Functional consequences of neurite orientation dispersion and density in humans across the adult lifespan

Arash Nazeri[1,2], M. Mallar Chakravarty[3,4], David J. Rotenberg[1], Tarek K. Rajji[1], Yogesh Rathi[5], Oleg V. Michailovich[6], and Aristotle N. Voineskos[1]

[1]Centre for Addiction and Mental Health, Toronto, ON, Canada, [2]Department of Psychiatry, University of Toronto, Toronto, ON, Canada, [3]Department of Psychiatry, McGill University, Montreal, QC, Canada, [4]Cerebral Imaging Centre, Douglas Institute, Verdun, QC, Canada, [5]Laboratory of Mathematics in Imaging, Harvard Medical School, Boston, MA, United States, [6]Department of Electrical and Computer Engineering, University of Waterloo, Waterloo, ON, Canada

Introduction: Dendrites are key sites for synaptic integration and neuronal connectivity in the brain. Post-mortem studies have demonstrated that morphological alterations in dendritic structures are hallmarks of aging in gray matter (GM), characterized by reduced complexity and regression of the dendritic tree in neocortex. In contrast, dendritic growth and increased dendritic complexity occur within paleocortex (parahippocampal gyrus) and archicortex (hippocampus) in successful human aging and senescent animals. Recent advances in diffusion-weighted magnetic resonance imaging have opened new vistas to examine brain tissue microstructure in vivo. These techniques utilize the diffusion properties of water molecules to estimate underlying cellular microstructural properties of brain tissue in the context of specific biophysical models. Neurite-orientation dispersion and density imaging (NODDI) is a recently proposed model that extends application of diffusion imaging from white matter to the GM tissue microstructure[1]. NODDI indexes neuritic density and dispersion of neurites in the brain tissue with intra-neurite volume fraction and orientation dispersion index, respectively. These indices can be used to assess dendritic organization in vivo in humans[1]. Here we adopted a GM-based spatial statistics (GBSS) approach[2] for voxel-wise analysis of NODDI-derived indices within the GM, including enhanced registration steps and customization to take full advantage of the potential of the NODDI model. Furthermore, we aimed to uncover the functional consequences of age-related GM microstructural changes using fMRI approaches, as well as assessment of cognitive performance in the same individuals.

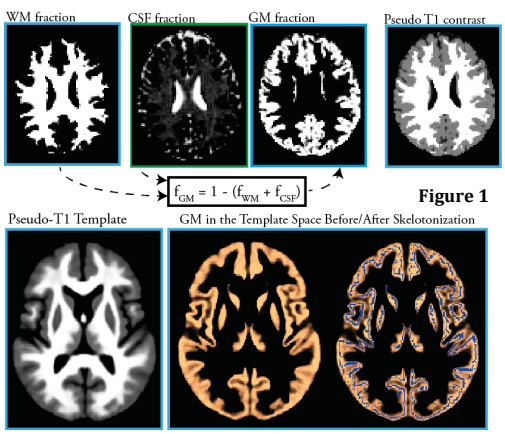

Figure 1

Overview of NODDI-GBSS: As in other voxel-based approaches, accurate cross-subject alignment of anatomically related regions is of paramount importance. This issue is even more critical with diffusion imaging analysis of the cortical regions (cerebellar and cerebral cortex), given the relatively thin cortical structures and sensitivity of diffusion metrics to partial volume contamination. To overcome these caveats, GBSS adapts the tract-based spatial statistics (TBSS)[2,3] framework for GM analysis by skeletonizing the GM and projecting diffusion metrics from the most probable local GM voxel on to the skeleton for group comparison. Unlike the original GBSS pipeline that tissue classification takes place in the structural images, we directly segmented brain tissues using the diffusion data. Here is a brief overview (Fig. 1):

(i) After preprocessing, NODDI and diffusion tensor models were fitted to the diffusion data.

(ii) CSF partial volume in each voxel was directly estimated using the NODDI model parameter, fCSF[2].

(iii) White matter segmentation was carried out on the FA images using Atropos (http://picsl.upenn.edu/software/ants/) for two-class classification (white matter/non-white matter) to derive fraction of white matter (fWM). Fraction of GM (fGM) in each voxel was determined by simply subtracting fractions of CSF and white matter from 1.

(iv) Diffusion parameter maps do not have sufficient gray/white/CSF contrast to allow for accurate registration of cortical GM. Thus, we generated maps with a contrast similar to T1 images (pseudo-T1 images), by multiplying partial volume estimations of each tissue class by their corresponding contrast.

(v) For group-wise nonlinear registration we used the buildtemplateparallel.sh script in the ANTS software package v1.9. Aligned GM probability maps were averaged across individuals and thinned (skeletonized) so that the skeleton represents the center of highly probable GM voxels. Each subject's (aligned) ODI and fGM image were then projected onto the skeleton. This is achieved, for each skeleton voxel, by searching perpendicular to the skeleton structure for the most probable local GM voxel[2]. Voxel-wise analysis was carried out using randomise, implemented in FSL.

