

# Dynamic model of normal neurodevelopment from childhood to adulthood: validation in 200 healthy subjects

J.M. <sup>1,2,3\*</sup>, Yasser Iturria-Medina<sup>1,2,3</sup>, José M. Mateos-Pérez<sup>1,2,3</sup>, and Alan C. Evans<sup>1,2,3</sup>

<sup>1</sup> Montreal Neurological Institute, *Montreal*, *QC*, *Canada* 

<sup>2</sup> McConnell Brain Imaging Centre, *Montreal*, *QC*, *Canada* 

**Results & Interpretation** 

<sup>3</sup> Ludmer Center for NeuroInformatics and Mental Health, *Montreal*, *QC*, *Canada* 





# Summary

# White-matter (WM) and grey-matter (GM) changes occur naturally in normal development and aging. For example, covariance patterns in the growth of cortical regions have been found during normal development using both grey matter density and cortical thickness [1-5]. These GM and WM changes also occur in an altered, disease-specific manner for many neurodegenerative, mental, and neurological diseases, including frontotemporal dementia [6], Alzheimer's disease [6], Huntington's Disease [7], and schizophrenia [8]. These changes are also present in premature babies [9] and disorders of brain development, such as autism spectrum disorder [10] and attention deficit hyperactivity disorder [11]. Here, we present the development of a mathematical, region-based model of GM change mediated by WM connectivity from childhood to adulthood for normal, healthy subjects. We analyzed multi-modal brain images for healthy subjects from a publicly-shared, large-scale database meant to provide a representative, heterogeneous sampling of the population. This data-driven model could serve as a baseline for allowing the early detection and classification of neurodegenerative disorders.

A model with two sets of parameters was chosen based upon its ability to best model temporal changes. This dynamic, deterministic model incorporates these parameter sets into a differential equation (Equation 2) describing the propagation of growth/atrophy patterns throughout the brain.

The modeled brain changes could be due to normal development and aging processes, mutual trophic reinforcement, and/or experience-related brain plasticity [5].

Each brain region has its own rate of growth or atrophy, while the entire brain shares a single susceptibility for changes impacting other regions over WM tracts (global a, regional B parameters, see Figure 1).

- Subcortical structures play an important role in normal brain development (the inclusion of subcortical structures allows the model to much more accurately fit the data, see Figure 1).

## Methods

Structural and diffusion-weighted MRI data from the Nathan Kline Institute-Rockland Sample database [12] were used to quantify GM density and WM connectivity, respectively. Image processing was performed using well-established neuroimaging tools. Brain region labels (83 cortical & subcortical structures) were provided by the Desikan-Killiany Atlas. The study included 200 subjects (68M, 132F) aged 7 to 84, with a history of neither psychological nor neurological disease. The NKI Institutional Review Board approved the research protocol to collect and share the data.

Regional GM density and between-region WM connectivity values were used as input to mathematical models which explored their inter-relation in a network with GM nodes and WM edges, using a variable number of parameters. 1 instrinsic () 1 extrinsic ()

$\frac{ds_i(t)}{dt}$	$ds_i^{instrast}(t)$	Т	$ds_i^{extrastc}(t)$	)
-dt	dt	Т	dt	

#### **Equation 1:** General form of the examined mathematical

Equation 1 illustrates the general form of the examined mathematical models. In this differential equation, the temporal structural changes occurring within brain region *i* (represented by s<sub>i</sub>) can be modeled at an arbitrary time *t* by the internal processes of the region (intrinsic influences, modeled by  $\frac{ds_i^{instrinsic}(t)}{dt}$ ) and the influence of connected regions (extrinsic influences, modeled by  $\frac{ds_i^{extrinsic}(t)}{dt}$ ). Multiple models were compared based on their ability to best model the temporal GM trajectories for all 83 brain regions. The model with the best fit was selected using the Bayesian Information Criterion (BIC) [13]: the model with the lowest BIC score results in the best fit for the data. In addition to choosing between different models, each model was evaluated with different parameters in order to determine which form of the differential equation best fits the data (Figure 1).

### BIC score with # of parameters

We hypothesize that the use of actual connectivity values allows the model to accurately estimate trophic influences [1,5] that cannot properly be computed otherwise: the model has a measurably lower BIC score when the actual connectivity matrix is used (ACP instead of the inverse connectivity matrix of 1/ACP or a matrix of constant connectivity, where each region of the brain is assumed to be fully connected to every other region, see Figure 1).



Figure 2. Model-derived grey matter density changes for 83 brain regions from ages 7 to 84.



Figure 1. BIC score evolution for the selected mathematical model. Red: BIC scores obtained using cortical thickness values. Blue: BIC scores obtained from cortical grey matter density values. Green: BIC scores obtained from grey matter density values for both cortical and subcortical structures. CT: cortical thickness. GMd: Grey matter density. ACP: Anatomical Connection Probability.

$$\frac{ds_i(t)}{dt_i} = \beta_i \cdot s_i(t) + \alpha_i \cdot \sum_{i \in I} C_{ii}(t) \cdot \beta_i \cdot s_i(t)$$

The GM changes derived from this model for the entire brain are illustrated in Figure 2. Example trajectories for two randomly selected brain regions are shown in Figure 3.

Gray matter density trajectory for left pars triangularis





Figure 3. Model-derived grey matter density trajectories for left pars triangularis (left) and right superior parietal lobe (right). **Dots:** grey matter density values for each subject. **Black curve:** trajectory generated by the mathematical model for the indicated region.

## Conclusion

A model was developed to characterize the growth and atrophy of each brain region as a function of its local tissue properties, its anatomical connection pattern and the concurrent changes occurring in the rest of the brain. This model currently characterizes normal GM changes mediated by WM connectivity, but it could be readily applied to disease-specific populations in order to determine region- and timespecific deviation from normal development in disease states and experience-driven brain plasticity.



**Equation 2:** Differential equation of the selected model

β models intrinsic processes of each region

 $\alpha$  models the susceptibility of each region to changes occurring in connected regions C<sub>ii</sub>(t) represents the connection strength between regions i and j at time t

 $\beta_i \cdot s_i(t)$  models the internal processes of region *i*  $\alpha_i \cdot \sum_{j \neq i} C_{ij}(t) \cdot \beta_j \cdot s_j(t)$  models how much of the processes occurring in all other brain regions affect region *i* 

## References

8. Zugman, A. et al. J. Psychiatr. Res. 71, 89-96 1. Mechelli, A., et al. J. Neurosci. 25, 8303-10 (2005). (2015). 2. Raznahan, A. *et al. Neuron* **72**, 873-84 (2011). 9. Balardin, J. B. et al. Cereb. Cortex (2015). 3. Raznahan, A. *et al. J. Neurosci.* **31**, 7174-7 (2011). 4. Khundrakpam, B. S. et al. Cereb. Cortex 23, 2072-8510.Sharda, M. et al. Cereb. Cortex (2016). 11.Li, X. et al. Psychiatry Res. 231, 273-8 (2015). (2013). 12. Nooner, K. B. et al. Front. Neurosci. 6, 152 5. Evans, A. C. *Neuroimage* **80**, 489-504 (2013). (2012). 6. Hafkemeijer, A. et al. Hum. Brain Mapp. 37, 978-88 13. Mallick, H. et al. J. Biom. Biostat. 55, 1-27 (2016). (2014). 7. Minkova, L. et al. Hum. Brain Mapp. 37, 67-80 (2016).