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Simplified gyral pattern in severe developmental microcephalies? New insights from allometric modeling for spatial and spectral analysis of gyrification

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ABSTRACT

The strong positive-allometric relationship between brain size, cortical extension and gyrification complexity, recently highlighted in the general population, could be modified by brain developmental disorders. Indeed, in case of brain growth insufficiency, the pathophysiological relevance of the "simplified gyral pattern" phenotype is strongly disputed since almost no genotype–phenotype correlations have been found in primary microcephalies. Using surface scaling analysis and newly-developed spectral analysis of gyrification (Spangy), we tested whether the gyral simplification in groups of severe microcephalies related to *ASPM*, *PQBP1* or fetal-alcohol-syndrome could be fully explained by brain size reduction according to the allometric scaling law established in typically-developing control groups, or whether an additional disease effect was to be suspected. We found the surface area reductions to be fully explained by scaling effect, leading to predictable folding intensities measured by gyrification indices. As for folding pattern assessed by spectral analysis, scaling effect also accounted for the majority of the variations, but an additional negative or positive disease effect was found in the case of *ASPM* and *PQBP1*-linked microcephalies, respectively. Our results point out the necessity of taking allometric scaling into account when studying the gyrification variability in pathological conditions. They also show that the quantitative analysis of gyrification complexity through spectral analysis can enable distinguishing between even (predictable, non-specific) and uneven (unpredictable, maybe disease-specific) gyral simplifications.

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Introduction

Human cortical folding is highly variable, as described by several frameworks (Fischl et al., 2008; Mangin et al., 2004; Régis et al., 2005; Van Essen et al., 2001; Zilles et al., 1997). This variability may be analyzed through two dimensions: i) folding intensity, which refers to the amount of buried cortical surface, and ii) folding pattern, which corresponds to the spatial arrangement of buried cortical surface into sulci and gyri. The variations in folding intensity are well assessed by conventional spatial morphometry: surface area scaling (Prothero and Sundsten, 1984; Toro et al., 2008) and gyrification indices (Lebed et al., 2013; Schaer et al., 2008; Toro et al., 2008; Zilles et al., 1988). The variations of folding patterns can be addressed *in the spatial domain* by object-based analysis of sulci shape (Mangin et al., 2004; Sun et al., 2012). Other domains of representation have been investigated with fractal analysis (Im et al., 2006; Kiselev et al., 2003; Thompson et al., 2005) or more recently spectral analysis of gyrification (*frequency domain*) (Germanaud et al., 2012).

Essentially, folding variability can be related to 1) age or developmental stage of the brain, 2) relative size or scaling factor between brains of the same age (Germanaud et al., 2012), 3) any factor affecting the development of gyrification, such as an underlying pathological condition, and eventually to a residual folding polymorphism of unknown origin (random developmental steps or specific genetic polymorphism) (Zilles et al., 2013).

1) Adult intensity of gyrification is reached as early as term birth (Armstrong et al., 1995), and even slightly decreases during childhood (Raznahan et al., 2011). From this age onwards, the effect of age on gyrification is expected to be small, at least before aging and neurodegenerative effects. By the age of 6 to 7, adult brain size is achieved (Brain Development Cooperative Group, 2012; Dobbing and Sands, 1973) or almost achieved (Giedd, 2004), with pronounced variation (at least 1000 cm^3 to 1500 cm^3) exhibited in the general population (Milner, 1990; Whitwell et al., 2001).
2) Adult brain size accounts for a large amount of the folding variability. If all brains were perfectly homothetic (i.e. *isometric scaling*), the cortical surface area would vary with brain size as a 2/3 power law. In the general population, the scaling exponent is clearly superior, around 0.9. This *allometric scaling* (i.e. proportion or shape changing with size) has been shown at the global or lobar level (Im et al., 2008; Toro et al., 2008) and with gyrification index (Toro et al., 2008), revealing that larger brains have a relative excess of folding intensity. To extend scaling analysis from folding intensity to folding pattern, we recently developed spectral analysis of gyrification (Spangy). Spangy allows quantification of the spatial frequency content of cortical curvature, taken as a folding descriptor. It also proposes an objective segmentation of the cortical folding pattern into primary, secondary and tertiary elements comparable to those defined developmentally. We showed that larger brains are more folded because of the increased number of ramifications of high spatial frequencies that follow the allometric increase of cortical surface to be buried, largely contributing to the folding pattern variability (Germanaud et al., 2012).
3) A pathological condition may contribute to the remaining folding variability. Developmental brain disorders with obvious disturbances of gyrification have been described going from too many too small folds (polymicrogyria) to excessively large and sparse folds (pachygyria-lissencephaly spectrum) (Barkovich et al., 2012). More subtle modifications of gyrification have also been reported, for instance in 22q11.2 deletion syndrome, with gyrification index (Schaer et al., 2006, 2008), combined with fractal indices in Williams syndrome (Gaser et al., 2006; Schmitt et al., 2002; Thompson et al., 2005), or in schizophrenia with sulci shape analysis (Cachia et al., 2008; Plaze et al., 2011). These atypical foldings may present with abnormal cortical thickness. Interestingly, a negative link between cortical thickness and folding tightness is also suggested by i) severe cortical dysgenesis – thinning is associated with some polymicrogyrias while thickening is characteristic of type 1 lissencephaly (Squier and Jansen, 2010); ii) comparison between gyrencephalic mammals – peculiarly dolphins show a dramatically thin and highly convoluted cortex (Hofman, 1985); iii) several theoretical models of corticogenesis (Mota and Herculano-Houzel, 2012; Toro and Burnod, 2005); and iv) recent analysis of healthy human data (Hogstrom et al., 2012; Im et al., 2006).

