Determinants of cortical gray matter volume:
Hypotheses on Developmental Cohorts with Normal and Abnormal Cortical Morphology

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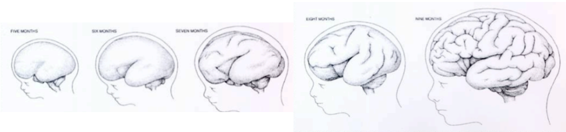
Background: cortical gray matter development

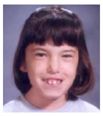


Cortical volume represents the amount and size of neurons, dendritic processes, and glial cells. During early brain development, the increase in cortical gray mater volume is allowed by thickening of the cortical mantle, and by expansion of the cortical surface through in brain size, and folding of the cortex (gyrification). Later, during childhood and adolescence, maturational processes such as pruning and neuronal loss are reflected by changes in gray matter volume, and thickness (Giedd, 1999[1]; Sowell, 2004[2]).

Cortical gray matter volume was shown to be positively correlated to cognitive abilities (Reiss, 1996)[3], and has frequently been reported altered in psychiatric or neurogenetic conditions. New methods aims at quantifying cortical thickness and gyrification, thus assessing the relationship between cortical thickness, folding, and brain perimeter will certainly help to a better understanding of normal and abnormal cortical development.

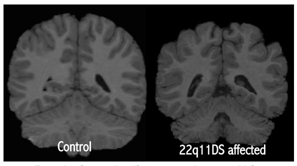
Impaired cortical development: 22q11 Deletion Syndrome (22q11DS)

A genetic disorder caused by a 3Mb deletion affecting 1 on 5'000 live births.



Typically characterized by:
- physical anomalies,
-cognitive and learning impairments
- increased risk for psychopathologies.

Gray matter alterations in children / adolescent affected with 22q11DS:
- Decreased gray matter volume, parietal lobe particularly affected
- Numerous cortical dysgenesis (most frequently frontal and parietal)
- Decreased Gyrification Index in the frontal and parietal lobes



Example of cortical malformation in the parietal lobe

In light of previous literature emphasizing an abnormal cortical development particularly in the parietal lobe, this study aims to further characterize the structural changes in parietal cortex of affected individuals.

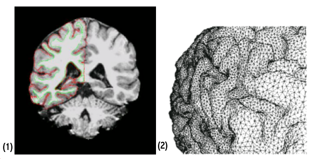
Method: three-dimensional characterization of cortical structure

Subjects 34 typically developing individuals with no history of psychiatric or neurological disorders (20 females - 14 males), mean age 16.44 ± 9.29 y.o. (range: 6.9-39.7), mean IQ 110.6 ± 12.7
34 patients with 22q11DS (22 females -12 males), mean age 17.15 ± 8.82 y.o. (range: 6.1 - 37.4), mean IQ 69.8 ± 10.6

Raw Imaging T1-weighted 1.5T MRI, voxel size: 0.94 x 0.94 x 1.5 mm

Image Processing Lobar gray matter volume were calculated according to (Eliez, 2000)[4] including: intensity normalization; skull stripping; gray-white matter segmentation; and lobar subdivision according to Talairach grid (Kates, 1999)[5].

1. 3D-Cortical reconstruction



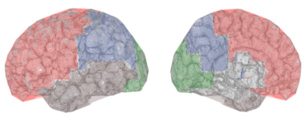
FreeSurfer Software was used to delineate the gray-white matter interface (1, green) and the pial surface (1, red). This technique allows obtaining 3D representation of the cortical surfaces (2) with a submillimeter accuracy. Cortical thickness was measured at each point of the cortical mesh, as the distance between the gray-white and the pial surfaces (Fischl, 2000)[6].

2. Perimeter computation in 3D

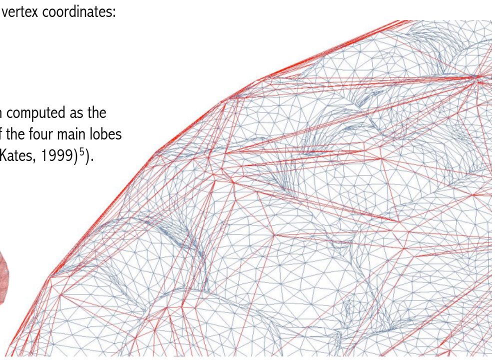
Algorithms implementations was done with Matlab. Each of the 150'000 faces composing the pial mesh (blue) is given by the following vertex coordinates:

$V_1 = (x_1 ; y_1 ; z_1)$
$V_2 = (x_2 ; y_2 ; z_2)$
$V_3 = (x_3 ; y_3 ; z_3)$

The outer perimeter of the brain (red) is then computed as the convex hull of the cortical surface, for each of the four main lobes (as defined with their Talairach coordinates (Kates, 1999)[5]).



