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Disrupted developmental organization of the structural connectome in fetuses with corpus callosum agenesis

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ABSTRACT

Agenesis of the corpus callosum is a model disease for disrupted connectivity of the human brain, in which the pathological formation of interhemispheric fibers results in subtle to severe cognitive deficits. Postnatal studies suggest that the characteristic abnormal pathways in this pathology are compensatory structures that emerge via neural plasticity. We challenge this hypothesis and assume a globally different network organization of the structural interconnections already in the fetal acallosal brain.

Twenty fetuses with isolated corpus callosum agenesis with or without associated malformations were enrolled and fiber connectivity among 90 brain regions was assessed using in utero diffusion tensor imaging and streamline tractography. Macroscopic scale connectomes were compared to 20 gestational age-matched normally developing fetuses with multiple granularity of network analysis.

Gradually increasing connectivity strength and tract diffusion anisotropy during gestation were dominant in antero-posteriorly running paramedian and antero-laterally running aberrant pathways, and in short-range connections in the temporoparietal regions. In fetuses with associated abnormalities, more diffuse reduction of cortico-cortical and cortico-subcortical connectivity was observed than in cases with isolated callosal agenesis. The global organization of anatomical networks consisted of less segregated nodes in acallosal brains, and hubs of dense connectivity, such as the thalamus and cingulate cortex, showed reduced network centrality.

Acallosal fetal brains show a globally altered connectivity network structure compared to normals. Besides the previously described Probst and sigmoid bundles, we revealed a prenatally differently organized macroconnectome, dominated by increased connectivity. These findings provide evidence that abnormal pathways are already present during at early stages of fetal brain development in the majority of cerebral white matter.

Introduction

The corpus callosum is the largest commissural structure in the human brain, formed by more than 190 million cross-hemispheric axons that are known to exhibit excitatory function (Tomasch, 1954; Bloom and Hynd, 2005). Callosal fibers emerge via multiple embryonic, fetal, and postnatal developmental steps that give rise to and sculpt the connections between cerebral hemispheres (Paul et al., 2007; Richards et al., 2004). The classification of developmental brain pathologies is either based upon the earliest time-point at which a certain developmental process (neuronal proliferation, migration, and organization) is disrupted (Barkovich et al., 2012), or upon the pattern of genetic expression (Sarnat, 2008). Many brain malformations are primarily characterized by abnormal axonal path-finding, regarded as axon-guidance disorders (Engle, 2010). The prenatal disruption of the normal commissuration can lead to partial or complete agenesis of the corpus callosum (= callosal agenesis, CCA) a common brain malformation with a combined prevalence of 0.02–0.5% (Paul et al., 2007; Jeret et al., 1985) in the population and 2–3% of patients with mental retardation (Jeret et al., 1985). CCA, and a wide range of associated neurodevelopmental abnormalities, can be assessed by ultrasound examination from mid-gestation (Santo et al., 2012; Vergani et al., 1994; Comstock et al., 1985), although fetal diagnostics becomes challenging for the fine-grained description of midline structures, as seen in cases

Abbreviations: CCA, corpus callosum agenesis; DTI, diffusion tensor imaging; FA, fractional anisotropy; FDR, false discovery rate; FWER, familywise error rate; GLM, general linear model; GW, gestational week; ROI, region of interest; SSE, sum of squares for errors.

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with hypoplastic corpus callosum. To overcome this limitation, recent fast in utero magnetic resonance imaging techniques provide valuable surrogate information for the prenatal counseling of neurodevelopmental disorders (Chung et al., 2000; Gowland and Fulford, 2004; Brugger et al., 2006; Glenn and Barkovich, 2006; Prayer et al., 2006a; Pugash et al., 2008; Mailath-Pokorny et al., 2012; Tang et al., 2009), and a growing spectrum of imaging sequences can now be applied during the fetal period.

Congenital syndromes that manifest in aberrant commissuration are good models for globally and profoundly impaired neural connectivity. One of the most striking manifestations of the disrupted connectivity is that the interhemispheric information transfer is blocked (Fischer et al., 1992; Quigley et al., 2003; Brown et al., 1999). Therefore, it was hypothesized that these patients may suffer from severe functional impairments. However, this hypothesis is challenged by the high variability in the functional phenotype observed in acallosal subjects, and the observation that cognitive functioning can be, unexpectedly, close to normal. CCA adds additional complexities due to the high diversity in the genetic background and the associated syndromes (Bedeschi et al., 2006; Bonneau et al., 2002; Sherr et al., 2005; Edwards et al., 2014), as well as the theoretical possibility of information transfer through surrogate pathways that may develop through long-rage neuroplasticity (Fischer et al., 1992; Tovar-Moll et al., 2014; Barr and Corballis, 2002).

The main motivation for our study was to characterize the common and convergent macroscopic-scale white matter architecture in fetuses with CCA, prior to the alterations of fiber structure in later life. This early experimental window is of particular importance, as, during infanthood and adolescence, white matter structure develops rapidly, and these physiological changes presumably affect the phenotype of acallosal brains (Prayer et al., 2006a; Dubois et al., 2013; Giorgio et al., 2008; Luders et al., 2010). The main mechanisms are axonal refinement and pruning during early postnatal development (Innocenti and Price, 2005) and experience-driven reorganization in later life (Fields, 2005; Scholz et al., 2009; Lövdén et al., 2010).

