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Sulcal pits and patterns in developing human brains

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Abstract

Spatial distribution and specific geometric and topological patterning of *early* sulcal folds have been hypothesized to be under stronger genetic control and are more associated with optimal organization of cortical functional areas and their white matter connections, compared to later developing sulci. Several previous studies of sulcal pit (putative first sulcal fold) distribution and sulcal pattern analyses using graph structures have provided evidence of the importance of sulcal pits and patterns as remarkable anatomical features closely related to human brain function, suggesting additional insights concerning the anatomical and functional development of the human brain. Recently, early sulcal folding patterns have been observed in healthy fetuses and fetuses with brain abnormalities such as polymicrogyria and agenesis of corpus callosum. Graph-based quantitative sulcal pattern analysis has shown high sensitivity in detecting emerging subtle abnormalities in cerebral cortical growth in early fetal stages that are difficult to detect via qualitative visual assessment or using traditional cortical measures such as gyrification index and curvature. It has proven effective for characterizing genetically influenced early cortical folding development. Future studies will be aimed at better understanding a comprehensive map of spatio-temporal dynamics of fetal cortical folding in a large longitudinal cohort in order to examine individual clinical fetal MRIs and predict postnatal neurodevelopmental outcomes from early fetal life.

Keywords

early cortical folding; fetal brain; sulcal pit; sulcal pattern

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Development of cortical folding

One of the most significant steps in the evolution of the human cerebral cortex is the enlargement of the cerebral cortex, which occurs mainly by areal expansion and folding of cortical surface without a comparable increase in cortical thickness (Rakic, 2009; Sun and Hevner, 2014). Cortical expansion during early brain development occurs through the proliferation and expansion of neural stem cells and neural progenitors in the ventricular and subventricular zones (Chenn and Walsh, 2002; Fernandez et al., 2016; Lui et al., 2011; Rakic, 2009; Sun and Hevner, 2014). The resulting increased cortical growth and folding in the human brain are important factors that are associated with our capacity for high-order cognitive abilities (Sun and Hevner, 2014). To date, several hypotheses and experiments have been proposed to support and explain developmental mechanisms of complex folding in the human cerebral cortex. Main hypotheses are: external skull constraints (Le Gros Clark, 1945), mechanical folding by differential growth of superficial and deep layers of the brain (Richman et al., 1975; Tallinen et al., 2016; Toro and Burnod, 2005), axonal tension in white matter between nearby cortical areas (Hilgetag and Barbas, 2006; Van Essen, 1997), differential proliferation of neural progenitors (Kriegstein et al., 2006), and differential cortical expansion related to cytoarchitecture (Ronan and Fletcher, 2015; Welker, 1990). There have been other recent hypotheses of cerebral folding such as a reaction-diffusion model involving Turing morphogens (Lefevre and Mangin, 2010) and an axonal pushing theory (Nie et al., 2012). These theories may not be competing alternatives but actually complementary, when considering the various phases of corticogenesis (Bayly et al., 2014; Hasnain et al., 2001, 2006; Striedter et al., 2015; Sun and Hevner, 2014). Although the precise mechanisms which cause stable patterns of primary sulci but high variations of minor sulci across individuals are not fully understood and demonstrated, it is widely accepted that normal cortical growth and the resulting folding patterns are crucial for normal brain function. Defects in neural development such as neuronal proliferation, migration and differentiation result in disrupted cortical folding that has been associated with a range of cognitive deficits in many genetic brain malformations and developmental disorders (Barkovich et al., 2012; Clark, 2001; Cykowski et al., 2008; Fernandez et al., 2016; Gaitanis and Walsh, 2004; Molko et al., 2003; Nakamura et al., 2007; Rakic, 2004; Shim et al., 2009).

To better understand mechanisms of normal and abnormal cortical folding, it is a matter of great importance to observe early cortical folding patterns in the developing brain. Human cerebral cortex shows the dramatic areal expansion and folding during fetal life with the most prominent and dynamic genetic regulation (Colantuoni et al., 2011; Kang et al., 2011; Miller et al., 2014). Since the primary cortical shape and sulcal folding pattern are prenatally determined and are under strong spatio-temporal genetic control (Hill et al., 2010; Kostovic and Vasung, 2009; Rakic, 2004; Sun and Hevner, 2014; Takahashi et al., 2012; White et al., 2010), disrupted cortical folding structure in many brain disorders may occur earlier than previously observed. Therefore, quantitative magnetic resonance imaging (MRI) measures that reflect genetically influenced abnormalities in early cortical folding may provide a useful tool for identifying the early signs of developmental brain disorders and enhance our understanding of developmental mechanisms of cortical folding structure.

