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No effect of obstetric complications on basal ganglia volumes in schizophrenia

Unn Kristin Haukvik [a,*], Thomas McNeil [b], Ragnar Nesvåg [a,c], Erik Söderman [d], Erik Jönsson [d], Ingrid Agartz [a,d,e]

[a] Institute of Psychiatry, section Vinderen, University of Oslo, P.O. Box 85 Vinderen, N-0319 Oslo, Norway
[b] Department of Psychiatric Epidemiology, Lund University Hospital USiL, SE-221 85 Lund, Sweden
[c] Department of Psychiatry, Vinderen DPS, Diakonhjemmet Hospital, P.O. Box 85, N-0319 Oslo, Norway
[d] Department of Clinical Neuroscience, HUBIN project, Karolinska Institutet and Hospital, R5:00, SE-171 76 Stockholm, Sweden
[e] Department of Psychiatric Research, Diakonhjemmet Hospital, P.O. Box 85, N-0319 Oslo, Norway

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ABSTRACT

Background: Heterogeneous findings have been reported in studies of basal ganglia volumes in schizophrenia patients as compared to healthy controls. The basal ganglia contain dopamine receptors that are known to be involved in schizophrenia pathology and to be vulnerable to pre- and perinatal hypoxic insults. Altered volumes of other brain structures (e.g. hippocampus and lateral ventricles) have been reported in schizophrenia patients with a history of obstetric complications (OCs). This is the first study to explore if there is a relationship between OCs and basal ganglia volume in schizophrenia.
Methods: Thorough clinical investigation (including information on medication) of 54 schizophrenia patients and 54 healthy control subjects was undertaken. MR images were obtained on a 1.5 T scanner, and volumes of nucleus caudatus, globus pallidum, putamen, and nucleus accumbens were quantified automatically. Information on OCs was blindly collected from original birth records.
Results: Unadjusted estimates demonstrated a relationship between increasing number of OCs and larger volume of nucleus accumbens in schizophrenia patients and healthy controls. No statistically significant relationships were found between OCs and the basal ganglia volumes when controlled for intracranial volume, age, and multiple comparisons. There were no effects of typical versus atypical medication on the basal ganglia volumes. The patients with schizophrenia had larger globus pallidum volumes as compared to healthy controls, but there were no case–control differences for accumbens, putamen, or caudate volumes.
Conclusion: The present results do not support the hypothesis that OCs are related to alterations in basal ganglia volume in chronic schizophrenia.

1. Introduction

Subtle anatomical brain abnormalities have been repeatedly reported from magnetic resonance imaging (MRI) studies of schizophrenia patients (Honea et al., 2005; Shenton et al., 2001; Steen et al., 2006). Whereas larger lateral ventricles, smaller hippocampi and thinner cortices are relatively consistently reported, findings from studies of the basal ganglia display more heterogeneous results (Ballmaier et al., 2008; Brandt and Bonelli, 2008; Mamah et al., 2007; Tamagaki et al., 2005).

The basal ganglia structures (putamen, globus pallidum, nucleus caudatus, and nucleus accumbens) are of particular interest in schizophrenia as they contain a high number of dopamine receptors. Disturbed dopamine metabolism is hypothesized to be a core feature in schizophrenia (Howes and Kapur, 2009). Use of typical antipsychotic medication (acting on dopamine D2 receptors, abundant in the basal ganglia structures) has been demonstrated to cause reversible alterations in basal ganglia volume (Corson et al., 1999; Lang et al., 2004). However, diverging findings from schizophrenia case–control studies suggest that other factors, such as illness progression (Tanskanen et al., in press; van Haren et al., 2007; Wang et al., 2008), genetic variation (Rajarethinam et al., 2007), or neurodevelopmental disturbances (Glenthoj et al., 2007), may also influence basal ganglia volume.

Disturbances of neuronal development have been hypothesized to be of aetiological importance in schizophrenia (Fatemi and Folsom, 2009; Marenco and Weinberger, 2000). A history of obstetric complications (OCs), i.e. adverse events occurring pre-, peri-, or postnatally, which often imply foetal hypoxia, has been related to increased risk of schizophrenia (Cannon et al., 2002a; Dalman et al., 2001; Geddes et al., 1999; Hultman et al., 1999), younger age at onset of illness (Verdoux et al., 1997), and more severe cognitive deficits (Brown et al., 2009; Ellman et al., 2009). Several studies have shown

Abbreviations: ICV, intracranial volume; MRI, magnetic resonance imaging; OCs, obstetric complications.

* Corresponding author. Tel.: +47 22029839; fax: +47 22495861.
E-mail address: unn.haukvik@medisin.uio.no (U.K. Haukvik).

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that a history of OCs is related to differences in brain morphology within patients, e.g. smaller hippocampi and larger ventricles (Ebner et al., 2008; Falkai et al., 2003; McDonald et al., 2002; McNeil et al., 2000; Schulze et al., 2003; van Erp et al., 2002). Cortical volumes have been reported to be reduced in patients with a history of foetal hypoxia (Cannon et al., 2002b), whereas cortical thickness was found to be unrelated to foetal hypoxia or obstetric complications in patients with schizophrenia in a previous study by our group (Haukvik et al., 2009). Thus, pre- and perinatal complications may be of importance to the aetiology of some of the morphological alterations observed in the brains of patients with schizophrenia.

