Investigating a structural network linked to development and aging with quantitative T1 imaging

Frauke Beyer[1,4], Shahrzad Kharabian Masouleh[5], H. Lina Schaare[1,2], Arno Villringer[1,2,3,4], A. Veronica Witte[1]

[1]Department of Neurology, Max Planck Institute for Human Cognitive and Brain Sciences, Leipzig, Germany
[2]LIFE – Leipzig Research Center for Civilization Diseases, University of Leipzig, Leipzig, Germany
[3]Clinic of Cognitive Neurology, University of Leipzig, Leipzig, Germany
[4]SFB 1052 – Obesity Mechanisms, University of Leipzig, Leipzig, Germany
[5] Institute of Neuroscience and Medicine (INM-7), Research Center Jülich, Jülich, Germany

fbeyer@cbs.mpg.de

Introduction

Cortical gray matter (GM) structure varies across individuals according to spatially distinct patterns and these common structural properties might arise from synchronized processes of development [1]. More specifically, a structural network of transmodal brain regions has been proposed to link maturation, healthy aging and heightened vulnerability to psychiatric disease [2] and cardiovascular risk factors [3]. This transmodal network shows an inverted-U-shape trajectory across the life span which seems to parallel the development of intra-cortical myelin [4]. It might thus reflect "last in- first out" processes [5].

Goals: In this study, we aim to replicate the inverted U-shaped GM network described in [2] and characterize it regarding a putative involvement of intra-cortical myelin, estimated with quantitative T1 imaging.

Research questions: Can we replicate the inverted U-shape network in an independent sample of healthy adults? Is it linked to R1-values, a proxy of intra-cortical myelin?

Methods

Study sample:

- 302 healthy participants from the Leipzig Study for Mind-Body-Emotion Interactions (no stroke, major brain pathology or intake of centrally active medication) in two age groups (20 – 50 years (N=228), 56 – 77 years (N=74), 178 males)

Magnetic resonance imaging (MRI)(3T Siemens Verio)

- T1-weighted and quantitative T1 images from MP2RAGE sequence with repetition time = 5000 ms, echo time = 2.92 ms, inversion time 1/2 = 700/2500 ms, field of view: 256 x 240 x 176, voxel size: 1mm^3)

Preprocessing of MRI data:

- Cortical thickness (CT) and surface area were obtained from the T1-weighted MR images using Freesurfer v.5.3.0
- The qT1 values were extracted at 25% of the cortical thickness from the white/gray matter boundary and inverted to obtain the relaxation rate R1 (in Hz) as a proxy for myelin.
- All surface values were downsampled to fsaverage5 template and smoothed with Gaussian kernel of FWHM 10mm
- FSL-VBM version 5.0.9 was used to extract gray matter density (GMD) estimates
- Two Linked Independent Component Analysis (FLICA) were performed with 70 components according to [2] in FSL 5.0.9.
- basic FLICA included VBM, CT, area and R1-FLICA additionally used R1 values.
- Spatial maps were upsampled to 2mm isotropic/fsaverage template for visualization purpose as described in [2].

Statistical analysis:

- For both analyses, retained components were selected based on the first knee in the scree plot.
- We calculated the spatial correlation of the warped VBM components with the publicly available template from [2] using FSL version 5.0.9 . We first warped the mean GM image of our sample to the mean GM image of the template. Then, we applied the warp to the GM independent components. FSL's fslcc was used to calculate spatial cross-correlation with the MNI mask.
- The quadratic relationship between the loadings of the components and age of the participants was tested against a null model including sex and age as a linear term in R version 3.2.3.

Results

Results of FLICA analysis

The Bayesian ICA algorithm implemented in FLICA reduced the number of components to N=57 for the basic FLICA, and N=69 for the R1-FLICA. Scree plot of the basic FLICA indicated 6 components to be retained, for R1-FLICA we selected 4 components for further analyis.

Description of the resulting components

Three global components were similarly retrieved in basic/R1-FLICA: IC1/IC2 was driven by GMD and thickness (weights: GMD=0.27/0.16, CT=0.72/0.84, area=0.01/0, R1=0/0), IC2/3 had strongest contribution from area (GMD=0.05/0.05, CT=0.03/0.05, area=0.87/0.9 R1=0.05) and IC3/IC4 were driven by thickness (and R1) (GMD=0.01/0.01, CT=0.95/0.27, area=0.03/0.01, R1=0.70). In basic-FLICA, three additional VBM-driven IC appeared which were not selected in R1-FLICA (IC4,5,6). In R1-FLICA, the main variance of R1 (84%) was captured in an additional component (IC1) (see Figure 1).