Early cortical folds and sulcal pits: Functional and genetic implications

Although the origin and mechanism of human cortical folding are still unclear, the first cortical folds to develop appear to be more stable in number, position, and orientation. The formation of the first cortical folds occurs during the early stage of radial growth of the cerebral cortex, and their formation may be closely related to functional specialization of the cortex and the protomap of cytoarchitectonic areas (Cachia et al., 2003; Hasnain et al., 2001; Im et al., 2010; Lohmann et al., 2008; Rakic, 1988; Regis et al., 2005). The sulci that form later during the tangential growth of the cerebral cortex appear to be more variable, both in appearance and in their relationship to functional areas (Hasnain et al., 2001, 2006). It is therefore important to identify the putative first cortical folds and examine their spatial distribution for understanding the anatomical and functional development of the human brain. The concept of ***sulcal roots*** was introduced to represent the first cortical folding locations by Regis et al. (2005). They suggested that the shape and location of sulcal roots may be stable across individual at the fetal stage and sulcal variability at the adult stage may result from the chaotic behavior of the folding process (Regis et al., 2005). It has been hypothesized that the first cortical folds develop into the deepest local regions of sulci with spatial invariance during development, which are termed ***sulcal pits*** (Im et al., 2010; Lohmann et al., 2008). Since the apparent immobility of the sulcal fundus locations has been reported (Smart and McSherry, 1986; Toro and Burnod, 2005), sulcal pits have been identified from MRI to reflect putative first cortical folds in mature brains. A sulcal pit can be identified in a sulcal catchment basin by using the structural information of small gyri buried in depths of sulci called *plis de passage* (the focal elevation of the sulcal bottom) (Fig. 1a). The *plis de passage*, which was described as the remnant of the development of separate sulcal segments (Cunningham, 1905), is located between two sulcal pits within a sulcus. Although we cannot guarantee that the initial deepest points are stationary during development and finally become the sulcal pits on the cortical surface, the spatial distribution of the sulcal pits was highly invariant and clustered across individuals compared to the more superficial cortical regions in a normal adult group, which is consistent with the sulcal root model (Im et al., 2010; Lohmann et al., 2008). The first surface-based sulcal pit study identified 48 and 47 sulcal pit clusters in the whole left and right hemispheres respectively with most major sulci containing 2 or more clusters (Im et al., 2010) (Fig. 1a). The frequency and spatial density of the sulcal pits were high in the clusters in the central, postcentral, intraparietal, subparietal, middle frontal, and collateral sulci, the junction between superior frontal and precentral sulci, and the junction between inferior frontal and precentral sulci. The first major folds in those areas might develop and deepen at similar positions between individuals. Moreover, sulcal pit extraction and distribution on the cortical surface were not random but highly reliable and reproducible according to different MRI scan sessions and scanners, and cortical surface extraction tools (Im et al., 2013a). In a recent longitudinal MRI study, the sulcal pits of the infant population were consistently concentrated in 54 cluster regions, particularly in major sulci such as the central, precentral, postcentral, superior temporal, and parieto-occipital sulci (Meng et al., 2014). During the cortex development from 0 to 2 years of age, the relative positions of cluster regions were almost unchanged. These results have supported the sulcal pit hypothesis, demonstrating that spatially consistent distributions of sulcal pits across individuals have already existed at term

birth and this spatial distribution pattern keeps relatively stable in the first 2 years of life (Meng et al., 2014) (Fig 1b). As recent interest in the sulcal pits has grown, algorithmic improvements in surface-based sulcal pit extraction have been proposed and have confirmed the assumption that deep sulcal pits have high reproducibility across subjects (Auzias et al., 2015) (Fig. 1c). This study identified 104 and 114 sulcal pit clusters in the left and right hemispheres respectively, including shallower and more variable folds.

A biological interpretation of stable spatial distribution of deep sulcal pits has been based upon functional regionalization of the cerebral cortex influenced by genetic factors. According to the radial unit hypothesis, the ventricular zone consists of proliferative units that form a protomap of cytoarchitectonic areas (Rakic, 1988). The protomap model proposes that the cells in the embryonic cerebral vesicle carry intrinsic programs for species-specific cortical regionalization (Fukuchi-Shimogori and Grove, 2001; Miyashita-Lin et al., 1999; Rakic, 1988, 2001). Genetic control has an effect on the protomap and cortical regionalization, and is important in the development and distribution of cortical convolutions (Piao et al., 2004; Rakic, 2004; Rubenstein and Rakic, 1999). The gyrogenesis hypothesis suggests that areas of rapid growth form gyri at the center of a functional area (Welker, 1990), and the differential tangential expansion hypothesis proposes that regional cortical expansion is predominantly driven by the pattern of the protomap and cytoarchitecture (Ronan and Fletcher, 2015). Accordingly, boundaries between functional areas following the protomap may be spatially related to sulcal fundi and pits (Im et al., 2010; Lohmann et al., 2008; Regis et al., 2005). Secondary and tertiary sulci may be formed more randomly by mechanical folding based on the differential tangential growth of the inner and outer cortical layers as well as other chaotic events occurring at later stages of corticogenesis (Hasnain et al., 2001, 2006; Regis et al., 2005; Richman et al., 1975). In summary, the first major folds appear to show greater spatial invariance during development as they deepen and have a stronger spatial covariance with functional areas under closer genetic control than later developing sulci. Invariant sulcal pit distributions across individuals may be due to the stability of a human-specific protomap that is consistently predetermined by the combinatorial expression pattern of various genes (Chen et al., 2012; Miller et al., 2014; O'Leary et al., 2007; Stahl et al., 2013). The ontogenetic protomaps of high-frequency and high-density regions might generally resemble each other more than those for other regions in human brains. One recent study in a large human pedigree cohort supported a genetic influence on the sulcal pits by estimating the heritability of the sulcal pits depth, and consolidated the hypothesis of genetic control on these structural landmarks (Le Guen et al., 2017).

