Parental Age Effects on Cortical Morphology in Offspring

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Introduction

People in Western countries are having children later in life: In the 1970s, the average ages for mothers and fathers were 26.4 years and 29.2 years, respectively which increased to 29.3 years and 32.1 years by 2002 (Bray et al. 2006). This trend has public health implications as advanced maternal age (usually defined as over 35 years) is associated with mental retardation syndromes including Down’s syndrome (Penrose 1967) and advanced paternal age is associated with lower intelligence (Saha et al. 2009) and elevated risk for neuropsychiatric disorders such as autism (Reichenberg et al. 2006; Cantor et al. 2007), Apert syndrome (Tolarova et al. 1997), hydrocephalus (Savitz et al. 1991), and schizophrenia (Malaspina et al. 2001). At the other end of the age spectrum, there are risks associated with younger parental age, operating independently of factors such as socioeconomic status. For example, younger maternal and in some studies, paternal age is associated with a child being less intelligent (Malaspina et al. 2005; Saha et al. 2009) and having more behavior problems (Fergusson and Woodward 1999; Jaffe et al. 2001). This implies a curvilinear effect of parental age with both age extremes associated with worse neurocognitive outcomes in children. Little is known of the neurobiology which might underpin these effects, particularly in humans. Here using data from a cohort of typically developing children, we examine the links between parental age with an offspring’s cortical volumes, testing the hypothesis that these links will be also be curvilinear with smaller volumes at age extremes, analogous to previous reports of associations between parental age extremes and suboptimal neurocognitive outcomes.

The determinants of cortical volume are complex and discussed later. In prenatal life, processes of proliferation and migration of neurons are critical (Rakic 1988; Rakic et al. 2009; Clowry et al. 2010), whereas postnatally, changes in morphology of dendrites, terminal axons, synapses, and supporting glial cells are pivotal determinants of cortical dimensions (Petanjek et al. 2008). Of particular relevance to the current study, there is increasing evidence that the constituents of cortical volume—cortical thickness and surface area—may be partially biologically distinct. According to the radial unit hypothesis of cortical development, cells within cortical columns share a common origin and migrate to their location during development (Rakic 1988; Rakic et al. 2009; Clowry et al. 2010). Cortical surface area is thought to be driven by the number of columns, whereas cortical thickness is determined by the number of cells within a column. Support for this hypothesis comes from demonstrations that the components can be manipulated independently in nonhuman animals (Pontious et al. 2008). Additionally, human twin studies suggest distinct genetic control of cortical thickness and area (Panizzon et al. 2009), and in vivo neuroimaging studies of healthy young adults suggest that while both cortical thickness and area are organized as networks, these networks have quite distinct organizational properties (Sanabria-Díaz et al. 2010). Finally, selective disruption of cortical surface area but not thickness has been linked with neurodevelopmental disorders such as dyslexia and autism (Frye et al. 2010; Raznahan et al. 2010). We thus complement our delineation of the impact of parental age on cortical volumes with a consideration of the possibility of differential effects of maternal and paternal age on cortical surface area and thickness.

We hypothesized that parental age would have a curvilinear effect on brain dimension—with smaller volumes in offsprings’ brains associated with parental age extremes, in keeping with a similar effect of parental age extremes on suboptimal neurocognitive outcomes in offspring.

Materials and Methods

One hundred and seventy-one children and adolescents (95 males and 76 females) from 106 separate families were studied. All were singleton births. Each child completed the Childhood Behavior Checklist as a screening tool and then underwent a structured diagnostic interview by a child psychiatrist to rule out any psychiatric or neurological diagnoses (Giedd et al. 1996). Intelligence quotients were determined from age appropriate versions of the Wechsler Intelligence Scales.
Familial Socioeconomic Status (SES) was assessed using the Hollingshead Two-Factor Index (Hollingshead and Redlich 1958), which provides a single score that is an index of the educational and occupational level of the head of the household. The scale ranges from a score of 20 indicating the head of household has a professional occupation with postgraduate level education, to 134 indicating that the head of household is an unskilled manual laborer with less than 7 years of education. For all subjects, the ages of both the biological mother and the father at the time of the child’s birth were obtained. No cases of technologically assisted pregnancies, such as in vitro fertilization were included. All offspring had had at least one neuroanatomic magnetic resonance imaging (MRI) scan, 131 (77%) had at least 2 scans, and 88 (51%) had 3 or more scans. The overall mean age of offspring age at scan acquisition was 13.1 years (standard deviation [SD] 4.3) and the age range was 4–22 years. All minors gave assent and their parents gave written informed consent for the study.