Our study aims to investigate callosal agenesis in three different aspects. First, we choose to use in utero diffusion magnetic resonance imaging to portray the distributed impairment in macroscopic-scale fiber bundles of the acallosal human brain, and reveal novel white matter abnormalities that recur in acallosal fetuses (Kasprian et al., 2008, 2010, 2013). In contrast to studies that suggest long-range plasticity as the main mechanism behind the formation of aberrant pathways, such as the Probst bundle or the sigmoid bundle, we hypothesize that fetuses with associated and isolated forms of callosal agenesis already show a substantially altered connectional structure, and this structure is expressed during early life. Second, it is not yet clear how the pathological white matter structures in axon-guidance disorders emerge and whether their morphological properties remain stable during prenatal development. We aim to broaden our understanding of the timing of callosal malformation by characterizing both the microstructural properties of aberrant white matter structures and picture the general macroscopic building principles of the connectome across mid- and late gestation. Finally, complex network analysis of connectivity is used to explicate the functional integration and segregation in pathologically wired fetal brains.

Methods

Fetal MRI was clinically indicated to rule out or confirm fetal or placental abnormalities. Prior ultrasound examinations were performed for initial diagnosis and to assess the gestational age. MRI comprised (1) multi-planar structural MRI examinations with T2-weighted sequences of the whole fetus and the fetal brain, (2) T1-weighted and echo planar T2-weighted sequences to rule out intracranial hemorrhage and/or blood breakdown products (Prayer et al., 2006b), and (3) surrogate examinations, such as DTI and resting-state BOLD fMRI, which are not directly used in clinical decision-making. The study protocol was approved by the local ethics committee, the mothers gave written, informed consent prior to the examination, and the research was conducted according to the principles expressed in the Declaration of Helsinki.

In utero structural connectivity: cohorts and image acquisition

During the study period of January 2010 to March 2014, in utero diffusion tensor MRI scans were acquired in 463 fetuses. Partial and complete corpus callosum agenesis was diagnosed in 43 cases. We excluded cases for the following criteria: bad quality of diffusion tensor images and excessive fetal motion during the scan ($n = 7$); extreme ventriculomegaly (>15 mm dilatation of the lateral ventricles) or large interhemispheric cyst ($n = 6$); fetal age under 22 gestational weeks (GW, $n = 4$); complex associated developmental abnormality affecting the brain in multiple lobes ($n = 2$); or when no ultrasound report and GW assessment were available to the institution at the time of image retrieval ($n = 4$). The final population consisted of 20 fetuses with corpus callosum agenesis (CCA): two partial and 18 with complete agenesis of the corpus callosum, and 11 fetuses with radiologically isolated CCA.

Table 1
Subject characteristics and imaging findings in fetuses with callosal agenesis. CCA: corpus callosum agenesis.

Identifier	Gestational age (week + day)	Study group	Corpus callosum status	Associated neuroimaging findings
Fetus 1	22 + 3	2nd trimester group	CCA (complete)	Pontocerebellar hypoplasia, parietooccipital abnormal gyrification
Fetus 2	22 + 0	2nd trimester group	CCA (complete)	Pontocerebellar hypoplasia, missing cavum septi pellucidi
Fetus 3	23 + 2	2nd trimester group	Isolated CCA	–
Fetus 4	22 + 6	2nd trimester group	Isolated CCA	–
Fetus 5	25 + 2	2nd trimester group	Isolated CCA	–
Fetus 6	24 + 4	2nd trimester group	Isolated CCA	–
Fetus 7	22 + 2	2nd trimester group	CCA (complete)	Dandy Walker variant
Fetus 8	22 + 0	2nd trimester group	Partial CCA	Migration abnormality in frontal lobe
Fetus 9	35 + 1	3rd trimester group	Isolated CCA	–
Fetus 10	29 + 0	3rd trimester group	Isolated CCA	–
Fetus 11	29 + 5	3rd trimester group	CCA (complete)	Cortical malformation
Fetus 12	36 + 2	3rd trimester group	Isolated CCA	–
Fetus 13	34 + 4	3rd trimester group	Isolated CCA	–
Fetus 14	31 + 6	3rd trimester group	Partial CCA (occipital parts present)	–
Fetus 15	26 + 2	3rd trimester group	CCA (complete)	Pontocerebellar hypoplasia, parietooccipital abnormal gyrification
Fetus 16	31 + 3	3rd trimester group	CCA (complete)	Pontocerebellar hypoplasia
Fetus 17	33 + 0	3rd trimester group	Isolated CCA	–
Fetus 18	27 + 6	3rd trimester group	Isolated CCA	–
Fetus 19	27 + 1	3rd trimester group	CCA (complete)	Abnormal frontomedial sulcation
Fetus 20	29 + 2	3rd trimester group	CCA (complete)	Gyration abnormality, interhemispheric cyst