Furthermore, several studies have demonstrated the importance of sulcal pits as anatomical features that relate to human brain function. Significant hemispheric asymmetries in the frequency and the spatial distribution of sulcal pits were mainly found in cortical language areas including superior temporal sulcus, which may be closely associated with asymmetric genetic programs and the lateralization of language functions in human brains (Im et al., 2010) (Fig. 2a). The asymmetric sulcal pit distributions and frequency have been supported and confirmed by other studies in different adult and infant groups (Auzias et al., 2015; Meng et al., 2014). Hemispheric asymmetries of the spatial distributions of sulcal pits existed consistently from birth to 2 years of age (Meng et al., 2014). Significant relationship

between the presence of sulcal pits and verbal intelligence was also found, supporting the functional implication of the sulcal pit (Im et al., 2011a). Specifically, a sulcal pit was more frequently present in the left posterior inferior frontal sulcus (that is close to Broca's area) and the right posterior inferior temporal sulcus (that has been reported to be regions of language function) in high verbal intelligence group (Im et al., 2011a) (Fig. 2b). As sulcal pits appear to be closely related to functional areas, it was suggested that increased functional specification and more distinct functional regions in those language areas might cause more apparent emergence of sulcal pits, leading to improved language function. Table 1 is provided to summarize the existing studies of sulcal pits extraction and analysis.

Sulcal pattern analysis using a sulcal pit-based graph structure

Sulcal pits have been employed for analyzing not only sulcal pit frequency and spatial variance but also geometric and topological ***sulcal pattern***. Although the spatial distribution of sulcal pits is relatively invariant across individuals, the global sulcal pattern- which means the global pattern of positioning, arrangement, number and size of sulcal folds and their inter-sulcal relationships - is complex and variable in human brains. Global sulcal pattern has been hypothesized to relate to optimal organization and arrangement of cortical functional areas and their white matter connections (Fischl et al., 2008; Klyachko and Stevens, 2003; Rakic, 2004; Sun and Hevner, 2014; Van Essen, 1997). Cortical areas do not develop independently but rather in relation to other functional areas. In an experiment on genetic manipulation during embryonic development, to decrease or increase the size of somatosensory and motor cortical areas resulted in significant deficiencies in tactile and motor behaviors (Leingartner et al., 2007). Such findings suggested that areas have an optimal size and position for maximum behavioral performance (Leingartner et al., 2007; O'Leary et al., 2007). Optimal arrangement of cortical functional areas can also be explained by an evolutionary design strategy that minimizes axonal length to reduce wiring costs and save energy and time when signaling between cortical areas (Kennedy et al., 1998; Klyachko and Stevens, 2003; Laughlin and Sejnowski, 2003; Van Essen, 1997). These aspects of early cortical functional organization might give rise to sulcal patterns, which show specific geometric and topological relationships of sulcal folds. A recent study found the significant link between sulcal anatomy and functional activation patterns in hand movement, silent reading, and reading (Sun et al., 2016). Abnormal patterns of cortical areas and their underlying white matter connections may affect cortical growth and expansion (Ronan and Fletcher, 2015; Van Essen, 1997; Welker, 1990), and possibly causing altered global sulcal patterns. Since the global pattern of primary gyri and sulci is prenatally determined and shows little change with age during postnatal cortex development (Cachia et al., 2016; Chi et al., 1977; Garel et al., 2001; Hill et al., 2010; Kostovic and Vasung, 2009; Meng et al., 2014; White et al., 2010), variations in global sulcal patterns may reflect variations in early brain development and manifest as individual variability in cognitive function, personality traits or psychiatric disorders.

There have been many approaches capturing various features of cortical folding, such as the gyrification index (GI), fractal dimension, curvature, sulcal depth, sulcal length, sulcal area, and sulcal fundus curves (Fish et al., 2016; Hill et al., 2010; Im et al., 2008; Im et al., 2006; Kao et al., 2007; Li et al., 2010; Lyu et al., 2010; Mangin et al., 2004; Pienaar et al., 2008;

Shi et al., 2008; Shimony et al., 2016; Zilles et al., 1988). However, they do not investigate the spatial, geometric and topological patterns of *sulcal* folding. Sulcal pattern variability was described in Ono's atlas by sulci categories based on the connection and interruption patterns to neighboring sulci (Ono et al., 1990). Using this categorization approach, superior temporal and anterior cingulate sulcal patterns were examined and the numbers of interruptions and folding segments in those sulci were shown to be associated with language amongst other cognitive functions (Cachia et al., 2014; Ochiai et al., 2004; Ono et al., 1990). Prior MRI studies have revealed abnormal sulcal arrangement, connection and interruption, or an unusual orientation in various disorders: schizophrenia (Kikinis et al., 1994; Nakamura et al., 2007), temporal lobe epilepsy (Kim et al., 2008), obsessive-compulsive disorder (Shim et al., 2009), bipolar disorder (Fornito et al., 2007), persistent developmental stuttering (Cykowski et al., 2008), and Turner syndrome (Molko et al., 2003). However, these sulcal pattern studies have been built around qualitative analysis methods based on visual inspection with observer-dependent criteria, which do not quantify relationships between sulcal segments, and categorizing the variable folding patterns is often beyond the capacity of the human visual function. This lack of quantification makes it difficult, complex, laborious, and time consuming to analyze sulcal patterns. To overcome this limitation, automatic categorization approach was suggested to cluster cortical folding patterns and extract and define the main patterns (Sun et al., 2009; Sun et al., 2007), but this cannot quantitatively compare sulcal patterns between individual brains over areas larger than one specific sulcus.

