Multivariate Association Between Cognitive Function and Brain Tissue in Healthy Older Adults

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Introduction:

The aging process is often accompanied by cognitive alterations, collectively known as cognitive aging, which can lead to a decline in functional capacity [1]. Normal aging is also accompanied by macro- and micro- structural changes in the brain, such as gray matter (GM) and white matter (WM) atrophy [2]–[4], iron accumulation, and demyelination [5]–[7]. Microstructural changes in the brain are interconnected; for instance, elevation in iron content is associated to demyelination, collectively contributing to synaptic density loss and brain atrophy [8]–[10]. Therefore, a comprehensive examination of these concurrent brain microstructural properties with respect to cognitive aging is imperative. This exploration can reveal regions in the brain that undergo changes at an earlier stage, potentially serving as early indicators preceding the onset of cognitive issues.

Methods:

This study investigates the association between cognition and various brain micro- and macro-structural properties, as assessed by multiparametric quantitative MRI maps, in healthy older adults (baseline: n=101, 31.68% male, follow-up: n=67, 32.84% male). Participants underwent cognitive assessments at baseline and after 2 years, resulting in composite scores for attention, executive function, and memory. The preclinical Alzheimer's cognitive composite (PACC5) was calculated for all participants [11]. Quantitative MRI data were obtained at baseline using a multiparametric mapping protocol. The association between cognitive composite scores and tissue properties, both at baseline and for the rate of cognitive decline over 2 years, was tested using univariate and multivariate general linear models.

Results:

The univariate analyses conducted at baseline revealed several significant associations between cognition and brain structural properties. Executive function showed a positive correlation with GM volume in the cerebellum, while memory exhibited positive associations with myelin content in the cerebellum and hippocampus. GM iron levels were linked to lower memory scores in the right insula. A significant positive correlation emerged between WM myelin content and PACC5 in the left middle temporal region. Conversely, higher iron levels in the medial orbitofrontal cortex were associated with smaller PACC5 values. Results from the univariate regression analysis are presented in Table 1. As illustrated in Figure 1, the multivariate regression analyses at baseline revealed significant associations between executive function and the combination of macro- and microstructural changes in the cerebellum, as well as between memory and combined changes in the cingulate gyrus and insula (See Table 2 for detailed results). Finally, multivariate regression did not reveal any significant correlations between the different maps and the rate of decline in cognition. Moreover, it is important to note that, throughout the study duration, we did not observe a decline in cognition among the subjects.

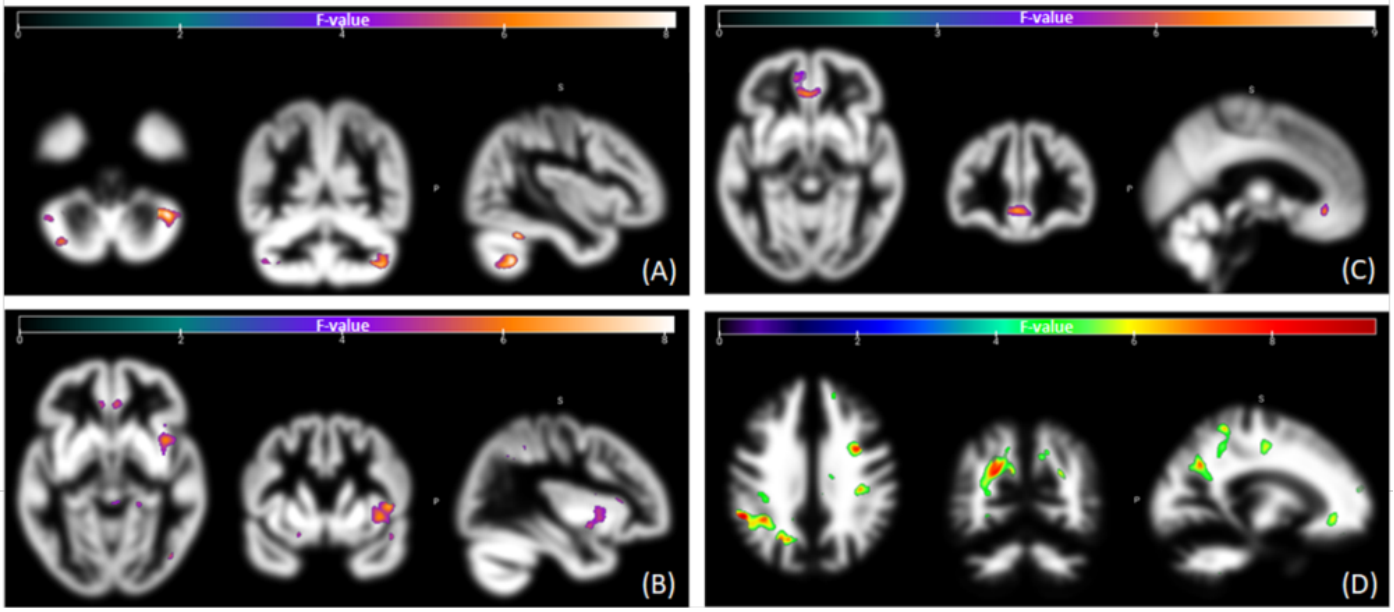

Figure 1. Statistical parametric maps (SPM) for the multivariate regression analyses within gray and white matter. The multivariate SPMs (mSPMs) show correlations between all modalities within either white matter or gray matter with respect to different cognitive composite scores (A) executive function, (B) memory, and (C) PACC5, within the gray matter; (D) memory within the white matter. The mSPMs are illustrated at p<.001 uncorrected for illustration purposes, and they are overlayed on the mean population gray matter and white matter maps in MNI space.

