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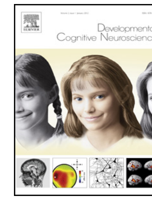

Longitudinal stability of the folding pattern of the anterior cingulate cortex during development

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ABSTRACT

Prenatal processes are likely critical for the differences in cognitive ability and disease risk that unfold in postnatal life. Prenatally established cortical folding patterns are increasingly studied as an adult proxy for earlier development events – under the as yet untested assumption that an individual's folding pattern is developmentally fixed. Here, we provide the first empirical test of this stability assumption using 263 longitudinally-acquired structural MRI brain scans from 75 typically developing individuals spanning ages 7 to 32 years. We focus on the anterior cingulate cortex (ACC) – an intensely studied cortical region that presents two qualitatively distinct and reliably classifiable sulcal patterns with links to postnatal behavior. We show – without exception–that individual ACC sulcal patterns are fixed from childhood to adulthood, at the same time that quantitative anatomical ACC metrics are undergoing profound developmental change. Our findings buttress use of folding typology as a postnatally-stable marker for linking variations in early brain development to later neurocognitive outcomes in *ex utero* life.

1. Introduction

Analysis of brain anatomy from in vivo structural magnetic resonance imaging (sMRI) has become a major tool in biological psychiatry and psychology. Disorders like schizophrenia and autism spectrum disorder, as well as traits like general cognitive abilities, have been linked to variation in diverse neuroanatomical features in postnatal life (Giedd and Rapoport, 2010; Kanai and Rees, 2011). However, there is a growing awareness that prenatal processes are likely to be critical for the differences in cognitive ability (Raznahan et al., 2012; Shenkin et al., 2004; Walhovd et al., 2012) and disease risk (Schlotz and Phillips, 2009) that unfold in postnatal life. Recognition of this has driven the search for neuroimaging features in late postnatal life that could serve as a proxy for earlier developmental events. A leading candidate in this effort has been typologies of cortical folding (Mangin et al., 2010; Sun et al., 2009).

Unlike *quantitative* features of the cortical sheet, such as thickness, surface area (Giedd and Rapoport, 2010) and curvature/gyrification (Armstrong et al., 1995; Li et al., 2014; Raznahan et al., 2011; White et al., 2010) – which can take decades to attain the levels observed in adulthood–the *qualitative* pattern formed by the characteristic set of primary, secondary and tertiary folds, or sulci, seen in human adulthood is already evident at birth (Chi et al., 1977; Mangin et al., 2010; Zilles et al., 2013). Inter-individual variation in this qualitative sulcal pattern–a classic example being the presence of a single or double parallel type of the ACC (Ono et al., 1990), determined between 10 and 15 weeks of fetal life (Chi et al., 1977) and present in 76 and 24% of adults respectively – has therefore been used as a marker for prenatal differences. Thus, ACC folding pattern has been linked to a host of cognitive domains including executive control (Cachia et al., 2014; Fornito et al., 2004), reality monitoring (Buda et al., 2011), temperament (Whittle et al., 2009) and social cognition (Fujiwara et al., 2007). The inference of these studies has been that observed qualitative differences reflect a constraint imposed by early neurodevelopmental processes on

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the subsequent abilities. However, a critical and as yet untested developmental assumption – upon which existing and future studies of sulcal pattern typology as an early developmental marker necessarily rest – is that the folding typologies are stable across postnatal brain development.

Here, we provide the first empirical test of this stability assumption using 263 magnetic resonance imaging (MRI) brain scans, taken from 75 healthy people longitudinally followed from 7 to 32 years. We focus on the ACC because it is a cortical region that presents two qualitatively distinct sulcal patterns (Ono et al., 1990) that can be easily and reliably classified with structural MRI from childhood (Cachia et al., 2014) to adulthood (Paus et al., 1996; Yucel et al., 2001). We evaluate the longitudinal stability of the ACC sulcal pattern from late childhood to adulthood, a developmental window characterized by significant structural remodeling of the brain as shown by the drastic ACC cortical thickness, surface area and curvature changes with time during this period (Hogstrom et al., 2013; Shaw et al., 2008). We complement our analysis of the longitudinal sulcal pattern stability by also investigating the longitudinal changes in cortical thickness.