A novel comprehensive and quantitative analysis technique of sulcal patterns was recently developed that is complementary to previous methods (Im et al., 2011b). This analytical method enables global examination of primary sulcal patterning in 3D space, which is difficult to assess by visual inspection of 2D slice images. The sulcal pattern was represented as a graph structure with sulcal pits and catchment basins as nodes. Sulcal pattern graphs between different individuals were optimally matched, and automatically compared using a spectral-based matching algorithm based on a similarity measure (Im et al., 2011b; Leordeanu and Hebert, 2005). The sulcal pattern comparison was performed using not only geometric features of sulcal folds themselves (position, depth, and size of sulcal pits and basins) but also their inter-sulcal geometric and topological relationships, emphasizing the interrelated arrangement and patterning of sulcal folds (Im et al., 2011b) (Fig. 3). This method was applied to a twin MRI study to investigate the genetic effect on the sulcal patterns from the perspective of the sulcal pit-based graph approach. The similarity of the sulcal graphs in twin pairs was significantly higher than in unrelated pairs for all hemispheres and lobar regions, supporting a genetic influence on sulcal patterning (Im et al., 2011b). In another application on polymicrogyria, the graph-based sulcal pattern comparison method provided discrimination of abnormal cortical folding patterns and the means to quantitatively measure the severity and extent of involvement of cortical malformation in a subject. This method showed higher sensitivity in detecting abnormal regions than mean cortical curvature, a largely used traditional cortical measure (Im et al., 2013b). It also clearly defined the cortical areas affected by a noncoding mutation in the *GPR56* gene in polymicrogyria (Bae et al., 2014). In another recent study, atypical global sulcal patterns were found in parieto-temporal and occipito-temporal cortical regions in preschoolers/

kindergarteners with a familial risk of developmental dyslexia even before a clinical diagnosis, supporting atypical early cortical growth and genetics as bases for developmental dyslexia (Im et al., 2016). Quantitative sulcal pattern analytical method has proven effective for characterizing genetically influenced early cortical development. As this graph-based sulcal pattern analysis has raised an interest in studying the topography of the cortex, sulcal pattern clustering method based on sulcal pits graph has been suggested and has identified multiple distinct and representative patterns for central sulcus, superior temporal sulcus, and cingulate sulcus from a large-scale dataset of neonatal brain MR images (Meng et al., 2016). A new sulcal pits graph-based approach has been recently introduced to analyze spatial organization and pattern of sulcal folding and used to reveal significant gender difference and cortical asymmetry in sulcal pits pattern (Takerkart et al., 2017) (Table 1).

Early cortical folding patterns in human fetal brains

Cortical arealization and connectivity begin early in fetal brain development (O'Leary et al., 2007; Takahashi et al., 2012) and, if defective, might lead to atypical sulcal topology. Therefore, it has been of great interest to detect early abnormalities in fetuses destined to have abnormal sulcal patterns at birth and develop a useful tool for identifying the early signs of developmental brain disorders using MRI. One of the greatest challenges of fetal MRI has been unconstrained fetal motion. With the possibility to perform fast 3D fetal MRI *in vivo* and head motion correction using post-processing technique (Gholipour et al., 2010; Keraudren et al., 2014; Kim et al., 2010; Kuklisova-Murgasova et al., 2012), previous MRI studies have quantified cortical growth and folding development in human fetal brains. The temporal changes of GI were observed during fetal life (Lefevre et al., 2016), and cortical surface curvatures and sulcal depth at the global level have been measured to quantify the overall degree of cortical folding from 22–39 weeks of gestational age (Clouchoux et al., 2013; Clouchoux et al., 2012; Dubois et al., 2008; Hu et al., 2013; Lefevre et al., 2016; Wright et al., 2014; Wu et al., 2015). The curvature and depth changes of cortical folding and local cortical expansion at the vertex level have also been observed using volume- or surface-based registration techniques (Clouchoux et al., 2013; Habas et al., 2012; Schwartz et al., 2016; Scott et al., 2013).

Unlike these prior studies, a quantitative sulcal pattern analysis technique using a sulcal pit-based graph structure has been recently used to examine the interrelated arrangement and global patterning of early primary cortical folds in human fetal brains (Im et al., 2017; Tarui et al., 2017). Sulcal pattern graphs of 9 normal fetal brain templates from 23 to 31 weeks of gestational age (Serag et al., 2012) were constructed and used as references to analyze individual fetal brains. Each individual fetal brain was quantitatively compared with the normal template brains and the sulcal pattern similarities to the templates were measured, which ranged from 0 to 1 (Fig. 4). A low similarity to the normal templates reflected high deviation from the normal sulcal pattern. The sulcal pattern similarities to the templates were compared between healthy fetuses and fetuses with brain abnormalities, with similarities significantly reduced in all abnormal individual fetuses compared to normal fetuses (Im et al., 2017). On the other hand, GI was not significantly different between the normal and abnormal groups (Im et al., 2017) (Fig. 5). In this pilot study, the sulcal pattern analysis approach outperformed the traditional GI in terms of sensitivity. This suggests that in brain

abnormalities associated with abnormal cortical folding, geometric and topological patterning of sulcal folds is more altered than the overall amount of cortical folding during early fetal brain development. Furthermore, in some abnormal cases, this quantitative analysis identified an abnormal sulcal pattern that was confirmed postnatally which was not detected in a qualitative fetal MRI assessment, showing higher sensitivity than qualitative visual assessment (Im et al., 2017) (Fig. 5).