Three-dimensional images with contiguous 1.5 mm axial slices were obtained using 3D spoiled gradient recalled echo in the steady state on a 1.5-T GE Signa scanner (Milwaukee, WI). Imaging parameters were echo time of 5 ms, repetition time of 24 ms, flip angle of 45°, acquisition matrix of 256 × 192, number of excitations equals 1, and 24 cm field of view. The same scanner was used throughout the study. Native MRI scans were masked (Smith 2002), linearly registered into standardized stereotaxic space (Grabner et al. 2006; Collins et al. 1994), corrected for nonuniformity artifacts (Sled et al. 1998), and then segmented (Zijdenbos et al. 2002; Tohka et al. 2004) to allow the quantification of gray and white matter volumes in frontal, temporal, parietal, and occipital lobes. To determine cortical thickness, the Constrained Lagrangian Anatomic Segmentation Using Proximities surface extraction procedure was used to generate surface meshes representing the white matter and gray matter interfaces (Kim et al. 2005). The root mean square thickness between corresponding nodes on the surface meshes was calculated in native space at 40 962 points in each hemisphere (MacDonald et al. 2000). Thickness measurements were aligned using surface registration to maximize thickness value correspondence between subjects in terms of gyral patterning (Robbins et al. 2004; Lyttelton et al. 2007). A 30-mm surface-blurring algorithm was used to reduce noise in the thickness measurements (Chung et al. 2003; Lerch and Evans 2005). Mean cortical thickness was calculated for the entire cerebrum and for each lobe. Cortical surface area was measured at the middle cortical surface, which lies at the geometric center between the inner and the outer cortical surfaces. This provides a relatively unbiased representation of sulcal versus gyral regions, whereas the inner cortical surface model which overrepresents sulcal regions and the outer cortical surface model which overrepresents gyral regions (Van Essen et al. 2006; Im et al. 2008). Area was estimated as the sum of the areas of the vertices in native space making up the surface mesh for each lobe.

Mixed model regression was used as our data contains both multiple observations per participant measured at different and irregular time periods and single observations per participant. Such unbalanced longitudinal data can be explored statistically by applying mixed effect models (Pinheiro and Bates 2000). To determine the relationship between parental age and each neuroanatomic variable, we used a step-down model selection procedure: Each variable was modeled testing for cubic, quadratic, linear, and constant (i.e., no change) age effects. If the cubic age effect was not significant at P < 0.05, it was removed and we stepped down to the quadratic model and so on. For gray matter lobar volumes, a quadratic model was appropriate; for white matter volumes, a constant model was appropriate. A random effect for each individual was nested within a random effect for each family, thus accounting for both within-person and within-family dependence. We used this approach to model the lobar volumes (represented by the letter k) of every individual (represented by the letter i) in each family (represented by the letter j). Thus, for lobar volumes with a quadratic model, the ith volume of the jth individual in the jth family was modeled as

\[ \text{Volume}_{ij} = \text{intercept} + d_j + \beta_1 \text{(parental}_{age}) + \beta_2 \left( (\text{parental}_{age})^2 \right) + e_{ijk}, \]

where \( d_j \) are nested random effects modeling within-person and within-family dependence, the intercept and \( \beta \) terms are fixed effects, and \( e_{ijk} \) represents the residual error. The effects of child (age at scan, sex, and IQ) and parental characteristics (socioeconomic status) were evaluated first by allowing each to interact with parental age terms in the determination of lobar volumes. No significant interactions were found and thus these variables were entered as covariates in the final model. To test for significant differences in maternal and paternal age effects on lobar volumes, the parent (mother vs. father) was entered as a fixed factor which interacted with parental age terms. Mixed model regression was also used to define the relationship between parental age IQ and SES, including family as a random factor to account for dependence arising from the fact that some individuals were from the same families.