2. Material and methods

2.1. Participants

Seventy five healthy participants (age range: 7.88–32.8 years old; age at first scan: 7.88–25.5 years old; age latest scan: 10.38–32.8 years old), including 26 females and 49 males, were selected from a larger prospective study (Giedd et al., 1999) on brain development at the National Institute of Mental Health (NIMH) based on the presence of at least two longitudinally acquired brain scans per subject (Fig. 1). Participants were free of lifetime medical or psychiatric disorders, which were determined through clinical examination and standardized interview. Psychiatric illness in a first degree relative was also exclusionary. Further details on this sample has been described previously (Giedd et al., 1999). The research protocol was approved by the NIMH institutional review board. Written informed consent was obtained from parents and controls older than 18 years, and written informed assent was obtained from minors.

2.2. MRI acquisition

All structural magnetic resonance imaging (sMRI) brain scans were T-1 weighted images with contiguous 1.5 mm axial slices, obtained on the same 1.5-T General Electric (Milwaukee, WI) Signa scanner using a 3D spoiled gradient recalled echo sequence with the following parameters: Echo time, 5 ms; Repetition time, 24 ms; flip angle 45 (DEG); acquisition matrix, 256 × 192; number of excitations, 1; and field of view, 24 cm. Head placement was standardized as previously described (Castellanos et al., 2001).

2.3. Sulcal segmentation

Sulcal segmentation was performed with BrainVISA 4.2 software using the Morphologist toolbox (http://brainvisa.info). An automated pre-processing step skull-stripped T1 MRIs and segmented the brain tissues. No spatial normalization was applied to MRIs to overcome potential bias that may result from the sulcus shape deformations induced by the warping process. The cortical folds were automatically segmented throughout the cortex from the skeleton of the gray matter/cerebrospinal fluid mask, with the cortical folds corresponding to the crevasse bottoms of the 'landscape', the altitude of which is defined by its intensity on the MRIs. This definition provides a stable and robust sulcal surface definition that is not affected by variations in cortical thickness or gray matter/white matter contrast (Mangin et al., 2004). For each participant, images at each processing step were visually checked. No segmentation error was detected.

2.4. ACC classification

Analyses of ACC typology stability were carries out using the first and last scan available for each subject (i.e. total number of scans = 150). The sulcal pattern of the dorsal part of the ACC was visually assessed using three-dimensional, mesh-based

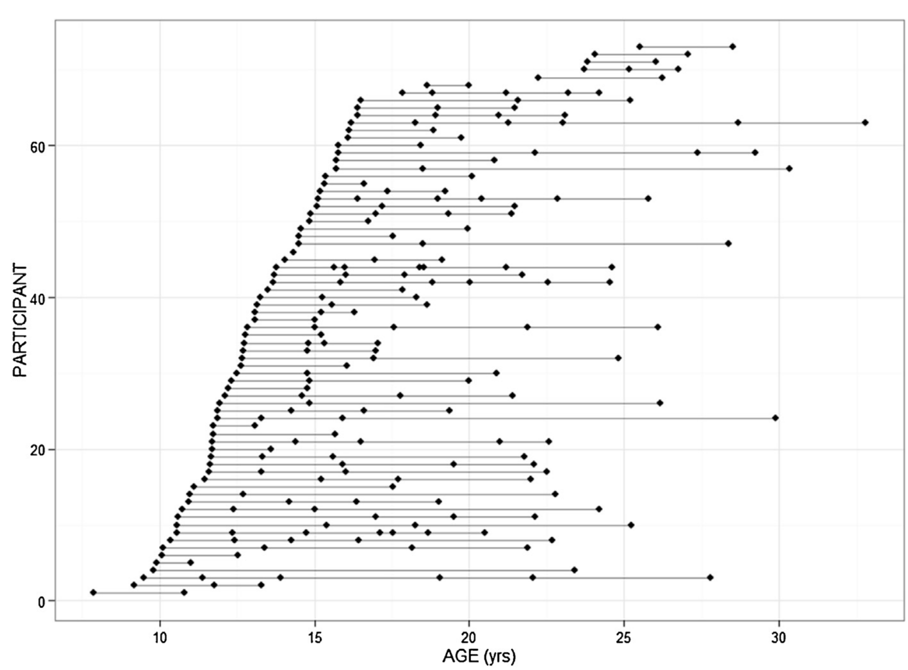

Fig. 1. Participant age at scan. Each dot represents a participant scan. Each line represents a participant with repeated scans.