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Cortical folding alterations in fetuses with isolated non-severe ventriculomegaly

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ABSTRACT

Neuroimaging of brain diseases plays a crucial role in understanding brain abnormalities and early diagnosis. Of great importance is the study of brain abnormalities *in utero* and the assessment of deviations in case of maldevelopment. In this work, brain magnetic resonance images from 23 isolated non-severe ventriculomegaly (INSVM) fetuses and 25 healthy controls between 26 and 29 gestational weeks were used to identify INSVM-related cortical folding deviations from normative development. Since these alterations may reflect abnormal neurodevelopment, our working hypothesis is that markers of cortical folding can provide cues to improve the prediction of later neurodevelopmental problems in INSVM subjects. We analyzed the relationship of ventricular enlargement with cortical folding alterations in a regional basis using several curvature-based measures describing the folding of each cortical region. Statistical analysis (global and hemispheric) and sparse linear regression approaches were then used to find the cortical regions whose folding is associated with ventricular dilation. Results from both approaches were in great accordance, showing a significant cortical folding decrease in the insula, posterior part of the temporal lobe and occipital lobe. Moreover, compared to the global analysis, stronger ipsilateral associations of ventricular enlargement with reduced cortical folding were encountered by the hemispheric analysis. Our findings confirm and extend previous studies by identifying various cortical regions and emphasizing ipsilateral effects of ventricular enlargement in altered folding. This suggests that INSVM is an indicator of altered cortical development, and moreover, cortical regions with reduced folding constitute potential prognostic biomarkers to be used in follow-up studies to decipher the outcome of INSVM fetuses.

1. Introduction

Cortical folding is a major developmental process the human brain embarks on during the intrauterine period to acquire its highly gyrencephalic adult morphology. In early gestation, the cortex is a smooth sheet that becomes intensively convoluted following an ordered sequence of sulcogyral formation, with primary and secondary sulci obeying stable spatio-temporal patterns, while more irregular patterns govern the emergence of tertiary sulci. These cortical convolutions are intrinsically related to the functional organization of the cortex. Consequently, alterations in the degree and pattern of cortical folding might have a profound impact on brain function (Fernández et al., 2016). In adults, several studies have revealed associations of altered folding with functional disabilities in a wide spectrum of disorders such as schizophrenia (Jou et al., 2005) and attention-deficit/hyperactivity disorder (Wolosin et al., 2009). These functional disturbances might involve early cortical folding malformations and manifest in adulthood as symptomatic consequences of said maldevelopment (Wolosin et al., 2009; Batty et al., 2015; Rehn and Rees, 2005; Powell, 2010).

Since gyrification commences early in pregnancy, gestation constitutes a vulnerable period for cortical folding, where prenatal diagnosis of cerebral abnormalities is of paramount importance. In the fetus, ventriculomegaly (VM) is the most frequent abnormal finding in prenatal ultrasound examination and occurs in around 1% of fetuses (Salomon et al., 2007; Huisman et al., 2012). Fetal VM is a condition in which the lateral ventricles are dilated, and is defined as an atrial diameter of ≥10 mm of one or both lateral ventricles at any gestational age (GA) from 14 weeks onwards (Cardoza et al., 1988), being 6–8 mm

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the width in normal fetuses. These measurements remain stable in the second and third trimesters (ISUOG Guidelines, 2007). In case of ventricular enlargement, an atrial diameter in the range of 10–15 mm constitutes non-severe VM, while a measurement larger than 15 mm refers to severe VM. Non-severe VM is further classified into mild (10–12 mm) and moderate (12–15 mm). In case of no other anomalies, it is called isolated VM.

Though studies have found associations of ventricular enlargement with attention-deficit/hyperactivity disorder (Lyoo et al., 1996) and schizophrenia (Wright et al., 2000; Vita et al., 2000), the implications of fetal VM in such disorders remain largely unclear due to scarce long-term follow-up studies and the appearance of confounding factors during development. Nevertheless, isolated non-severe ventriculomegaly (INSVM)-associated neurodevelopmental deficits have been observed in neonates and infants (Sadan et al., 2007; Leitner et al., 2009; Gómez-Arriaga et al., 2012). When VM is diagnosed, postnatal prognosis is highly dependent on the presence of other abnormalities and the degree of ventricular dilation (Griffiths et al., 2010). There is a high risk of poor neurodevelopmental outcome when other abnormalities are diagnosed and/or the ventricles are severely dilated. However, INSVM fetuses are not so prone to have neurodevelopmental problems (Melchiorre et al., 2009; Griffiths et al., 2010), and the ones that will have unfavorable outcome cannot be characterized solely by the atrial diameter (Beeghly et al., 2010). With altered cortical folding found in fetuses with INSVM (Scott et al., 2013), the assessment of cortical folding can play an important role in prognosis reliability (Li et al., 2011).

