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Comprehensive segmentation of subcortical brain volumes in early onset schizophrenia reveals limited structural abnormalities

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ABSTRACT

Structural brain abnormalities are well documented in adult schizophrenia, but there are few studies of brain structures in early onset schizophrenia (EOS) and findings are inconsistent. Most previous EOS studies have been limited to global morphometric measures, such as whole gray matter (GM) or cerebrospinal fluid (CSF), or to single brain structures. The purpose of this study was to compare specific volumes and hemispheric lateralization in a large number of subcortical brain structures, between EOS patients and a healthy control group. High-resolution structural magnetic resonance images (MRI) and automatic brain volume segmentation were performed on 18 EOS patients and 33 healthy controls (11–18 years). A total of 29 brain structures were studied. The patients showed marked bilateral enlargements of the lateral ventricles and of the fourth ventricle, and bilateral enlargement of the caudate nuclei compared to the controls. For all other subcortical brain structures, there were no significant differences between the EOS group and the healthy control group, contrary to findings from the majority of morphometric studies of childhood or adult onset schizophrenia.

1. Introduction

Schizophrenia is a severe mental illness that affects around 1% of the population. It is primarily characterized by abnormalities of perception and thinking, such as auditory hallucinations and paranoid ideas, but usually also involves chronic problems with behavior and emotion, often leading to profound social and occupational dysfunction (Rund, 1998, 2009). The onset of symptoms typically occurs in young adulthood (18–25 years) but in less than 5% of the patients who develop schizophrenia, symptom onset occurs before the age of 18 (early onset schizophrenia—EOS; Castle et al., 1991; Cannon et al., 1999). EOS is considered to be a more serious form of the disorder than adult schizophrenia, but there are similarities in phenomenology and cognitive deficits, as well as indications of genetic overlap, between EOS and adult schizophrenia (Kumra and Schulz, 2008).

A number of magnetic resonance imaging (MRI) studies in adult onset schizophrenia have demonstrated structural brain abnormalities (Shenton et al., 2001; Honea et al., 2005; Rimol et al., 2010), the most consistent volumetric findings being ventricular enlargements and reduced medial temporal lobe (MTL) volume (Shenton et al., 2001). However, there are only a limited number of MRI studies of EOS. This may be due partly to the low incidence of schizophrenia before the age of 18 (Cannon et al., 1999), which makes it difficult to recruit large numbers of patients for research.

We present an overview of the main brain structure findings from volumetric MRI studies on EOS in Table 1. The studies are categorized according to age of onset of the disorder: (1) adolescent onset schizophrenia (AOS; onset between 12 and 18 years), (2) EOS (onset before 18 years) and (3) COS (childhood onset schizophrenia, onset before 12th birthday). Studies of EOS

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normally have a majority of patients with illness onset in adolescence. In the present study, only two patients had an onset of illness before the age of 12. In the EOS literature on brain morphology, the most consistent finding is enlargement of the cerebral ventricles (see Table 1). Two EOS studies have reported reduced total brain volume (TBV; Matsumoto et al., 2001; Collinson et al., 2003), whereas other EOS studies have found no differences in TBV between patients and healthy controls (James et al., 1999; Pagsberg et al., 2007; Yoshihara et al., 2008). The only volumetric abnormality in MTL structures (hippocampus, amygdala) found in EOS is enlargement of the fornix (Davies et al., 2001). None of the AOS studies reported findings in subcortical structures. It is apparent from Table 1 that there have been more scientific studies on COS than EOS, and that findings of structural abnormalities have been more numerous in COS.

Deviation from normal brain asymmetry has been reported repeatedly in patients with schizophrenia (Crow, 1990). Typically, there is reduced—or complete lack of—leftward asymmetry in schizophrenia (Crow et al., 1989; Crow, 1990; Bilder et al., 1994), which may reflect etiological factors of neurodevelopmental or genetic origin. Reduced hemispheric asymmetry has been less prevalent in EOS studies than in COS studies. Of the studies presented in Table 1, only two EOS studies investigated hemispheric asymmetry, compared with five COS studies (Frazier et al., 1996; Jacobsen et al., 1996; Kumra et al., 2000; Levitt et al., 2001; Marquardt et al., 2005). One EOS study found reduced rightward hemisphere asymmetry in female patients, as well as reduced leftward asymmetry in male patients (Collinson et al., 2003). However, another study found no differences in asymmetry between EOS patients and controls in prefrontal, premotor, sensorimotor, temporal, or occipito-parietal lobar volumes (Hadjulis et al., 2004). Findings in COS studies include deviances in the amygdala (Jacobsen et al., 1996; Levitt et al., 2001), the hippocampus (Jacobsen et al., 1996; Levitt et al., 2001), the ventricles (Kumra et al., 2000) and the basal ganglia (Frazier et al., 1996; Kumra et al., 2000).

Most studies in COS and EOS have either focused on nonspecific volumetric measures, such as total brain volume (TBV), cerebrospinal fluid (CSF), total gray or white matter volume (GM or WM), or else on single brain structures that are delineated manually, such as the hippocampus or the thalamus (see Table 1). However, manual segmentation of single brain structures is time-consuming and inevitably leaves most of the brain unexplored. Recent developments in MRI data processing permit automatic segmentation of a large number of brain volumes in a single study (Fischl et al., 2002), which allows for comprehensive detailed examination of the entire brain (FreeSurfer; http://surfer.nmr.mgh.harvard.edu/). Another advantage of this approach is that it facilitates replication and comparison between studies.