The same fetal sulcal pattern analysis was applied on another brain malformation: “isolated” agenesis of corpus callosum, ACC, clinically diagnosed to have no cortical malformations and no other abnormalities. The hypothesis was that ACC and associated aberrant white matter organization might influence cortical folding and alter sulci patterning (Tarui et al., 2017). Indeed, disorganized patterns of early sulcal position in fetuses with ACC were found compared to healthy fetuses, showing significant alterations in absolute sulcal positions and relative inter-sulcal positional relationship (inter-sulcal vector). Positional identity of cortical functional regions is defined by the combinatorial expression pattern of various genes, with their areal expansion also under tight genetic control with distinct spatiotemporal characteristics (Chen et al., 2012; Miller et al., 2014; O'Leary et al., 2007; Stahl et al., 2013). Therefore, atypical patterns of sulcal locations in fetal brains prior to 30 weeks of gestational age are likely associated with defects in genetic control of cortical arealization and expansion. Again, GI could not detect aberrant sulcal development in ACC due to its intrinsic limitations. By definition, GI would sensitively detect sulcal aberrations when sulcal morphology is altered by area or depth. If sulcal aberrations are limited to the position of the sulci without affecting their depth or area, as shown in fetuses with ACC, GI may not detect such alterations (Fig. 6). These results revealed that even in the case of “isolated” ACC, there were more global alterations in cortical folding positions that were already present as early as the second trimester and continued throughout the fetal period (Tarui et al., 2017). As the traditional GI is a global index measured for the whole brain, local GI at the surface vertex level (Li et al., 2014; Schaer et al., 2008) should be compared with the sulcal pattern analysis technique for a future study. In summary, the graph-based quantitative sulcal pattern analyses in fetal brains demonstrated the feasibility and potential to detect emerging subtle abnormalities in cerebral cortical growth in early fetal stages that are difficult to detect using traditional cortical measures or via visual inspection.

Limitations and future works in cortical folding study on the developing human brains

MRI-based sulcal pattern analysis on the fetal brains is not free from limitations. Although fetal head motion in MRI can be corrected using image-processing technique (Gholipour et al., 2010; Keraudren et al., 2014; Kim et al., 2010; Kuklisova-Murgasova et al., 2012), MRI data can still be excluded due to low quality imaging with severe fetal head motion and low signal-to-noise ratio (SNR) and failure in the post-processing stages for head motion correction. Another limitation is the delay in the detection of cerebral sulci in MRI studies. Identification of some early sulci lags behind histopathology due to the limitation of fetal MRI resolution and contrast, and accuracy of image post-processing (Chi et al., 1977; Garel et al., 2001; Habas et al., 2012; Im et al., 2017; Nishikuni and Ribas, 2013; Rajagopalan et

al., 2011; Tarui et al., 2017; White et al., 2010). For example, one small sulcus, the olfactory sulcus, was reported to appear before 20 weeks (Chi et al., 1977; White et al., 2010), but it was not identified at such an early stage in MRI studies (Clouchoux et al., 2013; Garel et al., 2001; Habas et al., 2012; Im et al., 2017; Tarui et al., 2017). Advances and accelerations in fetal MRI acquisition with higher spatial resolution at equivalent SNR without or minimizing motion degradation and advancements in post-processing techniques will improve the success rate for volume reconstruction and detection of the early developing sulci.

Although cortical folding studies have been increasingly performed in fetal brains, spatio-temporal patterns and individual variability of early cortical folding in normal fetal brains are not fully quantified and understood because of low sample size and the lack of advanced analysis technique. The number of subjects must be enough to get a confident statistical variation for each gestational week from the second trimester of pregnancy when cerebral cortical fissures appear. For a high-quality, comprehensive map of the spatio-temporal cortical folding dynamics, inter-sulcal geometric and topological relationships as well as geometric sulcal features themselves need to be examined using multiple and multi-level cortical measurements. Normal spatio-temporal cortical folding patterns will provide valuable reference knowledge for analyzing individual clinical fetal MRIs and assisting clinical diagnosis and interpretation of abnormal cortical growth. Moreover, to the best of our knowledge, prior quantitative fetal MRI studies in human fetuses are exclusively cross-sectional. Analysis of fetal cortical structure at a single time point during the rapid growth phase of brain size and folding is susceptible to large inter-subject variability and may lack power to understand the developmental trajectories of normal and abnormal cortical folding. There is no knowing if abnormal cortical structure identified during fetal life is transient, persistent, or further diverges from normal pattern until postnatal stage. Since fully formed primary sulcal patterns are observed at early postnatal stage, other important step is to examine longitudinal trajectories of cortical folding development from fetal stage to neonatal/infant stage using innovative MRI measures. However, there has not been a perfect automatic processing pipeline of structural MRI for ages lower than 60 months due to incomplete myelination and the resulting low tissue contrast as well as differences in head size, motion artifacts, and image quality. The most challenging part in a longitudinal study during these stages will be to secure the sample size for sufficient statistical power by successfully acquiring longitudinal MRI and processing neonatal/infant MRI with a reliable tool.

