherlands.

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middle PFC gray matter volume. In conclusion, reduced PFC, but not amygdala, gray matter volume is associated with social cognitive deficits in schizophrenia.

1. Introduction

Emotional dysfunction is one of the core clinical features of schizophrenia, already described by Kraepelin (1893), who first delineated the disorder. Recognizing emotion, understanding the thoughts and intentions of others and interpreting social cues are part of the construct of 'social cognition', which refers to the cognitive processing of social information (Pinkham, 2014). 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 (Kohler et al., 2010), and ToM, i.e., the ability to infer the intentions and beliefs of other individuals (Bora et al., 2009), are important domains of social cognition, because they appear to be valid predictors of social functioning (Fett et al., 2011). 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).

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, 2009). This 'social brain' network comprises aspects of the prefrontal cortex (PFC), the temporal cortex, the parietal cortex and several deeper brain structures. Whereas particular areas of this network have been implicated in social cognitive processes such as social reward learning and social knowledge (Mathiak et al., 2011; Rilling et al., 2008), the frontal areas and amygdala have been specifically implicated in the social cognitive processes set out in the present study, i.e., emotion recognition and ToM. More specific, the processing of facial expressions depends critically on the amygdala and the orbitofrontal cortex (Adolphs, 2009), whereas in mentalizing-tasks, such as ToM, the medial and orbitofrontal cortices are critical (Adolphs, 2009; 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) and reduced activation of the PFC has been related to impaired performance on ToM-tasks (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 general cognition, i.e., IQ, and symptomatology was often disregarded. Although 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). Also, despite consistent evidence that severity of symptoms is negatively associated with gray matter volume (Boos et al., 2012), 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 cognition in schizophrenia is related to reduction of gray matter volume in the amygdala and PFC.

2. Experimental procedures

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 (American Psychiatric Association, 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