The relationship between volumes of the basal ganglia and OCs in patients with schizophrenia has, to our best knowledge, hitherto not been investigated. Such a relationship could be suggested to occur since in animal models, OCs have been demonstrated to cause altered dopamine-mediated behaviour (caesarean section) (Berger et al., 2000), altered dopamine receptor mRNA in the striatum (perinatal asphyxia) (Gross et al., 2005), decreased striatal dopamine turnover (caesarean section) and nucleus accumbens dopamine turnover (caesarean section + anoxia) (El-Khodor and Boksa, 1997), and greater neuronal spine density in the nucleus accumbens (caesarean section + anoxia) (Juarez et al., 2008).

Based on the fact that dopamine metabolism is both a core feature in schizophrenia and vulnerable to OCs, we hypothesized that increasing number of OCs would be related to basal ganglia volume in schizophrenia patients but not in healthy controls. The direction of this relationship was not hypothesized a priori. As neuroleptics may influence on basal ganglia volume (Scherk and Falkai, 2006; Smieskova et al., 2009), the effect of antipsychotic medication use was important to control for.

In the present study, we thus analyzed and compared the effect of OCs on the volume of four basal ganglia structures (nucleus accumbens, nucleus caudatus, globus pallidum, and putamen) in patients with schizophrenia and healthy control subjects.

2. Methods

2.1. Subject characterization

This study was part of the Human Brain Informatics Project (HUBIN) at the 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 (Haukvik et al., 2009; Jonsson et al., 2006). 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 from hospital staff, their relatives, or from a population register. They were interviewed by a trained psychiatrist and found to have no previous or current psychiatric disorders according to a semi-structured diagnostic interview. They were matched to the patients by age and gender (on a group level).

Exclusion criteria for all subjects were a history of head trauma with loss of consciousness>5 min, current treatment for substance abuse, and/or somatic disorders affecting brain function. Demographic characteristics, duration of illness, age at onset, and use of antipsychotic medication are described in Table 1. The antipsychotic medications used by patients in the present study were as follows: typical antipsychotic medication ($n=25$) included Perphenazine ($n=9$), Zuclopenthixole ($n=5$), Haloperidol ($n=10$), and Flupenthixole ($n=1$); atypical antipsychotic medication ($n=26$) included Risperidone ($n=8$), Clozapine ($n=9$), and Olanzapine ($n=9$). Two subjects had both typical and atypical antipsychotic medication and three patients had no medication at the time of MRI.

2.2. MRI assessment

2.2.1. MRI scan acquisition

MR images were obtained at the MR Research Centre at Karolinska Institutet, Stockholm, Sweden, using a 1.5 T GE signa Echo-speed (Milwaukee, Wis., USA) scanner. T1 weighted images were obtained using a three-dimensional spoiled gradient recalled (SPGR) pulse sequence with the following parameters; 1.5 mm coronal slices, no gap, 35° flip angle, repetition time (TR) = 24 ms, echo time (TE) = 6.0 ms, number of excitations (NEX) = 2, field of view (FOV) = 24 cm, and acquisition matrix = 256 × 192. T2-weighted images were acquired with the following parameters; 2.0 mm coronal slices, no gap, TR = 6000 ms, TE = 84 ms, NEX = 2, FOV = 24 cm, and acquisition matrix = 256 × 192. All scans included were visually judged to be without obvious motion artefacts. A trained neuroradiologist evaluated all scans to be without gross pathology.

Table 1
Demographic, clinical, and obstetric variables in patients with schizophrenia and healthy control subjects.

	Patients ($n=54$)		Controls ($n=54$)		Statistics	
	Mean (S.E.)	Range	Mean (S.E.)	Range	Test value	p-value
Age at MRI (years)	41.9 (1.1)	25–57	41.5 (1.2)	19–56	$t=0.28$	0.82
Age at onset (years) ($n=53$)	24.9 (0.78)	15.9–39.5	n/a		n/a	n/a
Birth weight (g)	3394 (86.4)	1770–5630	3397 (90.5)	1460–4720	$t=0.78$	0.44
Head circumference (cm) ($n=105$)	33.8 (0.21)	30–37	33.7 (0.23)	28–36	$t=0.30$	0.77
Gestational age (weeks)	39.2 (0.26)	32–42	39.4 (0.31)	31–43	$z=-0.64$	0.52
Maternal age (years)	27.5 (0.76)	17–43	27.9 (5.6)	18–39	$t=-0.36$	0.71
OCs	5.8 (0.72)	0–28	5.5 (0.63)	0–23	$z=-0.28$	0.78
	Number	%	Number	%		
Gender						
–Male/female	37/17	68/32	33/21	62/38	$\chi^2=0.65$	0.42
Medication						
–none/typical/atypical	3/25/26	6/46/48	n/a			n/a