Results

Mean maternal age at the time of the offspring’s birth was 30.8 years (SD 5.1; range 18.3–43.7 years); mean paternal age was 32.6 years (SD 5.1, range 19.9–46.2 years). Parental ages were correlated (r = 0.6, P < 0.001). Mean socioeconomic scale score was 38 (SD 19)—which corresponds to the head of household having a managerial position and undergraduate level education. There was no significant association between parental age and socioeconomic status (maternal t100 = 1.0, P = 0.31; paternal t110 = 0.8, P = 0.40). For the children in the study, the mean IQ was 117 (SD 12).

Maternal and paternal age had similar quadratic effects on offspring’s total gray matter volume (maternal quadratic age effect: t = 2.2, P = 0.03; paternal quadratic age effect: t = 2.4, P = 0.02) (see Fig. 1). Thus, volume increased with advancing parental age until around the early/mid 30s after which it fell (for mother, the estimated age associated with peak offspring gray matter volume was ~33 years and for father, it was ~34 years). Comparison of maternal and paternal age effects showed no significant difference in the shape of the curves (F1,745 = 0.003, P = 0.96). This general pattern of results held for each lobe (see Supplementary Fig. 1).

Figure 1. Relationship between paternal (A) and maternal (B) age and total gray matter volume is illustrated (estimate in bold with 95% confidence intervals for the estimate in dotted lines). The quadratic component of age is significant in the determination of gray matter lobar volumes for both paternal (V = 2.2, P = 0.03) and maternal (V = 2.4, P = 0.02) age.
For total cerebral surface area, there was a significant quadratic effect of paternal but not maternal age (Table 1 and Fig. 2). As for cortical volumes, the negative value of the quadratic age term defines an inverted "U"-shaped curve, with younger and older parental ages being associated with less surface area. At a lobar level, the paternal age effect reached significance for the parietal and temporal lobes (Table 1 and Fig. 2).

For mean cerebral cortical thickness, there was a trend to a quadratic effect of maternal but not paternal age (Table 1). At a lobar level, the maternal age effect was significant for the temporal lobe and in the expected direction for all the other lobes.

The metric of cortical thickness used affords a delineation of change at a sublobar level. The quadratic effect of maternal age was significant through the dorsolateral prefrontal cortex, the inferior postcentral gyri, and much of the lateral surface of the temporal lobes. Medially, quadratic maternal age effects were seen in the region of the posterior cingulate. Significant quadratic effects of paternal age were sparser and confined to the right dorsolateral prefrontal cortex, the left inferior, and right medial temporal cortex (Fig. 3).

By contrast, there were no significant effects of either maternal or paternal age on offspring's total white matter volumes, whether age was treated as a cubic term (maternal cubic age effect: $t = 1.51, P = 0.19$; paternal: $t = 0.88, P = 0.40$), quadratic term (maternal: $t = 1.08, P = 0.28$; paternal: $t = 1.47, P = 0.15$), or linear term (maternal: $t = 0.36, P = 0.76$; paternal: $t = 0.51, P = 0.61$) (Fig. 4). That is, a constant model of no significant change with parental age on total white matter lobar volume was appropriate. A similar lack of parental age effects was found for the white matter volume of each lobe.

### Discussion

To summarize the main results, we find that maternal and paternal age show similar effects on gray matter volume in offspring, with both age extremes being associated with lower volumes. There were no such effects on white matter volumes. The paternal age effect on cortical volumes appeared to be driven more by influencing surface area than cortical thickness; the reverse was true for maternal age. To our knowledge, this is the first demonstration of an association between the parental age and the cortical dimensions of offspring.

This effect of parental age was stable across the age range of offspring assessed, as reflected by the lack of a significant interaction between the child's age and the parental age terms in the determination of cortical volumes. Thus, while there is cortical development throughout childhood and adolescence into early adulthood, the effects of parental age on overall cortical dimensions hold across these developmental stages. Additionally, the effect held for both sexes and at all levels of the child's intelligence as indicated by the lack of a significant interaction between each of these variables and parental age terms in the determination of cortical volumes.

