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

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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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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

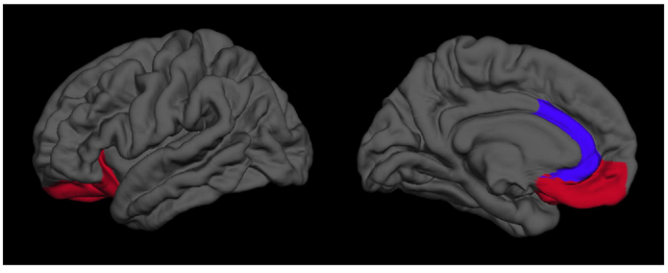

Fig. 1. Lateral (left) and medial (right) view of the left hemisphere, showing the studied orbitofrontal (red) and anterior cingulate (blue) cortical regions.

structures, left and right volumes were highly correlated (Table S1), and were therefore combined.

2.5. Statistical analysis

Statistical analyses were performed using SPSS version 18 (SPSS Inc., 2009), except for the explorative cortical thickness analyses where MATLAB version 7.9.0 (MATLAB and Statistics Toolbox Release, 2012) was used. Bonferroni–Holm correction was applied to control for multiple comparisons in all region-of-interest analyses (including follow-up analyses) of brain structure differences between PA and NPA patients. Explorative cortical thickness analyses were corrected using a 5% false discovery rate (FDR).

2.5.1. Demographic and clinical data

Group differences in demographic and clinical data were tested using Student's *t*-test for continuous normally distributed variables, Mann–Whitney *U*-test for variables with a non-normal distribution (DOI and DUP) and chi-square statistics for categorical data.

2.5.2. Hypothesis driven analyses

Linear regression models were performed with each region of interest (cortical thickness of left and right OFC and ACC, volumes of putamen, pallidum, caudate, accumbens, and thalamus) as dependent variables. Age, gender, and group (PA or NPA) were independent variables. In the subcortical volume analyses, intracranial volume (ICV) was used to control for inter-individual skull differences.

2.5.3. Explorative analysis

2.5.3.1. Cortical thickness. We performed a surface-based analysis by fitting a general linear model at each vertex with cortical thickness as dependent variable, and age, gender, and group (PA or NPA) as independent variables.

2.5.3.2. Subcortical volumes. Linear regression models, as described under Section 2.5.2, were used to explore group differences in structure volumes not included under the a priori hypothesis (volumes of ventricles, hippocampus, amygdala, and cerebellum).

2.5.4. Effect of clinical variables

Significant results were controlled for possible confounding variables such as dose of antipsychotics, severity of depressive symptoms (CDSS score), and positive psychotic symptoms (PANSS positive subscale, at baseline and follow-up) by entering them as separate independent variables in linear regression models.

2.5.5. Analyses within schizophrenia spectrum

To test for diagnostic specificity of significant group differences, analyses were repeated for patients with schizophrenia spectrum disorders (schizophrenia $N = 37$, schizophreniform disorder $N = 2$, and schizoaffective disorder $N = 7$) only.

2.5.6. Post hoc comparisons against healthy controls

Post hoc comparisons against a healthy control group (see Supplementary data for details) were performed in regions where significant differences between PA and NPA were found. Analysis of covariance (ANCOVAs) was used, controlling for age and gender (and ICV for subcortical volumes).

3. Results

3.1. Demographic and clinical data

Compared to NPA patients, PA patients were more often men, had longer DUP, worse psychosocial functioning (GAF-S and GAF-F), higher total PANSS scores, and more negative symptoms at both baseline and follow-up (Table 1). At follow-up, the PA group also scored higher on the PANSS positive subscale. There were no differences in medication dose or depression score (CDSS).

3.2. Hypothesis-driven analysis

The PA group had significantly thinner *left OFC* and *left ACC* (Fig. 2). There were trend level thinning of right ACC (Fig. 2) and trend level larger caudate volume (Table 2). One outlier case was removed in the ACC analyses, as it affected the linear regression model notably (see Supplementary data).

3.3. Explorative analyses

FDR-corrected vertex-wise comparisons of *cortical thickness* in PA versus NPA did not yield any significant results. For completeness, trend findings at uncorrected $p < 0.01$ at each vertex were also investigated. Cortical thinning was observed mainly in the left OFC, and in additional scattered regions (Fig. S1). There were no significant group

Table 1
Demographic and clinical data for first-episode psychosis patients with persistent apathy (PA) and without persistent apathy (NPA) at baseline and 12 months follow-up.