Since neurodevelopmental disabilities associated with abnormal brain development may have a prenatal origin, it is highly important to explain a significant component of postnatal neurodevelopmental outcomes and create a predictive model for neurodevelopmental disability risk in developmental brain disorders from early fetal life. However, there are no validated fetal MRI measures of early brain development that explain postnatal neurodevelopmental outcomes in healthy normal and abnormal fetuses.

Future studies will be aimed at better understanding spatio-temporal patterns and individual variability of fetal cortical folding using innovative MRI techniques in a large, longitudinal cohort, and predicting postnatal neurodevelopmental disability risk from early fetal life for

individual subjects. Furthermore, as genetics has been suggested to be highly influential on the geometric and topological pattern of early cortical folds, genetic variants and/or alterations in gene expression need to be examined and their associations with cortical folding patterns determined. This will enhance our understanding of neural mechanisms of abnormal cortical growth in developmental brain disorders.

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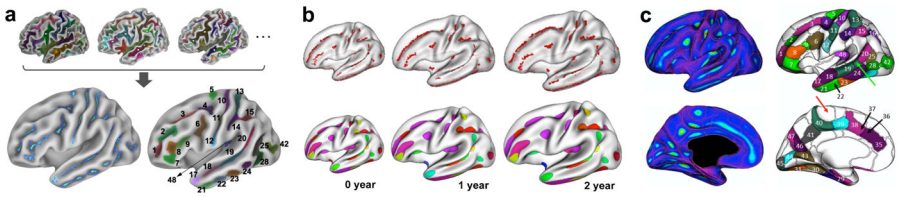

Fig. 1.

The group maps of sulcal pits from three studies. (a) Sulcal pit extraction for individual brains, and the distribution and cluster maps of sulcal pits from 148 normal adult brains (Im et al., 2010). (b) Spatial distribution of sulcal pits from 73 infants at 0, 1, and 2 years of age (Meng et al., 2014). (c) The group density and cluster maps of sulcal pits from 137 subjects (Auzias et al., 2015).

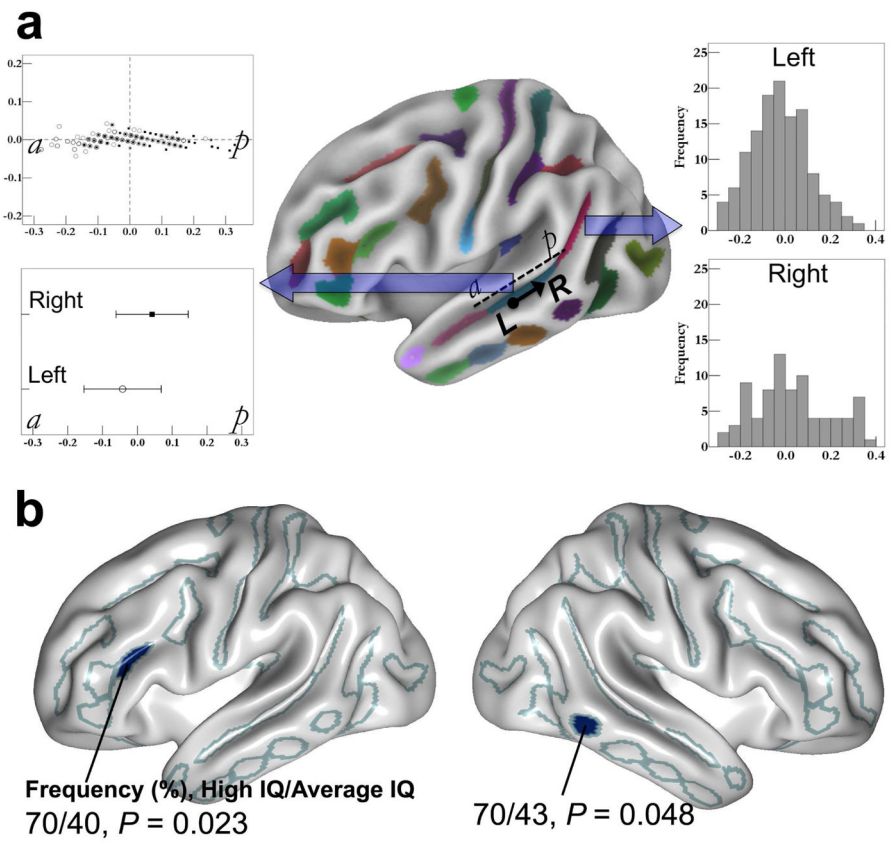

Fig. 2.

(a) Asymmetric spatial variance and distribution of sulcal pits in the superior temporal sulcus. The spatial variance of the pits in the right hemisphere is greater than that in the left hemisphere in the posterior superior temporal sulcus. The sulcal pits in the left are distributed in a more anterior region along the sulcal line compared with those in the right. (b) Significantly greater frequency of sulcal pits in high verbal intelligence group in the regions of left posterior inferior frontal and right posterior inferior temporal sulci. This figure is reproduced from (Im et al., 2011a; Im et al., 2010).