The study has several limitations. The range of parental ages was limited and did not include very young parents (under 18 years) nor older fathers (over 50 years) which may have attenuated our parental age effects. The study did not include potentially highly informative cases, such as children who were adopted away to parents of a different age from their biological parents. Paternal and maternal ages in this study were highly correlated as in the general population, and while the effects of parental age on cortical volumes, we detected were similar, we may thus have missed smaller differential effects. As mentioned earlier, our assessment of socioeconomic factors was limited and did not measure many facets of a child's environment which may be of importance, such as the quality of family and peer relationships and the school environment. Also, our study population was self-selected, very healthy (with no personal or peer relationships and the school environment. Also, our study population was self-selected, very healthy (with no personal or first degree family member history of mental illness), and predominately lived in an affluent region. This could affect the generalizability of the results and also might explain features such as high IQ of the sample.

We can only speculate whether this curvilinear effect of parental age on gray matter is biologically direct or mediated by social and environmental factors. Weighing against such socioeconomic mediation in the current study is the fact that higher socioeconomic status and advancing parental age were only modestly and nonsignificantly associated in our cohort. Additionally, the lack of an interaction between socioeconomic status and parental age in determining offspring brain volumes

### Table 1

The estimated parameters for the quadratic effect of maternal and paternal age on total and lobar cortical volume, surface, and thickness

|                    | Volume (mL) | Surface (mm²) | Thickness (10⁻² mm) |
|--------------------|-------------|---------------|---------------------|
|                    | Quadratic   | Quadratic     | Quadratic           |
|                    | β (SE)      | β (SE)        | β (SE)              |
| Maternal All      | -251(113)   | 2.2*          | -43(27)             | 1.6              |
| Maternal Frontoal | -81(42)     | 1.5           | -9(10)              | 0.9              |
| Maternal Parietal | -51(25)     | 2.1*          | -10(6)              | 1.6              |
| Maternal Temporal | -90(40)     | 2.3*          | -15(9)              | 1.6              |
| Maternal Occipital| -45(17)     | 2.6*          | -10(6)              | 1.8              |
| Paternal All      | -244(106)   | 2.4*          | -50(26)             | 1.9*             |
| Paternal Frontoal | -81(39)     | 2.1*          | -13(10)             | 1.4              |
| Paternal Parietal | -57(23)     | 2.5*          | -11(6)              | 1.9*             |
| Paternal Temporal | -81(40)     | 2.2*          | -18(9)              | 2.4*             |
| Paternal Occipital| -27(17)     | 1.6           | -7(5)               | 1.2              |

Note: Significant results are shown in bold text. SE, standard error.

*P < 0.05.

**Figure 2.** Relationship between paternal (A) and maternal (B) age and total cerebral surface area (estimates in bold with 95% confidence intervals for the estimate in dotted lines). The quadratic age component reached significance ($P < 0.05$) for paternal but not maternal age.
implies the effect held across socioeconomic class, and the results also held when socioeconomic status was controlled.

However, our measure of socioeconomic class is limited and does not capture many environmental factors which might influence cortical dimensions. Factors which could vary with parental age include the quality of parent–child interactions, access to health care, education, and nutrition (Fergusson and Woodward 1999). Considerable advances have been made in defining the cellular events which underpin postnatal cortical development and how these can be influenced by environmental factors. In a study of morphological changes in pyramidal neurons in layers IIc and V which are pivotal in human cognition (Fuster et al. 2000; Wang et al. 2006), several periods of growth were defined some occurring postnatally (Petajek et al. 2008). Of particular relevance to our study are a postnatal phase of dendritic growth at around 16 months to 2.5 years and a transient increase in pyramidal cell somata in layer IIc at around 5–6 years of age. This possible early phase of dendritic overgrowth occurs around the same age as axonal tree overgrowth (LaMantia and Rakic 1990; Innocenti and Price 2005) and increase in the number of synapses (Huttenlocher and Dabholkar 1997). Environmental factors appear to sculpt both these morphological changes and those which occur in later childhood and adolescence such as synaptic pruning and stabilization (Rakic et al. 1994; Huttenlocher and Dabholkar 1997). For example, as education level increases so do measures of the morphology of the complexity of basilar dendrites of pyramidal cells in Wernicke’s area (Jacobs et al. 1993). Early global environmental deprivation (seen in children raised in Romanian orphanages during the 1980s) has been shown to be associated with glucose hypometabolism in limbic and paralimbic structures, including the orbital frontal gyrus, infralimbic prefrontal cortex, hippocampus/amygdala, lateral temporal cortex, and in the white matter tracts connecting these regions (Chugani et al. 2001; Eluvathingal et al. 2006; Behen et al. 2009). These structural deficits are in turn linked with anomalies in cognition and behavior, specifically the occurrence of inattentive and overactive phenotype (Behen et al. 2008). Others have similarly found that the duration of very early childhood deprivation correlated with the degree of volume change in the amygdala—albeit with differing reports on the direction of