Variable mean (SD), unless otherwise stated	PA $N = 18$	NPA $N = 52$	$T/U/\chi^2$	p
Demographic				
Age at MRI, years	28.1 (7.9)	27.6 (7.3)	0.234	0.816
Gender (N = male (%))	14 (77.8)	24 (46.2)	5.4	**0.02**
Clinical baseline				
Diagnosis[a]				
Schizophrenia spectrum, *n*	17	29		
Bipolar spectrum, *n*	0	10		
Other psychosis, *n*	1	13		
Age of onset, years	22.9 (4.5)	24.3 (7.8)	−0.991	0.326
DUP, weeks (median range)	68.5 (20–1040)	31.5 (1–527)	300.00	**0.024**
DOI MR, years (median range)	3.0 (0–25)	2.0 (0–22)	358.50	0.136
GAF-S	35.9 (6.4)	44.4 (13.7)	−3.498	**0.001**
GAF-F	39.0 (12.5)	47.4 (13.5)	−2.399	**0.022**
PANSS positive	16.1 (5.3)	15.0 (5.9)	0.692	0.491
PANSS negative	20.0 (5.2)	13.3 (4.8)	4.951	**0.000**
PANSS total	70.9 (11.6)	58.8 (14.6)	3.201	**0.002**
CDSS	7.2 (4.3)	6.0 (4.2)	1.044	0.300
Antipsychotic medication at time of MRI[b]				
DDD FGA	0.03 (0.08)	0.04 (0.17)	−0.165	0.870
DDD SGA	1.18 (0.93)	0.80 (0.75)	1.752	0.084
DDD total	1.21 (0.94)	0.84 (0.76)	1.702	0.093
Clinical follow-up at 12 months				
GAF symptom	42.6 (11.6)	56.8 (17.7)	−3.869	**0.000**
GAF function	42.8 (9.8)	57.9 (16.6)	−4.616	**0.000**
PANSS positive	15.0 (4.5)	11.6 (5.4)	2.416	**0.018**
PANSS negative	18.4 (3.2)	12.0 (4.6)	5.488	**0.000**
PANSS total	66.4 (9.5)	49.0 (13.6)	5.014	**0.000**
CDSS	5.6 (3.9)	4.2 (4.0)	1.303	0.197

Group differences in demographic and clinical data were tested using Student's *t*-test for continuous normally distributed variables, Mann–Whitney *U*-test for non normally distributed variables (DUP and DOI), and chi-square statistics for categorical data (gender).
PA: persistent apathy, NPA: no persistent apathy, MRI: magnetic resonance imaging, DUP: duration of untreated psychosis, DOI: duration of illness, GAF: global assessment of function, PANSS: Positive and Negative Syndrome Scale, CDSS: Calgary Depression Scale, DDD: defined daily dose, FGA: first-generation antipsychotics, SGA: second-generation antipsychotics.

[a] Schizophrenia spectrum: schizophrenia, schizophreniform disorder, schizoaffective disorder. Bipolar spectrum: bipolar disorder type I, bipolar disorder type II, bipolar disorder not otherwise specified. Other psychoses: major depressive disorder with psychotic features, delusional disorder, brief psychotic disorder, psychosis not otherwise specified.

[b] 54 patients were on antipsychotic medication. Data on dose and type of medication were missing on one subject. Forty-eight patients used only SGA, 1 patient used only FGA and 5 patients used both types.

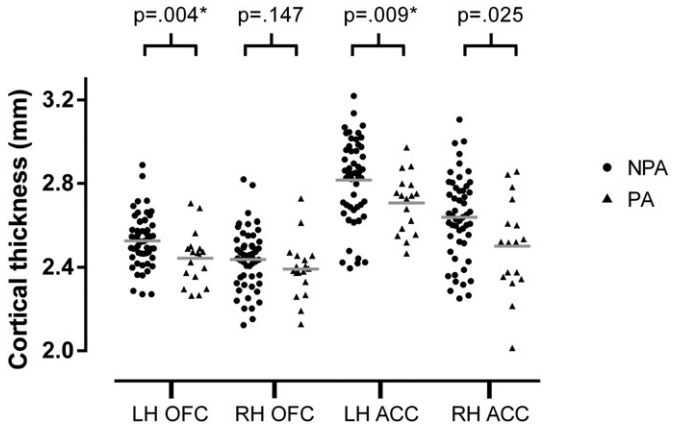

Fig. 2. Cortical thickness in left (LH) and right (RH) orbitofrontal (OFC) and anterior cingulate cortex (ACC) in psychosis patients with persistent apathy (PA) and without persistent apathy (NPA). Gray lines indicate unadjusted group means. *P*-values displayed are derived from linear regression models comparing cortical thickness adjusted for age and gender of each region of interest between PA and NPA patients. Significant results after applying Bonferroni–Holm correction are marked by an asterisk.

differences in amygdala, hippocampus, ventricles or cerebellum volumes (Table S2).

