Functional architecture of the aging brain

Roni Setton[1], Laetitia Mwilambwe-Tshilobo[1], Manesh Girn[1], Amber Lockrow[1], Giulia Baracchini[1], Alexander Lowe[2], Benjamin Cassidy[3], Jian Li[4,5], Danilo Bzdok[1,7,8,9,10], Richard Leahy[11], Tian Ge[12], Daniel Margulies[13], Bratislav Misic[1,8], Boris Bernhardt[1,8], W. Stevens[14], Felipe De Brigard[15,16], Prantik Kundu[17], Gary Turner[14], R. Nathan Spreng[1,8,18,19]

[1] Montreal Neurological Institute, McGill University, Montreal, QC, Canada

[2] Institute of Neurology, University College London

[3] Department of Psychiatry, University of Toronto, Toronto, ON, Canada

[4]Athinoula A. Martinos Center for Biomedical Imaging, Massachusetts General Hospital and Harvard Medical School, Charlestown, MA, USA

[5] Department of Neurology, Massachusetts General Hospital and Harvard Medical School, Boston, MA, USA

[6] National Institutes of Health, National Institute on Aging, Baltimore, MD, USA

[7] Department of Biomedical Engineering, McGill University, Montreal, QC, Canada

[8] McConnell Brain Imaging Centre, McGill University, Montreal, QC, Canada

[9] School of Computer Science, McGill University, Montreal, QC, Canada

[10] Mila – Quebec Artificial Intelligence Institute, Montreal, QC, Canada

[11] Department of Electrical Engineering-Systems, University of Southern California, Los Angeles, CA, USA

[12] Psychiatric and Neurodevelopmental Genetics Unit, Center for Genomic Medicine, Massachusetts General Hospital, Boston, MA, USA

[13] Integrative Neuroscience and Cognition Center (UMR 8002), Centre National de la Recherche Scientifique (CNRS) and Université de Paris, Paris, France

[14] Department of Psychology, York University, Toronto, ON, Canada

[15] Department of Philosophy, Duke University, Durham, NC, USA

[16] Department of Psychology and Neuroscience, Durham, NC, USA

[17] Icahn School of Medicine at Mount Sinai, New York, NY, USA

[18] Departments of Psychiatry and Psychology, McGill University, Montreal, QC, Canada

[19] Douglas Mental Health University Institute, Verdun, QC, Canada

Introduction

Alteration to the intrinsic network architecture of the brain is a significant feature of neurocognitive aging, but its measurement remains susceptible to several challenges. Recent advances can overcome these challenges to refine accounts of functional brain change in older adulthood. Multi-echo fMRI (ME-fMRI) can reliably distinguish between BOLD signal and noise[1], a crucial consideration when age group differences may be attributable to either BOLD or noise. Individualized, participant-specific, parcellations that preserve individual variability in functional organization have shown higher internal validity for older adults compared to standard parcellations[2] and improve behavioral predictions[3]. Here we leverage these

advances in combination with multivariate analytical approaches to provide a comprehensive account of the functional architecture of the aging brain.

Methods

Two ME-fMRI runs (TR=3000ms; TE1=13.7ms, TE2=30ms, TE3=47ms; 3mm isotropic voxels, 204 volumes) were collected in 181 younger (M=22.59y) and 120 older (M=68.63y) healthy adults. Imaging data were minimally preprocessed and optimally combined prior to denoising with multi-echo independent components analysis1. Group prior individualized parcellation[4] was then applied, where a group parcellation (400 parcels, 7 networks[5]) was refined by optimizing each participant's parcel boundaries with respect to their resting-state functional connectivity.

We defined "BOLD dimensionality" as the number of BOLD-like components remaining in the denoised time series and compared across groups. Partial least squares was then used to identify group differences in whole-brain functional connectivity. Brain connectivity scores were calculated from the resulting matrix to represent the degree to which a given participant expressed the connectivity pattern.

A subset of 283 participants (163 younger adults, 120 older adults) also underwent cognitive assessment involving tasks of episodic and semantic memory, executive function, and processing speed. Index scores were calculated for each task and associations with brain connectivity scores were examined.