Among developmental brain disorders, true microcephalies are characterized by a brain growth insufficiency that can be very severe (down to half the volume of the smallest normal adult brain), but contrasts with preserved brain anatomical organization. Severe developmental microcephalies result from early onset cellular dysfunctions or developmental perturbations *directly* affecting brain growth mechanisms and are suspected when standardized head circumference is below −3 standard deviations (SD) by the age of 3 months. Their causes are mainly genetic; however, they are sometimes related to early environmental toxic exposures (Miller and Blot, 1972; Wood et al., 1967). Qualitative or semi-quantitative radiological assessment of cortical folding intensity or pattern has distinguished between either normal or simplified gyral pattern (Barkovich et al., 2001; Vermeulen et al., 2010), but genetic studies from the past 10 years have found almost no phenotype–genotype correlations (Barkovich et al., 2012; Passemard et al., 2009), and gyral simplification was recently suggested to be a mere consequence of brain or white matter volume reduction (Barkovich et al., 2012).

Anyway, the occurrence and pathophysiological relevance of gyral simplification over severe developmental microcephalies remains ambiguous and needs to be further investigated. We thus selected 3 diseases that encompass the large pathophysiological landscape of these microcephalies, ranging from proliferation-specific to pleiotropic defect, genetic to toxic origin and isolated to syndromic presentation.

1) Autosomal recessive primary microcephalies – also named MCPH ("MicroCephaly Primary Hereditary") – are very uncommon diseases (<1/100,000 living birth) characterized by very severe brain size reduction (<−4 SD) without other major body malformation (Robert et al., 2002; Woods et al., 2005). Almost all of these are due to amorphic mutations of genes involved in cell proliferation, resulting into quantitative insufficiency of the neuroglial lineage. Mutations in the *ASPM* gene – coding for Abnormal Spindle-like Microcephaly-associated protein at the MCPH5 locus (Bond et al., 2002) – account for the large majority of described cases (for review see Kaindl et al. (2010)). In the few reported *ASPM*-mutated patients with standard MRI, gyral pattern was either normal or simplified (9 patients over 12 in Passemard et al., 2009; Desir et al., 2008).
2) Syndromic developmental microcephalies, in which brain growth restriction is associated with multiple congenital abnormalities, have been linked to many genes or chromosomal micro-rearrangements (for review see Abuelo (2007)). Among them, Renpenning syndrome is a very uncommon condition (75 reported cases), associating a severe microcephaly with growth restriction and a variety of inconstant somatic abnormalities (Germanaud et al., 2011; Kalscheuer et al., 2003; Renpenning et al., 1962). It has been related to recurrent null mutations in the X-linked gene coding for the transcriptional regulator PolyGlutamine Binding Protein 1 (*PQBP1*). The few MRI scans reported showed no evidence of gyral simplification (Germanaud et al., 2011).
3) The most frequent toxic-related developmental microcephaly is caused by prenatal alcohol exposure. Fetal alcohol effects belong to a large clinical spectrum going from conditions without malformation, to less common fetal alcohol syndrome (FAS), which almost always involves brain growth restriction (Astley et al., 2009; Spohr et al., 2007). Fetal alcohol spectrum disorders (FASD) studies