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Cerebral cortical thickness and a history of obstetric complications in schizophrenia

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ABSTRACT

Introduction: Magnetic resonance imaging (MRI) studies have demonstrated that patients with schizophrenia have thinner brain cortices compared with healthy control subjects. Neurodevelopment is vulnerable to obstetric complications (OCs) such as hypoxia and birth trauma, factors that are also related to increased risk of developing schizophrenia. With the hypothesis that OCs might explain the thinner cortices found in schizophrenia, we studied patients with schizophrenia and healthy controls subjects for association between number and severity of OCs and variation in cortical thickness.
Methods: MRI scans of 54 adults with schizophrenia or schizoaffective disorder and 54 healthy controls were acquired at Karolinska Institutet, Stockholm, Sweden. Measures of brain cortical thickness were obtained using automated computer processing (FreeSurfer). OCs were assessed from obstetric records and scored blindly according to the McNeil–Sjöström scale. At numerous cortical locations, putative effects of OCs on cortical thickness variation were tested for each trimester, for labour, for composite OC scores, severe OC scores, and hypoxia scores among patients and controls separately.
Results: Number and severity of OCs varied among both patient and control subjects but were not associated with cortical thickness in either of the groups. Patients demonstrated thinner brain cortices but there were no significant differences in number and severity of OC scores across groups.
Conclusion: In the present study, number and severity of obstetric complications were not associated with brain cortical thickness, in patients with schizophrenia or in healthy control subjects. The thinner brain cortices found in patients with schizophrenia were not explained by a history of OCs.

1. Introduction

1.1. Obstetric complications in schizophrenia

A growing body of evidence indicates that a detrimental prenatal environment and obstetric complications (OCs) are related to increased risk of schizophrenia (Byrne et al., 2007; Cannon et al., 2002a; Dalman et al., 2001; Geddes et al., 1999; Hultman et al., 1999). The occurrence of OCs may disturb the early brain development, and thereby increase the risk of later development of the illness (Marenco and Weinberger, 2000; Rapoport et al., 2005; Weinberger, 1987). Several adverse pre- and perinatal factors have demonstrated statistical association with an increased risk of schizophrenia; some of which are being subjected to maternal starvation (Hoek et al., 1998) or infection (Brown et al., 2004) during foetal life, late winter birth (Hultman et al., 1999), birth asphyxia (Dalman et al., 2001), or being born small for gestational age (Jones et al., 1998). These factors have been suggested to interfere with normal brain development through effects of pro-inflammatory cytokines such as Tumor Necrosis Factor alpha and Interleukin-6 in maternal starvation (Shen et al., 2008) and infection (Smith et al., 2007), or more generally through foetal hypoxia (Verdoux and Sutter, 2002). In the present study, OCs were defined as "...the broad class of somatic deviations from an expected, normal course of events and offspring development during pregnancy, labour-delivery, and the early neonatal period" (McNeil, 1988).

1.2. Structural MRI-findings in schizophrenia

A large number of magnetic resonance imaging (MRI) studies have demonstrated brain morphological alterations such as larger lateral ventricles, smaller hippocampal volumes (Honea et al., 2005; Shenton et al., 2001 for review) and thinner brain cortices (Kuperberg et al., 2003; Nesvåg et al., 2008; Voets et al., 2008) in patients with schizophrenia compared to healthy subjects. The neuropathology underlying the cortical thinning reported in schizophrenia is poorly understood (DeLisi et al., 2006; Harrison,

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1999; Keshavan et al., 2008). Localized increase in cell-density (Pakkenberg, 1993; Selemon et al., 1995), reduction in neuropil (Selemon et al., 1998) and reduction in neuron size (Rajkowska et al., 1998) in cortical grey matter have been demonstrated in schizophrenia, but not convincingly replicated (Arnold et al., 1995; Cullen et al., 2006; Harrison, 1999 for review).

Morphological brain abnormalities have been reported to be present in first episode schizophrenia (Narr et al., 2005), in subjects at high genetic risk (Job et al., 2003; Lawrie et al., 2001), and in subjects with prodromal symptoms of schizophrenia (Pantelis et al., 2003). A three hit model, in which (1) pre-and perinatal anomalies, (2) progressive grey matter loss around transition to illness (possibly related to hormonal changes), and (3) post-pubertal neurodevelopmental changes during the early stages of psychosis appear to be processes underlying the morphological alterations observed in schizophrenia, has been suggested (Pantelis et al., 2007). In consequence, it is of interest to investigate if early disturbances such as OCs may influence on adult brain morphology in schizophrenia.

1.3. Brain abnormalities related to OCs in schizophrenia

A relatively smaller number of MRI studies have reported brain morphological abnormalities to be associated with a history of OCs in schizophrenia. Enlarged lateral ventricles (Falkai et al., 2003; McDonald et al., 2002; McNeil et al., 2000) and smaller hippocampal volumes (Ebner et al., 2008; McNeil et al., 2000; Schulze et al., 2003; Stefanis et al., 1999; van Erp et al., 2002) have been reported to be more prominent in schizophrenia patients with than without OCs.

