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Adolescent maturation of the relationship between cortical gyrification and cognitive ability

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A B S T R A C T

There are changes to the degree of cortical folding from gestation through adolescence into young adulthood. Recent evidence suggests that degree of cortical folding is linked to individual differences in general cognitive ability in healthy adults. However, it is not yet known whether age-related cortical folding changes are related to maturation of specific cognitive abilities in adolescence. To address this, we examined the relationship between frontoparietal cortical folding as measured by a Freesurfer-derived local gyrification index (lGI) and performance on subtests from the Wechsler Abbreviated Scale of Intelligence and scores from Conner's Continuous Performance Test-II in 241 healthy adolescents (ages 12–25 years). We hypothesized that age-related lGI changes in the frontoparietal cortex would contribute to cognitive development. A secondary goal was to explore if any gyrification-cognition relationships were either test-specific or sex-specific. Consistent with previous studies, our results showed a reduction of frontoparietal local gyrification with age. Also, as predicted, all cognitive test scores (i.e., Vocabulary, Matrix Reasoning, the CPT-II Commission, Omission, Variabiltiy, *d*') showed age × cognitive ability interaction effects in frontoparietal and temporoparietal brain regions. Mediation analyses confirmed a causal role of age-related cortical folding changes only for CPT-II Commission errors. Taken together, the results support the functional significance of cortical folding, as well as provide the first evidence that cortical folding maturational changes play a role in cognitive development.

1. Introduction

Human brain anatomy consists of characteristic folds that form sulci and gyri within the cerebral cortex (see Striedter et al. (2015) for recent review). The degree of cortical folding, or gyrification (Zilles et al., 1989, 2013), can be measured on scans obtained by magnetic resonance imaging (MRI) by the ratio of the total folded cortical surface over the perimeter of the brain (Zilles et al., 1988). Regionally-specific gyrification also can be quantified using 3-dimensional measurements of the ratio of a vertex-based 25 mm radius circular region of interest of folded pial surface to the corresponding surface area of a tight-fitting contour enveloping the cortex's outer perimeter (Schaer et al., 2008). Such measurements are typically termed local gyrification indices (lGI). Studies that used such approaches have confirmed all brain regions are folded to some extent. Brain regions with the greatest gyrification are found in the prefrontal cortex and temporal-parietal cortex association regions (Zilles et al., 2013). Theories argue that gyrification reflects underlying structural connectivity as evidenced by the association between gyrification and measures of cortical connectivity, both functional (Dauvermann et al., 2012) and structural (Schaer et al., 2013). Cortical folding is believed to be related to more efficient communication as surface area expands in the developing brain (Laughlin and Sejnowski, 2003). Importantly, there is evidence that gyrification undergoes developmental changes. Changes from a lissencephalic brain to more complex gyrencephalic structure begin *in utero* (Sun and Hevner, 2014). Although the most striking cortical folding changes occur during the third trimester of pregnancy, gyrification continues to change in different ways throughout the first decades of life. After a peak in toddlerhood, both global and local measures of gyrification in frontal, temporal, parietal and occipital cortices gradually decrease throughout adolescence into the early adult years (Aleman-Gomez et al., 2013; Klein et al., 2014; Mutlu et al., 2013; Raznahan et al., 2011a; Su et al., 2013).

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While some researchers seek to understand the underlying neurophysiological processes and resultant biomechanics that cause the cortex to fold or unfold in characteristic ways across development (Bayly, 2014; Striedter et al., 2015; Sun and Hevner, 2014), an equally important question involves the functional significance of cortical folding and its developmental changes. Inter-species comparison suggests that larger brain surface area yielded by greater overall cortical folding might support the higher intelligence seen in primates and cetaceans (Roth and Dicke, 2005, 2012). Supporting this idea, there is evidence that gyrencephalic malformations are associated with cognitive impairment (Guerrini and Carrozzo, 2001; Guerrini et al., 2003). Emerging research also has found an association between variations in regional gyrification and specific cognitive abilities in adults. Following an early report that lateralization differences in gyrification were linked to executive cognition (Fornito et al., 2004), several studies have asked if local gyrification corresponds with cognitive ability. In one such study, intelligence scores were positively correlated with a curvature-based measure of temporal-occipital lobe regions (Luders et al., 2008). Greater gyrification in adults' bilateral medial and superior frontal cortex has been linked to better verbal working memory and mental flexibility task performance (Gautam et al., 2015). The most recent study of a large sample found lGI in lateral prefrontal cortex, cingulate, insular cortices, inferior parietal lobule, temporoparietal junction regions, and fusiform gyrus was positively associated with a composite measure of general cognitive ability, or "*g*" in both samples of healthy adults and of children and adolescents (Gregory et al., 2016).