Figure 3. Regions where there was a significant quadratic effect ($P < 0.05$) of parental age on cortical thickness of offspring. In all the colored regions, an inverted “U” curve described the relationship between parental age and thickness, with both younger and older parental age being associated with a thinner cortex. Maternal age (shown in panel A) had a more extensive effect on cortical thickness than paternal age (panel B).

Figure 4. Relationship between paternal (A) and maternal (B) age and total white matter volume (estimate in bold with 95% confidence intervals in dotted lines). There was no significant effect of parental age.
the change (Mehta et al. 2009; Tottenham et al. 2010). Studies on children who suffered another form of early adversity, namely physical maltreatment with subsequent posttraumatic stress disorder found gray and white matter deficits impacting on several key areas related to regulation of behavior and disruptions to interhemispheric connectivity (De Bellis et al. 2002; Woon and Hedges 2008). Similarly, in a longitudinal study, the quality of parental care at the age of 4 but not 8 years was found to predict hippocampal volume in adolescence (Rao et al. 2010). Nonhuman animal models have allowed a direct examination of the effects of environmental manipulations. A host of studies find that environmental enrichments have trophic effects which might increase gray matter volume including increase in the size of the soma and nucleus of neurons, glia, and capillary dimensions (Greenough and Volkmar 1973; Kleim et al. 1996; Sur and Rubenstein 2005). In summary, given the evidence for the importance of environmental factors on sculpting the cortex, it is important to consider the possibility that environmental factors related to parental age (some of which we did not measure) could partly explain our results.

Other mechanisms might also underpin the parental age effects we report. The detrimental effects of advanced parental age on offspring’s neurocognition are often attributed to direct biological mechanisms such as an accumulation of DNA mutations in germ line cells with advancing parental age (Bosch et al. 2003) which could adversely affect gray matter. Less is known of mechanisms which might account for smaller gray matter volumes in children born to younger parents, although a similar association has been reported in rats (Ryzhavskii et al. 2004).

Some clues into biological mechanisms at play might be gained from the finding that while paternal age influences cortical surface area more than thickness, maternal age had the opposite association. This could arise due to the imprinting of genes controlling cortical development—a process of epigenetic regulation that results in the preferential expression of paternal or maternally inherited alleles of certain genes. Recent work suggests that an unexpectedly high number of genes regulating neurodevelopment are imprinted (Gregg et al. 2010). A key mechanism for gene silencing is the methylation of DNA; inherited methylation patterns are stable in somatic cells but are erased and reestablished in spermatogenesis and oogenesis. This process could become impaired with age, for example, through altered levels of enzymes regulating this methylation (Lopatina et al. 2002). Other mechanisms have been proposed to explain differentially severe effects of paternal age effects, including mutagenesis with point mutations and structural chromosomal alterations in rapidly dividing spermatogonia (Penrose 1955; Crow 2000; Green et al. 2003).

While it is overly simplistic to state that increased gray matter volumes are always advantageous, meta-analyses have established that a modest correlation between gray matter volume and intelligence is one aspect of the complex links between brain structure and intelligence (McDaniel 2005). Additionally some neuropsychiatric disorders are associated with decreased overall gray matter volume—including schizophrenia (Ward et al. 1996) and most mental retardation syndromes (Pinter et al. 2001). Decreased gray matter volume might thus be considered a risk factor for some poor neurocognitive outcomes, which as mentioned earlier tend to cluster at parental age extremes.

This is the first demonstration of parental age effects on gray matter morphology in offspring. This may throw light into the mechanisms which link parental age extremes with suboptimal neuropsychiatric disorders and suboptimal cognitive functioning.

**Supplementary Material**

Supplementary material can be found at: http://www.cercor.oxfordjournals.org/.

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**Notes**

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