Results

Younger adults displayed greater BOLD dimensionality than older adults ($t(298)=16.83$, $p<.001$; Cohen's $d=1.81$;Figure 1A). BOLD dimensionality decreased with age according to a power function ($R2=.547$; Figure 1B). Quantitative comparison of interregional functional connectivity between younger and older adults revealed a significant pattern of differences (Figure 2; permuted $p=0.0001$). Both increases and decreases were observed across the connectome (Figure 2E). Older adults demonstrated lower within-network connectivity across all 7networks (Figure 2F) and greater between-network connectivity of the visual and somatomotor networks (Figure2G). A higher brain connectivity score for each participant conveys stronger adherence to the pattern of connectivity observed for their age group. When brain connectivity scores were related to cognition, a single negative correlation emerged with executive function in older adults ($r(118)=-.350$, $p<.001$): greater between-network and lower within-network connectivity was associated with worse executive function in older adults.

Conclusion

Using a combination of advanced approaches, we observed that functional integration, reflected in reduced BOLD signal dimensionality and increased between-network connectivity, is a core feature of brain aging. Early developmental trajectories of functional brain change are marked by increasing functional integration, associated with cognitive gains. Our findings demonstrate that functional integration, and resultant dedifferentiation of intrinsic networks, continues into older adulthood and becomes negatively associated with complex cognition. We suggest that this lifespan trajectory of network integration includes an inflection point, marking a transition from adaptive to maladaptive functional organization of the aging brain.

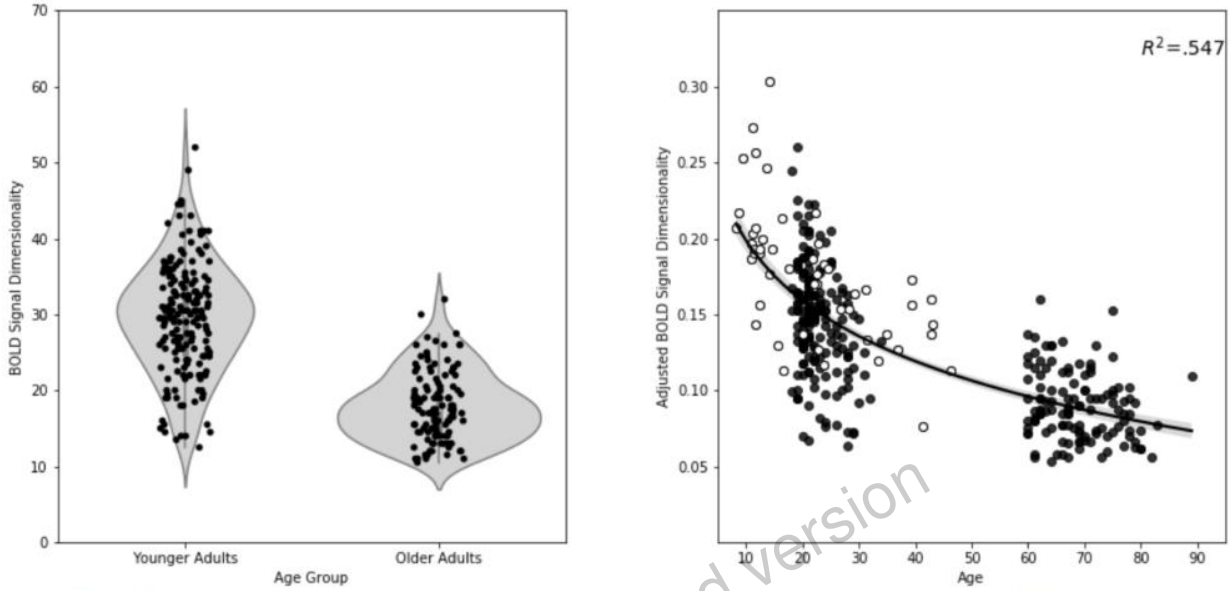

Figure 1. BOLD signal dimensionality as a function of age. **(A)** Violin plots show distributions of BOLD signal dimensionality, averaged across runs, by age group. **(B)** The scatter plot shows BOLD signal dimensionality by age with a power distribution and 95% confidence intervals overlaid. Points in white comprise data from an independent developmental sample (N=51, M_{age}=21.9y; age range, 8.3 – 46.2y (6)). Adjusted BOLD signal dimensionality = Total number of accepted BOLD components / number of time points acquired.

