Schizophrenia Research 164 (2015) 59–64

Contents lists available at ScienceDirect

Schizophrenia Research

journal homepage: www.elsevier.com/locate/schres

Brain structure abnormalities in first-episode psychosis patients with persistent apathy

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ARTICLE INFO

Article history:
Received 8 May 2014
Received in revised form 2 March 2015
Accepted 2 March 2015
Available online 26 March 2015

Keywords:
Psychosis
First-episode
Apathy
Negative symptoms
Magnetic resonance imaging
Cortical thickness

ABSTRACT

Background: Apathy is an enduring and debilitating feature related to poor outcome in patients with first-episode psychosis (FEP). The biological underpinnings of apathy are unknown. We tested if FEP patients with persistent apathy (PA) differed from FEP patients without persistent apathy (NPA) in specific brain structure measures in the early phase of illness.
Methods: A total of 70 Norwegian FEP patients were recruited within 1 year of first adequate treatment. They were defined as having PA ($N = 18$) or NPA ($N = 52$) based on Apathy Evaluation Scale score at baseline and 1 year later. MRI measures of cortical thickness and subcortical structure volumes were compared between the PA and NPA groups.
Results: The PA group had significantly thinner left orbitofrontal cortex and left anterior cingulate cortex. The results remained significant after controlling for depressive symptoms and antipsychotic medication.
Discussion: FEP patients with persistent apathy in the early phase of their illness show brain structural changes compared to FEP patients without persistent apathy. The changes are confined to regions associated with motivation, occur early in the disease course and appear selectively in PA patients when both groups are compared to healthy controls.

1. Introduction

Apathy is a predictor of poor functioning in psychosis patients (Evensen et al., 2012; Faerden et al., 2009, 2013; Fervaha et al., 2013; Foussias et al., 2011; Kiang et al., 2003; Konstantakopoulos et al., 2011). Together with anhedonia, apathy constitutes a subdomain within the negative symptom construct in schizophrenia (Blanchard and Cohen, 2006).

Negative symptoms that persist are associated with poor functional outcome and may have distinct underlying neuropathology (Hovington and Lepage, 2012). Antipsychotic treatment has only a limited effect on negative symptoms. Investigating the different components of the negative symptom construct, such as apathy, is important for developing better treatment (Kirkpatrick et al., 2006). The Apathy Evaluation Scale (AES) offers a specific assessment of apathy (Marin et al., 1991). In an overlapping sample, we found that apathy is a persistent feature in 30% of first-episode psychosis (FEP) patients and related to poorer general functioning (Faerden et al., 2010). The biological underpinning of apathy in psychosis is unknown.

Numerous magnetic resonance imaging (MRI) studies have shown structural brain differences in schizophrenia patients compared to healthy controls both in cortical regions (Rimol et al., 2010; Bora et al., 2011; Rimol et al., 2012), and subcortical structures (Haijma et al., 2012; Shepherd et al., 2012). Knowledge on how structure abnormalities relate to the symptoms of psychosis and clinical outcome in patients with psychotic disorders is limited. Results from neuroimaging studies focusing on persistent negative symptoms are inconsistent. Frontotemporal volume reduction was found in patients with so-called deficit schizophrenia, i.e. enduring primary negative symptoms for at least 12 months (Kirkpatrick et al., 1989), compared to patients with non-deficit schizophrenia (Galderisi et al., 2008; Cascella et al., 2010; Fischer et al., 2012), although other studies have not found differences in these regions (Buchanan et al., 1993; Turetsky et al., 1995; Quarantelli et al., 2002; Voineskos et al., 2013). Most studies of subcortical structures in deficit schizophrenia have been negative (Buchanan et al., 1993; Galderisi et al., 2008; Fischer et al., 2012; Voineskos et al., 2013), but smaller volumes of putamen and substantia

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http://dx.doi.org/10.1016/j.schres.2015.03.001

nigra (Cascella et al., 2010) have been reported. Reduced gray matter volumes in frontal orbital gyrus and parahippocampal gyrus in FEP patients with persistent negative symptoms, i.e. presence of negative symptoms for 6 months in a stable period of psychosis (Buchanan, 2007) have been reported (Benoit et al., 2012). Inconsistencies in findings could be due to variation of MR methods, use of different regions of interest and underpowered samples.

Neither the definition of deficit schizophrenia, nor the broader definition of persistent negative symptoms considers the different subdomains of the negative symptom construct. There is only one published study of the relationship between brain structure and level of apathy in psychosis patients. Roth et al. (2004), found smaller frontal lobe volumes in chronic schizophrenia patients with high apathy levels compared with low apathy patients.

In patients with Alzheimer's disease, apathy has been related to the orbitofrontal cortex (OFC) and the anterior cingulate cortex (ACC) (Guimaraes et al., 2008; Tunnard et al., 2011; Stanton et al., 2013). A correlation between apathy and smaller gray matter volumes of the caudate and putamen has also been reported (Bruen et al., 2008). Apathy has been observed in patients with lesions in basal ganglia (Bhatia and Marsden, 1994) and thalamus (Ghika-Schmid and Bogousslavsky, 2000; Carrera and Bogousslavsky, 2006).