3.4. Clinical variables

DDD of antipsychotic medication was associated with cortical thinning in the left OFC ($B = -0.044$, $p = 0.012$). When DDD was included in the model, the difference between PA and NPA patients was reduced, however it remained significant ($B = -0.080$, $p = 0.015$). Positive symptoms at baseline correlated with cortical thinning of left ACC ($B = -0.010$, $p = 0.009$). Adjusting for positive symptoms did not affect the difference between PA and NPA patients in this region ($B = -0.122$, $p = 0.015$). Controlling for depression or positive symptoms at follow-up did not alter the results.

3.5. Schizophrenia spectrum

Follow-up analysis within schizophrenia spectrum ($N = 46$) confirmed thinner cortices in the PA group ($N = 17$) compared to the NPA group ($N = 29$) in left OFC ($B = -0.089$, $t = -2.242$, $p = 0.030$) and left ACC ($B = -0.124$, $t = -2.016$, $p = 0.050$). The results were only trend level significant after Bonferroni–Holm correction.

3.6. Post hoc comparisons against healthy controls

PA patients showed reduced cortical thickness in left OFC ($p < 0.001$) and left ACC ($p = 0.007$) compared to healthy controls. NPA patients did not differ from healthy controls (Table S3).

Table 2
Volumes (ml) of basal ganglia and thalamus in first-episode psychosis patients with persistent apathy (PA) and without persistent apathy (NPA).

	Predicted mean volume (SE)		*t*	*p*
	PA	NPA		
Thalamus	13.833 (0.226)	14.018 (0.128)	−0.706	0.483
Putamen	12.472 (0.241)	12.227 (0.136)	0.876	0.384
Pallidum	3.812 (0.084)	3.782 (0.048)	0.301	0.764
Caudate	8.355 (0.188)	7.837 (0.107)	2.374	0.021
Accumbens	1.412 (0.042)	1.393 (0.024)	0.407	0.685

Dependent variables: subcortical structure volumes for hypothesized regions of interest. Independent variables: age, gender, and intracranial volume. After applying Bonferroni–Holm none of the results remained significant. Predicted means (ml) are covaried for age = 27.76 and intracranial volume = 1571.6 ml.

4. Discussion

The main finding was that FEP patients with PA show cortical thinning in left hemisphere OFC and ACC compared to FEP patients without PA. Trend level cortical thinning in right ACC and increased caudate volume in PA patients were also found. Alterations in left OFC and ACC were selective to the PA group when both groups were compared to healthy controls. To our knowledge this is the first study to investigate how apathy is related to cortical thickness and subcortical volumes in FEP patients.

Previously, we have shown that PA patients differed from NPA patients in global functioning (Faerden et al., 2010). Brain structural abnormalities restricted to the PA group suggest that PA is a subgroup of patients with distinct neurobiological underpinnings. Thinner frontal cortex is a consistent finding in unselected schizophrenia samples (Kuperberg et al., 2003; Nesvag et al., 2008; Rimol et al., 2010; Schultz et al., 2010). Our results are in line with previously reported smaller volumes of OFC in schizophrenia patients with persistent negative symptoms (Benoit et al., 2012), and reduced regional blood flow in OFC in patients with deficit schizophrenia (Kanahara et al., 2013). Although larger OFC volumes with severity of negative symptoms in schizophrenia patients have been reported (Lacerda et al., 2007), most studies find negative correlations between negative symptom severity and OFC size (Baare et al., 1999; Gur et al., 2000).

The larger caudate volumes found in PA patients did not survive adjustment for multiple comparisons. The few studies of subcortical volumes in patients with persistent negative symptoms have mainly been negative (Buchanan et al., 1993; Galderisi et al., 2008; Fischer et al., 2012; Voineskos et al., 2013). Trend-level larger caudate volumes in deficit schizophrenia have been reported (Buchanan et al., 1993). We did not replicate previously reported putamen volume reduction (Cascella et al., 2010).