CAMH Aging Study: Forty-five healthy participants across the adult lifespan (21-84) years of age; female/male: 24/21) were recruited at the Centre for Addiction and Mental Health (CAMH) in Toronto. Diffusion, structural and functional images were acquired for all subjects on a 3 Tesla GE Discovery MR750 system (General Electric, Milwaukee, WI) equipped with an 8-channel head coil. For the diffusion imaging, a multi-shell protocol was acquired along 30 non-collinear directions at 3 b-values (1000, 3000, 4500 s/mm^2) in addition to 15 interspersed b=0 images using a single shot echo-planar sequence. The acquisition parameters were as follows: TE/TR=108/12000 ms, voxel dimension of 2×2×2 mm^3, 82 slices. Resting-state functional scans were acquired using an axial spiral fMRI acquisition with the following parameters: TE/TR=30/2000 ms, 210 volumes, voxel dimension of 3.4×3.4×5 mm^3, 31 slices. During the resting-state fMRI participants were requested to close their eyes and let their mind wander. All subjects also underwent a battery of cognitive testing. Cortical thickness measurement, and subcortical segmentation were carried out on structural T_1 images using the FreeSurfer toolkit v5.1. After denoising functional data using FMRIB's ICA-based Xnoiseifier (FIX) v1.0.6. Functional connectivity analysis was performed using MELODIC and dual-regression analysis.

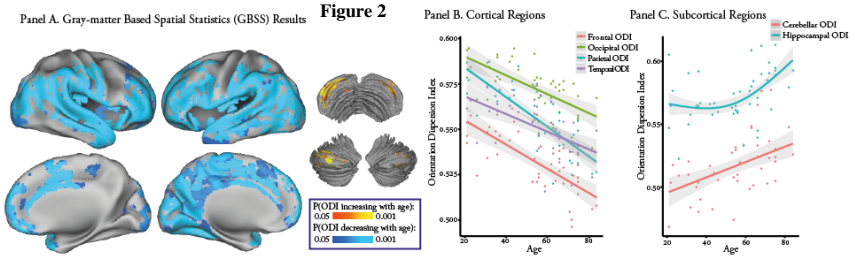

Figure 2

Results: Using NODDI-GBSS we found a significant age-related decrease in neocortical-ODI (most prominently in frontoparietal regions), while increased ODI was observed in cerebellum with advancing age (Fig. 2). We replicated these findings using follow up region-of-interest analysis and also observed a nonlinear increase in hippocampal ODI (Fig.2). Neocortical-ODI outperformed other measures of brain aging (cortical thickness and white matter fractional anisotropy) for the prediction of chronological age in the same individuals. Functional connectivity of brain resting-state networks with known age-related susceptibility (default-mode [DMN] and visual association networks [VAN]) was significantly associated with GM ODI sampled from these networks, while the task-positive networks tended to show no association or even an opposite effect (Fig. 3). Frontal pole-ODI mediated negative impacts of age on executive function, while hippocampal-ODI mediated its protective effects.

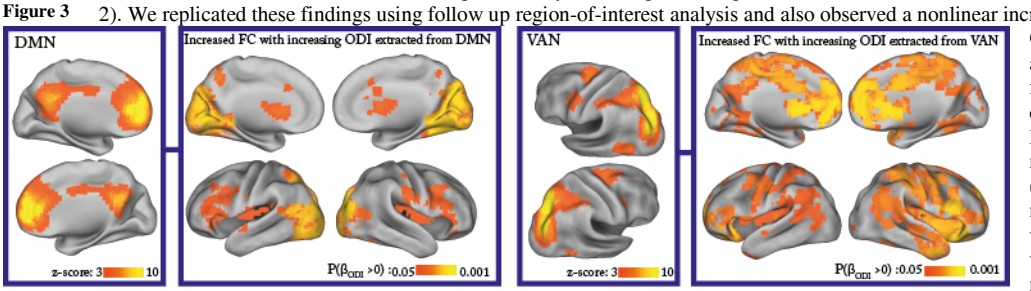

Figure 3

Interpretation: NODDI-GBSS provides a voxel-wise whole brain framework for identifying GM microstructural differences. Our in vivo findings align very closely with the postmortem data, and provide evidence for vulnerability and compensatory neural mechanisms of cognitive-aging in gray matter microstructure that have functional and cognitive impact in vivo.

References: 1. Zhang H, Schneider T, Wheeler-Kingshott CA, Alexander DC. NODDI: practical in vivo neurite orientation dispersion and density imaging of the human brain. NeuroImage. 2012;61:1000-1016. 2. Ball G, Srinivasan L, Aljabar P, et al. Development of cortical microstructure in the preterm human brain. PNAS. 2013;110:9541-9546. 3. Smith SM, Jenkinson M, Johansen-Berg H, et al. Tract-based spatial statistics: voxelwise analysis of multi-subject diffusion data. Neuroimage. 2006; 31:1487-1505.