Regarding cortical volume Cannon et al. (2002b) reported that foetal hypoxia predicted smaller grey matter cortical volume in 64 schizophrenia patients and their healthy siblings ($n = 51$) but not in healthy control subjects ($n = 54$) in a Finnish subject sample. The reductions were most prominent in the temporal lobe. Since cortical volume reflects both thickness and area, the reported reduction may have been caused by reduced cortical thickness, reduced cortical area, or both (Voets et al., 2008).

1.4. Development of the cerebral cortex

The human cerebral cortex is a complex structure, in which development is genetically regulated and susceptible to harmful environmental factors (Arnold and Rioux, 2001; Hatten, 2002). Neuronal migration from the germinal zone to the cortex is position specific (Rakic, 2007) and takes place during early and mid gestation, before the establishment of synaptic connectivity (Rakic et al., 1994). In animal models, different OCs have been demonstrated to be related to altered cortical morphology (Boksa, 2004 for review; Rees et al., 2008). In rodents, exposure to maternal protein restriction during early pregnancy has been demonstrated to cause cortical thinning (Gressens et al., 1997), but this thinning was normalized in adult rats. Foetal hypoxia has been related to altered cortical structure in sheep (Rees and Inder, 2005). The results from animal studies may also be valid for the integrity and development of the human cortex. Thinner cortices in several brain regions have been demonstrated in 15-year-old adolescents with a birth weight of less than 1500 g (Martinussen et al., 2005). The findings could be relevant to the further search for possible explanations to the thinner cortices demonstrated in MRI studies of the adult brain in schizophrenia (Kuperberg et al., 2003; Nesvåg et al., 2008).

1.5. Hypothesis

Previous scientific findings suggest that in patients with schizophrenia exposure to OCs may interfere with brain development, with consequences detected in the adult brain decades later. Hitherto, no study has specifically investigated putative effects of OCs and/or foetal hypoxia on cortical thickness variation in adult patients with schizophrenia or healthy subjects. Such investigation is of interest also considering previously reported findings of effects of OCs on brain cortical structure in animal models (Boksa, 2004).

In the present study, we hypothesized, that (1) number and/or severity of OCs and/or foetal hypoxia would be significantly associated with thinner brain cortices, and (2) if OCs, including foetal hypoxia, were found to be related to cortical thinning in schizophrenia, OCs would (a) either be more frequent or (b) cause more cortical disturbances in schizophrenia patients than in healthy control subjects.

2. Participants and methods

2.1. Subject characterization

This study was part of the Human Brain Informatics Project (HUBIN), Karolinska Institutet, Stockholm, Sweden. HUBIN is a comprehensive database of genetic, brain morphological, neuropsychological, and clinical information obtained from schizophrenia patients and healthy subjects. The subject inclusion took place between 1999 and 2003. All participants gave written informed consent. The project was approved by the Research Ethics Committee at Karolinska Institutet and the Swedish Data Inspection Board (“Datainspektionen”). The study was performed in accordance with the Helsinki Declaration.

The subject sample consisted of unrelated Caucasian men and women currently resident in the Stockholm Area, and has previously been described in detail (Jönsson et al., 2006; Nesvåg et al., 2008). Briefly; invited patients from the out-patients clinic underwent a comprehensive clinical assessment protocol using validated operational instruments (Ekholm et al., 2005; Vares et al., 2006) including verification of diagnosis by a trained psychiatrist (EGJ). Patients fulfilled DSM-III-R or DSM-IV criteria for schizophrenia ($n = 50$) or schizoaffective disorder ($n = 4$).

Control subjects were recruited using three different approaches. The first group ($n = 25$) had previously (2–19 years earlier) served as healthy comparison subjects in biological psychiatric research at the Karolinska Institutet (Damberg et al., 2004), and were reassessed for lifetime psychiatric diagnosis (Jönsson et al., 2000). A second group of controls ($n = 14$) was recruited from hospital staff or their relatives for the present study. A third control group ($n = 15$) was recruited from a population register for the present study. Given the large dropout rates when subjects are recruited from the general population for demanding biological psychiatric research, sometimes approaching 95% (Oxenstierna et al., 1996), we decided to use this combined recruitment strategy. The control subjects included in the present study were interviewed by a trained psychiatrist and they were found to have no previous or current psychiatric disorders according to a semi-structured diagnostic interview (SCID-non-patient version Spitzer et al., 1986). They were matched to the patients by age and gender.

Exclusion criteria for all subjects were a history of head trauma with loss of consciousness >5 min, a diagnosis of substance abuse and/or somatic disorders affecting brain function.

Demographic characteristics, duration of illness, age at onset, and use of anti-psychotic medication are described in Table 1.

2.2. MRI assessment

2.2.1. MR scan acquisition

MR images were obtained at the MR Research Centre at Karolinska Institutet, Stockholm, Sweden, using a 1.5 T GE signa