The purpose of the present study was to perform a comprehensive comparison of subcortical brain structures, including the hippocampus, between patients with EOS and healthy controls in the same age range. Thus, we investigated all 27 subcortical structures segmented using the software suite FreeSurfer 4.0.4 (http://surfer.nmr.mgh.harvard.edu/), as well as TBV and intracranial volume (ICV), a total of 29 brain structure volumes. This is to our knowledge the first comprehensive examination of a large number of subcortical volumes in EOS. In addition, cerebral asymmetry was investigated in all 27 subcortical structures.

2. Materials and methods

2.1. Subjects

The patients were participants in a broader research project on early onset psychotic disorders at the University of Oslo, Norway (Holmen et al., 2009). Between the years of 2005 and 2008, patients were recruited from different inpatient and outpatient units in Oslo and the region of Eastern Norway (Østlandet). Inclusion criteria were a diagnosis within the schizophrenia spectrum (schizophrenia and schizoaffective disorders) and age of onset below 18 years (EOS). Of a total of 28 scanned patients, 18 were used for further analysis. Exclusion criteria were a diagnosis of Psychotic Disorder Not Otherwise Specified (Psychosis NOS, six patients) and insufficient MR scan quality (four patients).

The control group consisted of 33 subjects who had been recruited through personal letters to a group of randomly selected individuals from the Norwegian population register and through advertisements in four schools in Oslo and the Østlandet (Norway) region. All controls attended regular school classes at normal grade levels. The group was screened for mental problems using the Mini-International Neuropsychiatric Interview (M.I.N.I.) screening module (Sheehan et al., 1998). A positive response to any of the questions was grounds for exclusion from the study.

General exclusion criteria for the study were any known brain injury or neurological disease, along with standard MRI contraindications and IQ<70. A clinical neuroradiology specialist inspected all image series for pathology. This inspection led to the identification of a low-grade glioma in one of the participants of the control group, who was excluded from the study and given appropriate medical follow-up at the hospital. One patient with a small arachnoid cyst remained in the study.

After the study and the MRI procedures had been fully described to the subjects, written informed consent was obtained from both patients and controls, as well as from their parents if the adolescent was younger than 16 years of age. All participants were informed that they were allowed to withdraw from the study for whatever reason at any given time. The study was approved by the local Regional Committee for Medical Research Ethics and the Norwegian Data Inspectorate.

2.2. Clinical assessment

2.2.1. Diagnosis and symptom evaluation

Diagnostics were carried out using the Structural Clinical Instrument of Diagnosis for DSM-IV Axis I disorders (SCID-I), modules A–D. All interviewers (MJL, RT, and AH) were clinical psychologists who had participated in a training course in SCID assessment based on a training program at University of California, Los Angeles for this purpose. The mean overall *kappa* for the SCID was 0.77. Psychiatric symptoms were assessed using the Positive and Negative Syndrome Scale (PANSS; Kay et al., 1987) and the Global Assessment of Functioning—Split version (Split-GAF; Pedersen et al., 2007). An estimated duration of untreated psychosis (DUP) was obtained through the interviews. The definition of onset of psychosis was the first time any positive symptom on the PANSS reached four points (measured in weeks). Table 2 summarizes the clinical and demographic data in the patient group and the healthy control group.

2.2.2. IQ assessment

IQ assessment was carried out by clinical psychologists trained in standardized neuropsychological testing (MJL, RT, and AH). Calculation of the IQ estimate was based on the four sub-tests of the Wechsler Abbreviated Scale of Intelligence (2007, Vocabulary, Similarities, Block Design and Matrix Reasoning), using Norwegian norms.

2.2.3. Medication

Thirteen patients (72%) received antipsychotic medication (AP), while five patients did not receive any AP. All of the medicated patients received second generation antipsychotic medication (SGA). Two patients (11%) were given a combination of first generation antipsychotic medication (FGA) and SGA. For purposes of statistical analysis, the dosages were converted to a measure of defined daily dose (DDD; the average maintenance dose per day for a drug used for its main indication in adults; WHO Collaborating Centre for Drug Statistics Methodology, 2010), which indicates the relative measure of the antipsychotic potency of the neuroleptics used by the patients. The DDD measure does not take into account the duration of medication. Detailed information on medication is provided in Table 3.

2.3. MRI acquisition

All images were acquired using a 1.5 T Siemens Sonata scanner (Siemens Medical Systems, Erlangen, Germany). Image acquisition included two high-resolution 3D Spoiled Gradient Recalled (3D-SPGR) T1-weighted image series, with the following acquisition parameters applied: 124 contiguous 1-mm coronal slices, flip angle = 35°, repetition time (TR) = 24 ms, echo time = 6.0 ms, field of view (FOV) = 256 mm, acquisition matrix = 256 × 256, giving an isotropic voxel size of 1 mm^3. In addition, for neuroradiological inspection only, a whole-brain coronal T2 Turbo spin echo sequence (TR = 8000 ms/TE = 11 ms), 128 slices, slice thickness 2 mm, FOV = 256 mm, acquisition matrix = 256 × 214, was acquired for each participant.

All patients and controls were examined during the same study period and there was no scanner up-grade during this time.

2.4. Image segmentation

All image segmentation was performed using the automatic brain segmentation software tool FreeSurfer version 4.0.4. The two T1-weighted images were averaged and rigid-