Lateral and Medial Views of pial and outer surfaces for each lobe



3. Measurements

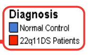
For the current study, only the parietal lobe was considered.
- Mean cortical thickness was computed as the average thickness of all the vertices belonging to the parietal lobe.
- Areas of the outer perimeter surface and pial surfaces were calculated using the following equations:

$$\Delta = \frac{1}{2}\sqrt{\begin{vmatrix} y_1 & z_1 & 1 \\ y_2 & z_2 & 1 \\ y_3 & z_3 & 1 \end{vmatrix}^2 + \begin{vmatrix} z_1 & x_1 & 1 \\ z_2 & x_2 & 1 \\ z_3 & x_3 & 1 \end{vmatrix}^2 + \begin{vmatrix} x_1 & y_1 & 1 \\ x_2 & y_2 & 1 \\ x_3 & y_3 & 1 \end{vmatrix}^2}.$$

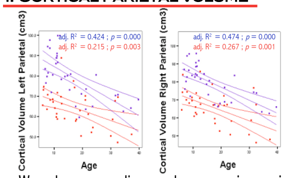
$$Total\ Area = \sum_{j=1}^{n} \Delta_j$$

- 3D-Gyrification Index, as a measure of cortical folding, was computed as the ratio of the pial area divided by the outer perimeter area.

Results

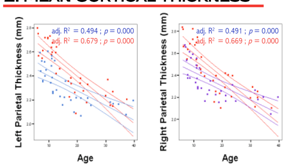


1. Cortical parietal volume



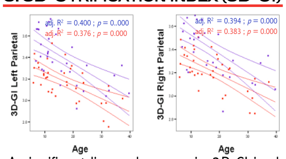
We observe a linear decrease in parietal gray matter volume with age, with control subjects having higher values than patients.

2. Mean cortical thickness



Cortical maturation proceeds with thinning in both subgroups. Interestingly, patients have thicker cortex than comparison subjects (Left: $F_{1,66}=8.547$, $p=0.005$; Right: $F_{1,66}=4.292$, $p=0.042$).

3. 3D-Gyrification index (3D-GI)



A significant linear decrease in 3D-GI is shown, with patients having lower values than control (Left: $F_{1,66}=20.886$, $p=0.000$; Right: $F_{1,66}=17.04$, $p=0.000$). Brain perimeter was smaller in patients (Left: $F_{1,66}=46.024$, $p=0.000$; Right: $F_{1,66}=43.77$, $p=0.000$), but stable with age.

4. Main determinants of cortical volume

We used a stepwise multiple regression model to identify which factors could predict parietal cortical volume, among perimeter, 3D-GI, and mean cortical thickness.

Right Parietal Lobe			
CONTROL	**R2 Change**	**Beta**	**p**
Gyrification Index	34%	0.396	0.006
Thickness	11%	0.393	0.004
Perimeter	8%	0.302	0.026
22q11	**R2 Change**	**Beta**	**p**
Perimeter	49%	0.828	0.000
Thickness	37%	0.539	0.000
Gyrification Index	7%	0.276	0.000

Left Parietal Lobe			
CONTROL	**R2 Change**	**Beta**	**p**
Gyrification Index	45%	0.316	0.004
Thickness	16%	0.459	0.000
Perimeter	17%	0.459	0.000
22q11	**R2 Change**	**Beta**	**p**
Perimeter	46%	0.767	0.000
Thickness	33%	0.487	0.000
Gyrification Index	10%	0.329	0.000

According to this model, the main determinant of parietal cortical volume is gyrification in control subjects, and perimeter in patients. Together, perimeter, gyrification and cortical thickness account for 76.0/87.5% of the control/patient variance in volume, respectively right: 52.5/91.8 %.

Implications for our comprehension of normal & abnormal brain development

Our results suggest **that the more important structural factor contributing to the variance in cortical gray matter volume in normal individuals is gyrification process**. When the gyrification process is disrupted in its early brain development, as in 22q11DS, cortical volume is primarily accounted for by brain perimeter, and normal gray matter volume are not reached.

We also observed decreased gyrification with age, which reflects **continuous shape remodeling of the maturing cortex**. Thus, the processes contributing to the well-known developmental course of gray matter volume may not only rely on cortical thickness changes, but also on maturational morphological changes that are important enough to affect cortical area.

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Acknowledgements
This research was supported by a grant from Swiss National Research Funds to Marie Schaer (323500-111165), as well as to Dr. Stephan Eliez (3200-063135, 3232-063134, and PP00B-102864).
This work also was partially supported by a grant from the NARSAD Institute to Dr. Eliez, as well as by the Center for Biomedical Imaging (www.cibm.ch).

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