Collectively these studies most often implicate gyrification in frontal and parietal lobe cortices in relation to cognitive ability. The reasons for these associations between individual differences in local gyrification and cognitive ability are not well understood. Similar brain-behavior relationships have been found in these regions when examining brain activation using functional neuroimaging. Lateral prefrontal and posterior parietal cortex form specialized neural networks engaged for various goal-directed cognitive tasks requiring executive oversight and control (Braver, 2012; Dosenbach et al., 2008; Vakhtin et al., 2014; Zanto and Gazzaley, 2013). In particular, lateral prefrontal cortex appears to be a core region in this network, as its functional connectivity and aspects of its structure are important to general cognitive control (Cole et al., 2015; Cole and Schneider, 2007), overall intelligence (Jung and Haier, 2007), and various executive functions (Fuster, 2002; Sakagami and Watanabe, 2007; Yuan and Raz, 2014).

Associations like these raise the possibility that individual differences in local frontoparietal gyrification might causally contribute to gains in specific types of cognitive task performance across development by virtue of neurobiological advantages in brain structure that have yet to be fully described or understood. Adolescent maturation is a useful framework to better understand if gyrification causally contributes to cognitive function because both brain structure and cognitive abilities change in characteristic developmental trajectories. Although executive and attention abilities are at near-adult levels by puberty, numerous studies describe they continue to be refined (Nguyen et al., 2016) and improve in various ways until about ages 15 to 17 (Best, 2010; Murty et al., 2016). These developmental trajectories offer a quasi-experimental context wherein one can determine if gyrification-cognition relationships differ across stages of adolescent cognitive development to see if decreasing regional gyrification has a functional impact on cognitive ability. If local changes to gyrification play a causal role in typical maturational gains, associations between specific frontoparietal gyrification values and cognitive abilities should show a meaningful developmental profile. For instance, there might be a gradual linear increase in the strength of relationships between regional lGI and cognitive test performance throughout adolescent development, ultimately resembling adult profiles. Alternatively, the youngest adolescents might show disorganized relationships between local gyrification and cognitive performance, which could shift around mid-adolescence when cognitive gains typically plateau. Regardless, if adolescent lGI maturation contributes to cognitive development, relationships between regional lGI and cognitive ability should differ across adolescence, and those differences should be causally significant.

This study asked if the normative reduction in cortical gyrification that occurs in many brain regions throughout adolescence contributes to adolescent cognitive maturation. If so, the descriptive results can contribute towards theory-building and hypothesis-generation to better understand the specific neurobiological basis of gyrification-cognition relationships. We tested this developmental hypothesis using a mix of statistical moderation and mediation analyses to examine the relationship between local gyrification and various cognitive tests that quantified verbal and nonverbal intellectual ability, sustained attention, inhibitory control, motor response variability, and perceptual sensitivity. The moderation analyses identified which brain regions had different relationships between cortical gyrification and test performance at different ages, then mediation analyses tested whether gyrification at each regional peak exerted a causal influence on the relationship between age and test performance. It is useful to consider several different cognitive domains to ascertain whether any such maturational relationships between gyrification and test performance are commonly found, or are selective to specific cognitive abilities. A secondary objective was to characterize sex-specific gyrification differences in adolescence, including any influence of sex on gyrification maturation and the relationships between gyrification change and cognitive change. Different brain regions have gyrification sex differences during different developmental periods. Greater gyrification variably has been linked to left lateral prefrontal, occipital and right inferior temporal regions in infant girls (Kim et al., 2016), left paracentral cortex and precuneus cortex in two year-old boys (Li et al., 2014) and right prefrontal cortex in the period of 6–30 years old (Mutlu et al., 2013). As previous findings have been so mixed, we made no *a priori* hypotheses for gyrification sex differences or for interactions of sex and age throughout adolescent-to-young adult development. Instead, we used a statistical inference framework adequate for searching the whole brain. Finally, given increasing recognition of how important it is to replicate prior neuroimaging results (Barch and Yarkoni, 2013), we attempted to confirm regional gyrification decreases from puberty until early adulthood observed in prior studies (Klein et al., 2014; Mutlu et al., 2013; Raznahan et al., 2011b) and the association of frontoparietal gyrification with individual differences in overall intelligence and general cognitive ability found in adults (Gregory et al., 2016; Luders et al., 2008).

2. Methods

2.1. Participants

A total of 244 healthy adolescents and young adults with no history of neurological or psychological illness collected from two separate NIMH-funded neuroimaging studies R01MH080956 ($n = 106$) and R01MH081969 ($n = 138$) performed at the Olin Neuropsychiatry Research Center. Among them, three participants having poor quality were not included (see below for more details about quality control). Thus, a final sample was 241 healthy participants (age range 12–24 years, mean 17.38 (±3.33), 116 females). No participants were left-handed. Participants were recruited by community advertisements. Informed consent for study participant and parental permission were obtained both from the participants and a parent. The Hartford Hospital Institutional Review Board approved all consents and study procedures. The participants' lack of psychiatric diagnoses was confirmed using the Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version (K-SADS-PL; Paus et al. (2008) using standard administration guidelines. Semi-structured interviews were conducted by trained staff. Diagnostic decisions were made in weekly consensus meetings supervised by a licensed clinical psychologist with over 14 years of experience using the K-SADS-PL (MCS).