Although ultrasound is the most used imaging modality for evaluating pregnancies, VM is a common indication for fetal magnetic resonance imaging (MRI) (Rutherford, 2001). Indeed, MRI of the *in vivo* fetal brain has recently attracted increasing attention from the neuroscientific community and is becoming an important tool in the study of *in utero* brain development (Benkarim et al., 2017; Studholme and Rousseau, 2014). There are several works in the literature that use 3D MRI to investigate the intrauterine cerebral growth in healthy populations (Habas et al., 2012; Clouchoux et al., 2012; Wright et al., 2014, 2015). These neuroimaging studies attempt to identify and set the normative morphological and functional changes the fetal brain undergoes during its maturational course. On the other hand, neuroimaging of diseased brains provides the means to find disease-specific deviations from the aforementioned normative development and the discovery of stable biomarkers that accurately discriminate such diseases. Using 3D reconstructed MRI, isolated VM has been previously studied in Scott et al. (2013) and Kyriakopoulou et al. (2014). Scott et al. (2013) analyzed volumetric and cortical folding differences between 16 cases and 16 controls in the age range of 22–25.5 gestational weeks (GWs). Volumetric analysis was carried out by Kyriakopoulou et al. (2014) in 60 controls and 65 cases within the GA range of 22–38 weeks. Among their findings, Kyriakopoulou et al. (2014) showed increased cortical volume in fetuses with VM, and Scott et al. (2013) found reduced cortical folding in both hemispheres, although in a narrow area near the parieto-occipital sulcus.

In this work, 3D reconstructed fetal brain MR images were used to investigate the relationship of INSVM with alterations in gyrification between a cohort of 25 healthy controls and 23 INSVM fetuses within the age range of 26–29 GWs. There are no studies that investigated cortical folding under VM in the third trimester of gestation. During this period, numerous cortical landmarks are prominently developed in the normal fetal brain (e.g., superior temporal sulcus and calcarine fissure) (Clouchoux et al., 2012), which allow susceptible deviations in gyrification to be reliably detected. Cortical folding was quantified using several curvature-based folding measures (e.g., mean curvature, shape index and curvedness). These descriptors offer a different perspective into intrauterine neurodevelopment than brain volumetry. Curvedness, for instance, was shown to provide different information and be more accurate in the prediction of GA than brain volume (Hu et al., 2013; Wu et al., 2015). With several descriptors we can, furthermore, capture different shape characteristics of the cortex. Positive and negative versions of some folding measures (e.g., positive and negative mean curvature) were further incorporated to respectively account for folding confined in gyral and sulcal areas, which affords a separate inspection of cortical folding. The cortex was parcellated in several regions to study cortical folding differences in a regional basis. Statistical analysis and sparse regression approaches were adopted to analyze folding differences related to ventricular enlargement and identify cortical regions with altered folding. The present study seeks to add to previous studies by providing insights into the gyrification alterations potentially associated with INSVM at mid-third trimester of gestation (where the majority of primary sulci are formed), assessing the relationship from different methodological approaches, and characterizing the implication of ventricular enlargement laterality in cortical alterations.

2. Materials and methods

2.1. Subjects

For our study, we included 25 healthy controls and 23 subjects diagnosed with INSVM from a larger prospective cohort of 81 subjects within a research project on congenital isolated VM. INSVM was defined as unilateral or bilateral ventricular width between 10 and 14.9 mm. All fetuses were from singleton pregnancies and met the inclusion criteria of having no abnormal karyotype, infections or malformations with risk of abnormal neurodevelopment. Approval was obtained for the study protocol from the Ethics Committee of the Hospital Clínic in Barcelona — Spain (HCB/2014/0484) and all patients gave written informed consent. Fetal MRI was performed between 26 and 29 GWs. Pregnancies were dated according to the first-trimester crown-rump length measurements (Robinson and Fleming, 1975). Table 1 presents the number of subjects and mean GA per cohort, with INSVM cases grouped by left, right or bilateral ventricular enlargement.

2.2. MRI acquisition and reconstruction

T2-weighted MR imaging was performed on a 1.5-T scanner (SIEMENS MAGNETOM Aera syngo MR D13; Munich, Germany) with a 8-channel body coil. All images were acquired without sedation and following the American college of radiology guidelines for pregnancy and lactation. Half Fourier acquisition single shot turbo spin echo (HASTE) sequences were used with the following parameters: echo time of 82 ms, repetition time of 1500 ms, number of averaging = 1, 2.5 mm of slice thickness, 280×280 mm field of view and voxel size of $0.5 \times 0.5 \times 2.5$ mm^3. For each subject, multiple orthogonal acquisitions were performed: 4 axial, 2 coronal and 2 sagittal stacks. Final 3D motion-corrected reconstructions were obtained from these 8 stacks of thick 2D slices. Brain location and extraction from 2D slices was carried out in an automatic manner using the approach proposed by Keraudren et al. (2014), followed by high-resolution 3D volume reconstruction

Table 1
Demographics. Number of subjects (*N*), mean GA and standard deviation expressed in GW, and gender (M/F, where M and F stand for male and female, respectively) per cohort. The INSVM cohort is further divided in 3 subgroups (left, right and bilateral) according to unilateral or bilateral VM diagnosis.

	N	GW	M/F
Control	25	27.6 ± 0.9	14/11
INSVM			
Bilateral	5	27.3 ± 0.9	4/1
Left	8	28.1 ± 0.8	8/0
Right	10	27.2 ± 1.0	9/1
Total	23	27.5 ± 1.0	21/2