Interestingly, the cortical thinning in OFC and ACC in PA patients is in agreement with findings in neurologic disorders where apathy is a common feature. Gray matter reduction in the OFC and ACC has been associated with apathy in patients with Alzheimer's disease (Apostolova et al., 2007; Bruen et al., 2008; Guimaraes et al., 2008; Tunnard et al., 2011; Stanton et al., 2013). In patients with amyotrophic lateral sclerosis, severity of apathy was correlated with atrophy in OFC and dorsolateral prefrontal cortex (Tsujimoto et al., 2011). Although differences in methods used complicate direct comparisons, it has been widely acknowledged that apathy is a common feature in a range of different disorders (van Reekum et al., 2005; Foussias et al., 2014). Putative neural associations of reward processing in OFC, ACC and basal ganglia have been addressed in two recent reviews on motivational deficits in schizophrenia patients (Strauss et al., 2013; Kring and Barch, 2014). Our results support the importance of these structures in motivational deficits in patients with psychosis.

The PA patients represent a subgroup of psychosis patients with a more severe illness as reported in Faerden et al. (2010, 2013), showing worse psychosocial functioning already at time of inclusion. At 1-year follow-up, but not at baseline, they had higher PANSS positive score than the NPA patients. This complicates the interpretation as to whether the observed group differences are effects of illness severity, or medication, or are specifically related to apathy. Positive symptoms did not affect the cortical thickness differences in left OFC or ACC between PA and NPA patients. We found an association between antipsychotics and cortical thickness in the left OFC, which partly explained the difference observed between PA and NPA patients. However, a significant group difference remained after controlling for antipsychotic medication, and there was no effect of current dose of antipsychotics in the left ACC. Severity of illness, psychosocial functioning, and medication are inter-related and can effect both apathy and brain structure. Nevertheless, evidence towards involvement of OFC and ACC in aspects of motivation (Strauss et al., 2013; Kring and Barch, 2014), taken together with previously reported associations between these regions

and apathy in Alzheimer's patients, indicates that the alterations observed in our study are indeed associated with apathy.

Strengths of the present study include thorough clinical characterization of a representative FEP patient sample and a large number of cortical and subcortical structures using validated automated methods. Apathy was assessed both at time of inclusion and after a year, which allows for predicting persistent apathy over the first year after inclusion. The AES-scale offers a more specific assessment of the apathy dimension of negative symptoms than more general symptom scales, such as PANSS (Faerden et al., 2008).

Some limitations apply to our findings. First, the sample size, although hitherto one of the largest, could limit the capacity to detect smaller group differences. Second, correcting for multiple comparisons increases the risk of running type II errors. Therefore we have also presented nominal significant results from hypothesized regions that did not survive adjustment for multiple tests, such as right ACC and caudate. When a $p < 0.01$ at each vertex was applied, exploratory analyses on cortical thickness across the entire cortical surface showed only a few additional scattered areas of thickness reduction in PA patients (Fig. S1). Third, some subjects had a delay from time of clinical assessments to MR scanning. This should have little influence on the main analyses as apathy has been measured as a stable feature over two time points. Fourth, although the AES is specifically designed to evaluate motivational deficits, and has been shown to be correlated with a social amotivation factor of negative symptoms in PANSS (Liemburg et al., 2015) we cannot strictly exclude that the observed group differences are not also related to other negative symptoms such as diminished expression.

In the present study we find brain structure differences between PA and NPA FEP patients. This indicates that PA patients may constitute a subgroup of psychosis patients with a distinct neuropathology. The observed cortical thinning in PA patients was seen in regions hypothesized to be involved in motivation and goal directed behavior and may be neurobiological markers of apathy in psychosis patients. Our study contributes to the important research on neuropathology of subdomains of negative symptoms. The OFC and ACC are important regions of interest for future studies on the neurobiology of apathy in psychosis.

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Contributors

AF, OAA, IM and IA took part in designing the study. Authors LMJ, UKH and RN undertook the statistical analysis. Author LMJ managed the literature search and wrote the first draft of the manuscript. All authors have contributed to and approved the manuscript.

Conflict of interest

Disclosures: OAA has received speaker's honorarium from pharmaceutical companies Osaka, GSK and Lundbeck. Authors LMJ, RN, AF, UKH, KNJ, EHL, IM and IA report no conflict of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.schres.2015.03.001.

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