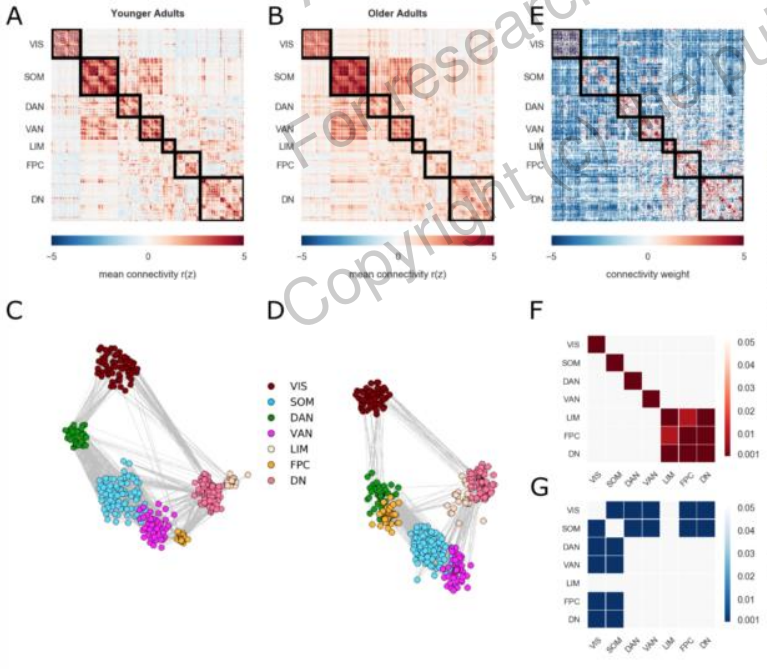

Figure 2. Functional connectomics in younger and older adults. Mean RSFC parcellated for the 400-parcellated MEFC data in **(A)** younger and **(B)** older adults. Spring-embedded plots with a 7-network solution (5% edge density) of the mean correlation matrices for **(C)** younger and **(D)** older adults. **(E)** Multivariate PLS analysis was used to identify age-related differences in RSFC between younger and older adults. Red color indicates greater RSFC in younger adults, and blue color indicates greater RSFC in older adults. **(F-G)** Network contributions reflecting differences in large-scale distributed networks. **(F)** Greater within- and between- network connectivity in younger, lower in older adults. **(G)** Greater within- and between- network connectivity in older adults, lower in younger adults. The mean positive **(F)** and negative **(G)** bootstrap ratios within and between networks are expressed as a p-value for each z-score relative to a permuted null model. Higher values indicate greater connectivity than predicted by the null distribution. VIS = visual, SOM=somatomotor, DAN= dorsal attention, VAN = ventral attention, LIM = limbic, FPC= frontoparietal, DN= default.

References

1. P. Kundu, S. J. Inati, J. W. Evans, W.-M. Luh, P. A. Bandettini, "Differentiating BOLD and non-BOLD signals in fMRI time series using multi-echo EPI", *NeuroImage*, vol. 60, no. 3, pp. 1759–1770, 2012. DOI: 10.1016/j.neuroimage.2011.12.028.
2. L. Han, N. K. Savalia, M. Y. Chan, P. F. Agres, A. S. Nair, G. S. Wig, "Functional parcellation of the cerebral cortex across the human adult lifespan", *Cerebral Cortex*, vol. 28, no. 12, pp. 4403–4423, 2018. DOI: 10.1093/cercor/bhy218.
3. R. Kong, et al., Individual-specific areal-level parcellations improve functional connectivity prediction of behavior (preprint). Neuroscience. DOI: 10.1101/2021.01.16.426943.
4. M. Chong, C. Bhushan, A. A. Joshi, S. Choi, J. P. Haldar, D. W. Shattuck, R. N. Spreng, R. M. Leahy, "Individual parcellation of resting fMRI with a group functional connectivity prior", *NeuroImage*, vol. 156, pp. 87–100, 2017. DOI: 10.1016/j.neuroimage.2017.04.054.
5. A. Schaefer, R. Kong, E. M. Gordon, T. O. Laumann, X.-N. Zuo, A. J. Holmes, S. B. Eickhoff, B. T. T. Yeo, "Local-global parcellation of the human cerebral cortex from intrinsic functional connectivity MRI", *Cerebral Cortex*, vol. 28, no. 9, pp. 3095–3114, 2018. DOI: 10.1093/cercor/bhx179.