1

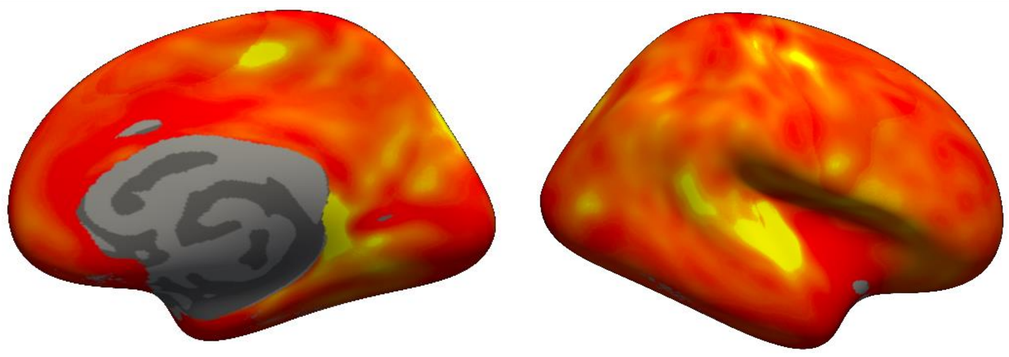

Figure 1: Right hemisphere view of IC1 from R1-FLICA. The component is entirely driven by R1 and captures most R1 variance (84%). The Z-values range from 10 to 12.

Comparison with the inverted-U-shape network

IC1/IC2 in basic/R1-FLICA respectively were most strongly correlated with the previously proposed inverted-U-shape network on GMD maps (r^2=0.45). Yet, compared to the original results, CT weight was higher, and GMD weight was lower in basic/R1-FLICA. Also, the GMD map did not show the pronounced deep gray matter loading (see Figure 2). Therefore, IC1/2 might rather represent the global linear component of age-related atrophy and cortical thinning which was captured in a separate network in the original publication [2]. IC1/2 explained 18%/10%, 52/50% of total variance in GMD/CT for basic/R1-ICA, respectively. The components R1 values did not contribute to this component in the R1-FLICA. No other GMD maps revealed by basic/R1-FLICA were similar to the inverted-U-shape network.

