Mode of variation in brain structure identifies network linking protracted development, early degeneration and vulnerability to disease

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Introduction and Objective

Several theories tie in developmental and ageing processes in humans. One model for brain structure is for instance the "last-in-first-out" hypothesis, whereby age-related degeneration in the grey matter mirrors development, with the areas of the brain thought to develop the latest degenerating first (Raz *et al.*, 2005). However, direct evidence for such a link in human brain structure between ageing and development remains elusive. Here, we have taken a purely data-driven approach to assess inter-subject brain structure variability among 484 healthy subjects across the lifespan.

Methods

- 484 right-handed healthy volunteers covering the lifespan (age range from 8 to 85 years old, 220 males)
- 12-channel head coil, 1.5-T Siemens Avanto scanner (Siemens Medical Solutions, Erlangen, Germany), no hardware upgrades and only minor software upgrades, whole-brain T1w images using MPRAGE: TR/TE/TI=2400/3.61/1000ms, flip angle of 8°, matrix 192 × 192, FOV 240mm, voxel size 1.25×1.25×1.2 mm3, 160 sagittal slices, two repeats.
- Brain extraction of T1w images using FreeSurfer, measures of GM volume using FSL-VBM (Douaud *et al.*, 2007), GM thickness and GM area using FreeSurfer (Fischl and Dale, 2000).
- All GM images were given as input to linked-ICA with 70 components. Linked-ICA is an entirely data-driven approach which makes it possible to combine several imaging modalities. Its main goal is to model the imaging data as a set of interpretable features (independent components), each one characterising a single, biophysically plausible mode of variability across all subjects' images.

Results

- From this decomposition based solely on the structural information in the images (e.g., the analysis was "blind" to the participants' age), we identified one large-scale component comprising most transmodal areas (Mesulam, 1998): lateral PFC, FEF, intra-parietal sulcus, superior temporal sulcus, posterior cingulate cortex and medial temporal lobe (**Figure 1**). Post-hoc, we show a strong quadratic relationship of this cross-modal component with age peaking at 40y. This component intrinsically describes a network of GM regions developing at a young age relatively slowly *compared with the rest of the brain*, but presenting accelerated age-related degeneration at an old age = "last-in-first-out".
- GM regions of this component show vulnerability to disorders that impact on brain structure during adolescence and ageing: this network matched GM regions atrophic in Alzheimer's (**Figure 2 left**, r=0.55, $p<10^{-3}$), and GM regions showing an altered developmental trajectory in adolescent-onset schizophrenia (**Figure 3 left**, r=0.44, $p<10^{-3}$). This component also allowed for good discrimination of the Alzheimer's and schizophrenic patients compared with their corresponding controls: 72% and 83% accuracy, respectively.
- Regression analyses showed specific, high linear correlation between the network's strength and intelligence scale (PIQ) and episodic memory (CVLT-DR) in the 484 healthy subjects (r=0.30 and r=0.40 respectively, $p<10^{-3}$), two cognitive measures that are hallmarks of schizophrenia and Alzheimer's respectively (**Figures 2, 3 right**).

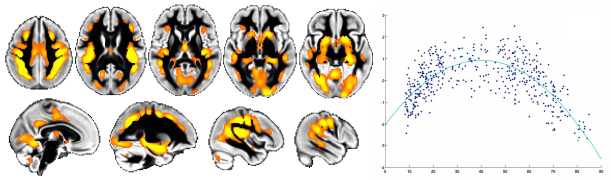

Figure 1: Last-in-first-out network of gray matter regions shows post-hoc quadratic relationship with age.

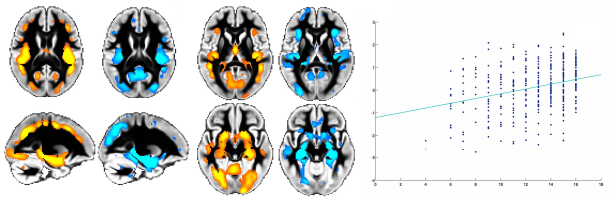

Figure 2: Last-in-first-out network spatially corresponds to structural pattern of abnormalities in Alzheimer's (blue) and correlates with episodic memory in healthy subjects.

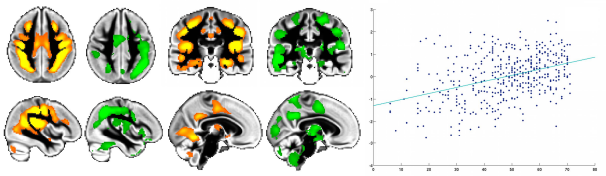

Figure 3: Last-in-first-out network spatially corresponds to structural pattern of abnormalities in schizophrenia (green) and correlates with intelligence scale in healthy subjects.

Conclusion

Here, we have been able to characterise **a network of grey matter regions intrinsically defining the "last-in-first-out hypothesis"** in healthy subjects. We show how this network, derived solely from **healthy subjects' brain structure**, remarkably **explains the pattern of structural abnormalities seen in two disorders at both ends of the life spectrum**: schizophrenia and Alzheimer's, how it relates to their main cognitive symptoms and accurately predicts these two disorders. We suggest that the spatial pattern in these two disorders is therefore not so much specific to the respective disease process itself, as it is to its **timing in interfering with healthy cerebral development and aging**.