·Statistical parametric maps (SPM) for the multivariate regression analyses within gray and white matter.

Table 1. Univariate regression results at the baseline, showing the correlation between different maps and cognition. Brain regions were labeled with the AAL3 atlas toolbox in SPM. Coordinates are reported in MNI space. FWER correction was applied for $p < 0.05$ at either voxel or cluster level.

peak [x y z] Coordinates	Tissue	Modality	Cluster P-value FWERcorr (voxel-level)	Cluster Size #voxels	Brain Region
Executive function (df=96)					
[35 -53 -45]	GM	GMvol	0.000(0.000)	6156	Right Cerebellum
[39 -27 -17]	WM	PD	0.020(0.003)	1170	Right Fusiform
Global memory (df=96)					
[-11 -46 -45]	GM	MTsat	0.009(0.026)	1991	Left Cerebellum
[-29 -18 -14]	GM	MTsat	0.002(0.004)	1105	Left Hippocampus
[9 -48 -23]	GM	MTsat	0.011(0.631)	1908	Right Cerebellum
[-24 -64 29]	WM	MTsat	0.000(0.009)	16565	Left Mid. Occipital
[-9 -48 -27]	WM	MTsat	0.003(0.009)	7305	Left Cerebellum
[9 -33 57]	WM	MTsat	0.000(0.054)	23922	Right Paracentral lobule
[-17 5 -18]	GM	PD	0.040(0.372)	1359	Left Olfactory bulb
[36 -26 35]	WM	PD	0.033(0.010)	1025	Right Postcentral
[29 37 19]	WM	PD	0.004(0.019)	1662	Right Mid. Frontal Gyrus
[-52 -45 40]	WM	PD	0.676 (0.023)	236	Left Inf. Parietal
[-31 -32 48]	WM	PD	0.017(0.030)	1218	Left Postcentral
[-14 55 17]	WM	PD	0.385(0.046)	390	Left. Sup. Frontal Gyrus
[46 13 0]	GM	R2*	0.005(0.214)	2276	Right Insula
PACC5 (df=96)					
[-60 -28 -12]	WM	MTsat	0.467(0.036)	652	Left Mid. Temporal Gyrus
[0 36 -9]	GM	R2*	0.138(0.032)	979	Left Pre ACC

Key: GM: gray matter, WM: white matter, ACC: anterior cingulate cortex.

Table 2. Multivariate regression results at the baseline, showing the correlation between different maps together (in GM or WM) and cognition. Brain regions were labeled with the AAL3 atlas toolbox in SPM. Coordinates are reported in MNI space. FWER correction was applied for $p < 0.05$ at voxel or cluster level.

peak [x y z] Coordinates	Tissue	Cluster P-value (voxel-level)	Cluster Size #voxels	Brain Region
Executive function				
[41 -53 -45]	GM	0.026(0.089)	1370	Right Cerebellum
Global memory				
[3 34 -12]	GM	0.015(0.057)	1557	Right ACG
[47 10 4]	GM	0.005(0.435)	1974	Right Insula
[-50 -47 31]	WM	0.001(0.005)	3402	Left Supramarginal
[30 37 19]	WM	0.074(0.016)	1253	Right Mid. Frontal
[-21 -62 29]	WM	0.003(0.036)	3011	Left Sup. Occipital
[33 3 36]	WM	0.210(0.045)	794	Right Mid. Frontal
[-49 -49 33]	WM	0.000(0.000)	1577	Left Sup. Marginal area
[32 4 37]	WM	0.002(0.000)	801	Right Mid. Frontal gyrus
PACC5				
[-2 36 -9]	GM	0.026(0.254)	1379	Left ACG

Key: ACG: anterior cingulate Gyrus

·Univariate and multivariate regression results at the baseline

Conclusions:

In summary, these findings highlight the intricate connections between cognition and brain micro- and macro-structural properties in aging, with a particular emphasis on the role of the cerebellum in cognitive aging. However, a more prolonged study is needed to further explore the association between the decline in cognition and concurrent changes in the brains.

Higher Cognitive Functions:

Executive Function, Cognitive Control and Decision Making

Lifespan Development:

Aging [1]

Modeling and Analysis Methods:

Multivariate Approaches [2]

Novel Imaging Acquisition Methods:

Multi-Modal Imaging

Keywords:

MRI
Multivariate
Other - cognitive aging, aging, quantitative MRI, MTsat, R2*, PD, memory, PACC5, Attention, Executive function

[1|2]Indicates the priority used for review

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Other

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Was any human subjects research approved by the relevant Institutional Review Board or ethics panel? NOTE: Any human subjects studies without IRB approval will be automatically rejected.

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Not applicable

Please indicate which methods were used in your research:

Structural MRI
Other, Please specify - quantitative MRI

For human MRI, what field strength scanner do you use?

3.0T

Which processing packages did you use for your study?

SPM
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Provide references using author date format

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