To search for brain structural markers of persistent apathy in psychosis patients we tested if preselected brain regions differed between FEP patients with persistent apathy (PA) compared to FEP patients without persistent apathy (NPA). Measures of cortical thickness and subcortical structure volumes were obtained by MRI within a year after start of first adequate treatment. First, based on findings from studies of Alzheimer's disease (Guimaraes et al., 2008; Tunnard et al., 2011; Stanton et al., 2013) and brain lesions (Bhatia and Marsden, 1994; Ghika-Schmid and Bogousslavsky, 2000; Carrera and Bogousslavsky, 2006), we hypothesized that the PA group shows cortical thinning in OFC and ACC and reduced basal ganglia (caudate, putamen, pallidum, and accumbens) and thalamus volumes. Second, due to the limited number of studies on the topic, we explored group differences in cortical thickness across the entire cortical surface, and in all available subcortical structure volumes (hippocampus, amygdala, ventricles, and cerebellum) that were not included in the hypothesis-driven analyses.

2. Materials and methods

2.1. Subjects

Seventy patients participated in a longitudinal study on FEP with 1 year follow-up. Patients between ages 18 and 65 years were recruited from psychiatric departments and outpatient clinics in Oslo between 2004 and 2007 as part of the Thematically Organized Psychosis (TOP) Research study. A previous FEP study on apathy (Faerden et al., 2010) included 65 of the patients in the current sample. Subjects were considered FEP patients if antipsychotic naive or up to 52 weeks after start of first adequate treatment (hospitalization or receiving antipsychotic medication for at least 12 weeks or until remission). Exclusion criteria were: IQ < 70, a psychosis better accounted for by substance abuse or somatic illness, a brain illness or a previous moderate/severe head injury. All participants signed a written informed consent. The study was approved by the Regional Committee for Medical Research Ethics and the Norwegian Data Inspectorate, and conducted in accordance with the Helsinki declaration.

2.2. Clinical assessments

The clinical assessments, including a diagnostic evaluation using the Structured Clinical Interview for DSM-IV axis I disorders (SCID-I) modules A–E (First et al., 2002), were performed by trained psychologist or physicians at baseline and at 1 year follow-up. Apathy was assessed using the clinical version of AES (AES-C) (Marin et al., 1991) at both occasions. A shortened 12 item version (AES-C-Apathy) of the original 18 items was used in the analyses as it has previously demonstrated better psychometric properties than the full scale (Faerden et al., 2008). Patients were defined as having PA if they at both time points had a score ≥27 on the AES-C-Apathy. This cut-off value is two standard deviations (2 SD = 8.6) above the mean sum scores (mean = 18.0) of the AES-S-Apathy in healthy controls from the TOP study (previously reported in Faerden et al., 2009). Eighteen patients were included in the PA group, and 52 patients in the NPA group.

The split version of the Global Assessment of Function (GAF) scale (Pedersen et al., 2007), the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987) and the Calgary Depression Scale for Schizophrenia (CDSS) (Addington et al., 1996) were administered. Dose of current antipsychotic medication at time of MRI was converted to Defined Daily Dose (DDD) (WHO Collaborating Centre for Drug Statistics Methodology, 2014). Age of onset was defined as age when first experiencing positive psychotic symptoms. Duration of illness (DOI) at the time of MRI scan was calculated in years from age of onset to age of MRI scan. Duration of untreated psychosis (DUP) was estimated as number of weeks with positive psychotic symptoms scoring above 4 on the PANSS without adequate treatment.

2.3. MRI acquisition

All participants underwent MRI at baseline in a 1.5 T Siemens Magnetom Sonata (Siemens Medical Solutions, Erlangen, Germany) equipped with a standard head coil. After a conventional 3-plane localizer, two sagittal T1-weighted magnetization prepared rapid gradient echo (MPRAGE) volumes were acquired with the Siemens tfl3d1_ns pulse sequence (TE = 3.93 ms, TR = 2730 ms, TI = 1000 ms, flip angle = 7°; FOV = 24 cm, voxel size = $1.33 \times 0.94 \times 1\ mm^3$, number of partitions = 160) and subsequently averaged together, after rigid-body registration, to increase the signal-to-noise ratio. There was no scanner upgrade or change of instrument during the study period. Median time from clinical interviews to MR scanning was 122 days (range 21–1040 days).

2.4. MRI post-processing

MRI scans were processed using FreeSurfer 4.5.0 software. The post-processing involves surface reconstruction (Dale et al., 1999; Fischl et al., 1999) to obtain measures of cortical thickness at approximately 160,000 vertices across the cortical surface (Fischl et al., 2002). The cortical surface is further divided into 32 parcellations in each hemisphere according to an anatomical atlas (Desikan et al., 2006). As part of the post-processing, volumes of 34 subcortical structures are automatically estimated (Fischl et al., 2002). For the present study we applied cortical thickness maps smoothed with a full width at half maximum Gaussian kernel of 30 mm. For the hypothesis driven analyses on cortical thickness of OFC and ACC, we used left and right mean cortical thickness of OFC (combining lateral and medial OFC) and ACC (combining rostral and caudal ACC) (Fig. 1). For subcortical

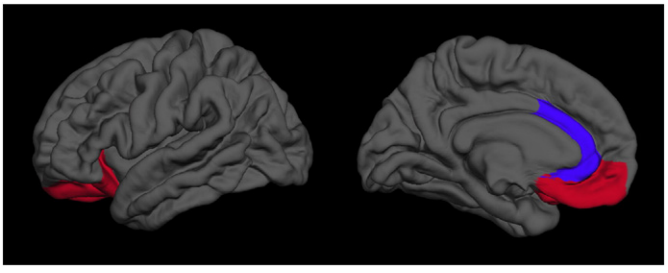

Fig. 1. Lateral (left) and medial (right) view of the left hemisphere, showing the studied orbitofrontal (red) and anterior cingulate (blue) cortical regions.