2

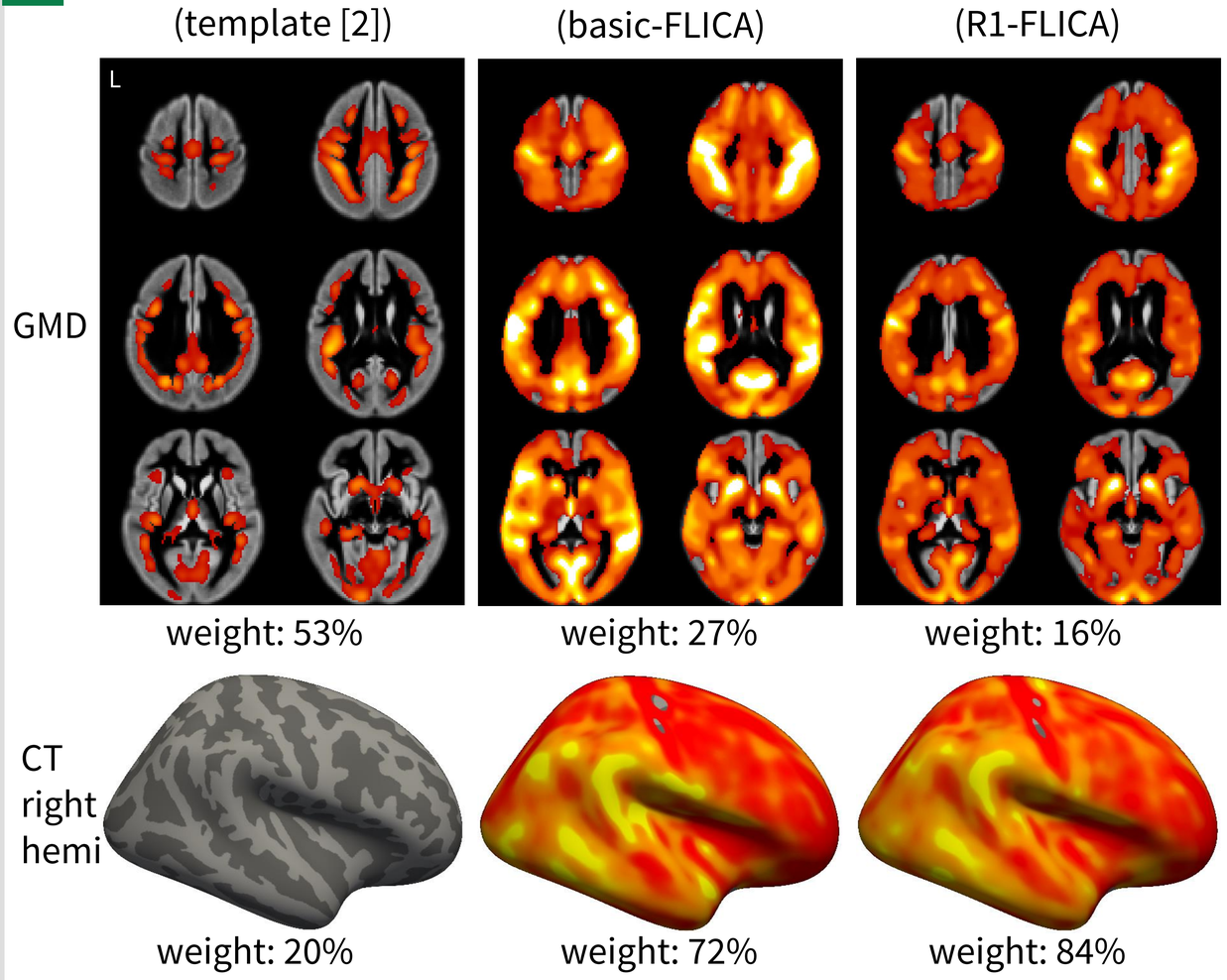

Figure 2: GMD and right hemisphere CT maps from(A) inverted-U-shape network from [2] (B) IC1 from basic-FLICA and (C) IC2 from R1-FLICA. GMD/CT: Z-scale: 3 – 15

Association of age and IC1/2

Older adults had lower IC strength than younger adults in both analyses. A linear model described the association of age and GMD of IC1/2 better than a quadratic model (quadratic vs. linear model: F=1.9, p=0.18). This further indicates that IC1/2 does not represent the inverted-U-shape but rather reflects general age-related atrophy.

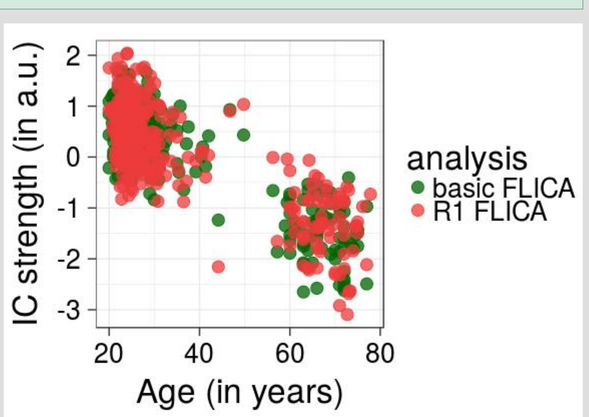

Figure 3: Assocation of Age and IC1/2

Discussion

We failed to replicate the inverted-U-shape network in a FLICA analysis conducted according to [2]. Instead, we found a component of age-related atrophy with spatial overlap but different modality weights and age trajectory than the component of interest. Therefore, we speculate that the inverted U-shape network could not be separated from the global age-related atrophy component, possibly due to the limited age range of the sample.

Importantly, when repeating FLICA with R1-values we did not see a contribution of R1-values to the global atrophy component. Instead, most of the variance of R1-values was captured in IC1 of R1-FLICA. Possibly, the low variability in R1 values might have caused the segregation into a single component. Taken together, we could not replicate the inverted-U-shape network nor show an involvement of R1 in our sample. We therefore suggest to further characterize the inverted-U-shape network, and its role for vulnerability to psychiatric disease, in a sample with more uniform age distribution and more precise measures of intra-cortical myelin, like T1w/T2w imaging.

References

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