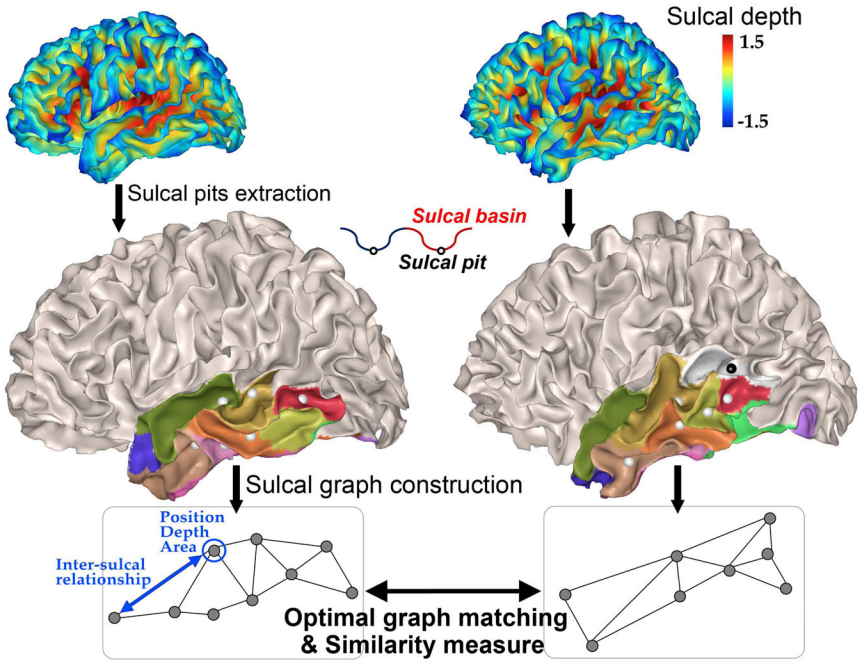

Fig. 3.

Sulcal pits and their sulcal catchment basins are identified on the white matter surface using the watershed segmentation applied to sulcal depth map. Each sulcal pit corresponds to a node in the graph structure. Two sulcal graphs are optimally matched and their similarity is measured by using the geometric features of nodes (3D position, depth and area of sulcal basin) and their relationship. The sulcal basins paired by matching are marked with the same color and unmatched sulcal pits are colored black. This figure is reproduced from (Im et al., 2013b).

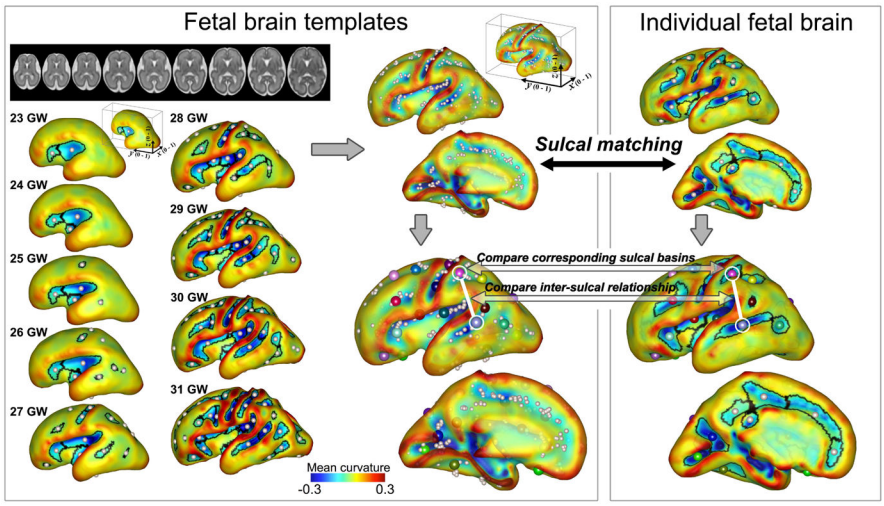

Fig. 4.

Sulcal basins of the individual fetal brain are identified on the cortical plate surface and optimally matched and compared with the set of sulcal folds generated from 9 fetal brain templates (23–31 gestational weeks). The spheres with the same color represent the matched corresponding sulcal basins between the templates and individual brain. Sulcal pattern similarity to the templates is measured for the individual brain. This figure is reproduced from (Tarui et al., 2017).

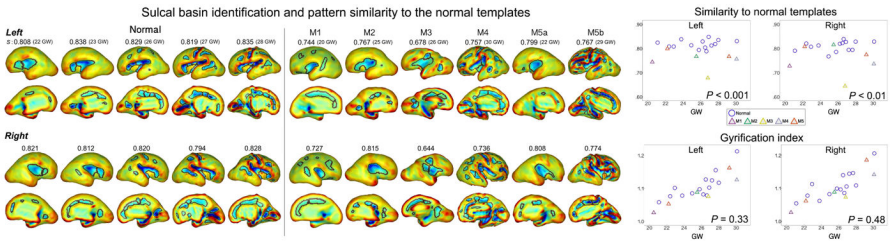

Fig. 5.

Sulcal pattern similarity (*S*) to the templates measured with the whole set of features for 5 normal and abnormal fetal brains (M1–5). The fetuses with abnormal brains show significantly lower sulcal pattern similarities to the templates compared with the normal fetuses in both hemispheres. On the other hand, GI is not statistically different between the normal and abnormal fetal groups in either hemisphere. This figure is reproduced from (Im et al., 2017).

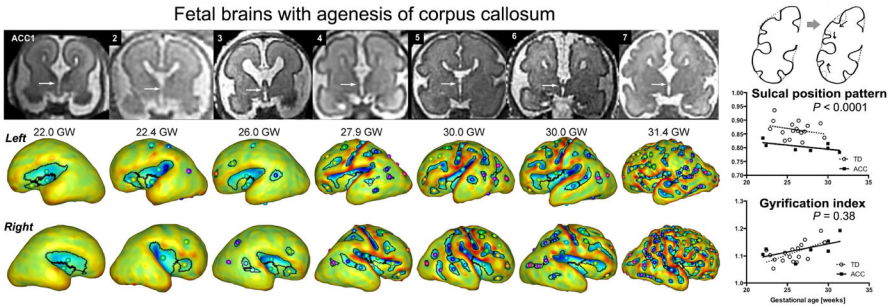

Fig. 6.

Sulcal positional pattern similarities to the templates are lower in fetuses with ACC compared to normal fetuses ranged from 22 to 31 gestational weeks. GI is not statistically different between the normal and ACC fetal groups. This figure is partially reproduced from (Tarui et al., 2017).

Table 1

Sulcal pit and pattern studies and findings

Sulcal pit extraction and analysis studies			
Study	**Subjects**	**Age**	**Study aims and findings**
Lohmann et al., Cereb Cortex 2008	96 right-handed healthy subjects (males/females, 48/48)	29.2 (mean), 18 – 60 (range) years	- Sulcal pit extraction on volume image - Regular spatial arrangement of sulcal pits - 11 major and 12 minor sulcal pit clusters in the lateral brain area
Im et al., Cereb Cortex 2010	148 healthy subjects (83/65): 124 right-handed, 15 left-handed, 9 unknown	25.0 ± 4.9 (mean ± SD), 18 – 44 years	- Sulcal pit extraction on the whole-brain cortical surface - Invariant spatial distribution of sulcal pits (high frequency and density in specific focal areas) - 48 and 47 sulcal pit clusters in the left and right hemispheres respectively - Asymmetry in the frequency and spatial variance of sulcal pits in the superior temporal, postcentral, calcarine, and parieto-occipital sulci
Im et al., Neuroimage 2011a	78 healthy subjects (39/39)	22.7 ± 1.9, 17.6 – 27 years	- Studying the relationship between the presence of sulcal pits and intelligence - Higher sulcal pit frequency in the left posterior inferior frontal sulcus and the right posterior inferior temporal sulcus in high verbal intelligence group
Im et al., PLoS One 2013a	10 healthy subjects (7/3)	26.1 ± 2.9 years	- Reliability test of sulcal pit extraction from MRI - High reliability of Im's sulcal pit extraction method according to different scan session, scanner, and surface extraction tool (MNI and FreeSurfer pipelines)
Meng et al., Neuroimage 2014	73 healthy infants (42/31) 64 healthy adults (29/35)	Longitudinal design 0 year, 25.5 ± 10.8 days 1 year, 392.8 ± 22.1 days 2 years, 758.1 ± 38.1 days 18.9 ± 1.4 years	- Longitudinal analysis of spatial distribution of sulcal pits from healthy infants - 54 sulcal pit clusters - Relatively stable sulcal pit distribution in the first 2 years of life consistent with the distribution in young adults - Asymmetry of sulcal pit distribution in the central, superior temporal, and postcentral sulci. - Consistently deeper sulcal pits in males than in females
Auzias et al., Neuroimage 2015	137 right-handed healthy subjects (69/68)	18 – 34 years	- Algorithmic improvement in the extraction of sulcal pits - 104 and 114 sulcal pit clusters in the left and right hemispheres respectively - Asymmetry in sulcal pits frequency in the parietotemporal region, insula, anterior cingular region, medial frontal gyrus, cuneus and collateral sulcus
Guen et al., Cereb Cortex 2017	897 healthy subjects	28.8 ± 3.7, 22 – 37 years	- Estimation of the heritability of the sulcal pits depth - Highly heritable sulcal pits depth in the central, cingulate, collateral, occitotemporal, parieto-occipital, and superior temporal sulci
Sulcal pit-based sulcal pattern analytical methods			
Im et al., Neuroimage 2011b	48 healthy subjects (20/28)	20.7 ± 1.8, 18.3 – 24.9 years	- Quantitative sulcal pattern comparison using sulcal pits graph - Higher similarity of the sulcal graphs in twin pairs than in unrelated pairs
Meng et al., Med Image Comput Comput Assist Interv 2016	677 healthy neonates	---	- Sulcal pattern clustering based on sulcal pits graph - Identification of multiple distinct and representative patterns for central sulcus, superior temporal sulcus, and cingulate sulcus

Sulcal pit extraction and analysis studies			
Study	**Subjects**	**Age**	**Study aims and findings**
Takerkart et al., Med Image Anal 2017	134 right-handed healthy subjects (67/67)	18 – 34 years	- Structural Graph-Based Morphometry (SGBM): Automatic brain morphometry method based on the spatial organization of sulcal pits - Gender difference and cortical asymmetry analyses using the SGBM