

Investigation Of The Association Of WMH Progression Within The Cholinergic Pathways With Cognitive Decline And The Potential Mechanism



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Background: We aimed to explore the association between white matter hyperintensities (WMH) progression within the cholinergic pathways and cognitive decline and to further reveal the potential mechanism underlying the relationship between WMH progression and cognitive decline by investigating whether the atrophy of brain structures receiving cholinergic projections is involved.

Methods: In the Taizhou Imaging Study (TIS) cohort, 321 participants were included in this study. Global cognitive function was evaluated using MMSE. Quantitative imaging analysis was performed to extract normalized WMH volume at baseline and follow-up, then to assess WMH progression. Meanwhile, longitudinal changes of subcortical regions and cortex that receive cholinergic projections were analyzed. Multivariable linear regression and partial correlation tests were performed to investigate the association of WMH progression in the cholinergic pathways with cognitive decline and longitudinal changes of brain structures, as well as the relationship between changes of brain structures and cognitive decline. The longitudinal changes of brain structures related to WMH progression were included as covariates in the analysis of the association between cholinergic WMH progression and cognitive decline.

Results: The baseline mean age of the study population was 59.58 (SD: 2.59) years. After a 6-year follow-up, the median of WMH progression in the whole brain was 0.79 (IQR: 0.33-2.01) mL. Both normalized global WMH progression (β = -0.150, P = 0.001) and cholinergic WMH progression (β = -0.350, P = 0.038) were associated with MMSE decline. Cholinergic WMH progression was also related to longitudinal changes of the volume of each subcortical region (FDR-corrected P < 0.05), but no significant correlation was found with longitudinal changes of cortex. When the longitudinal changes of amygdala, hippocampus, thalamus, and striatum were included as covariates in the analysis, the association coefficients between cholinergic WMH progression and cognitive decline were all reduced.

Conclusion: The longitudinal progression of WMH within the cholinergic pathways was closely related to global cognitive decline and the atrophy of subcortical structures projected by cholinergic fibers. The atrophy of subcortical structures could reduce the association between cholinergic WMH progression and cognitive decline. These results suggest that WMH progression within the cholinergic pathways may influence cognitive function by affecting the subcortical structures projected by cholinergic fibers.

Table 1. Association between global and cholinergic WMH progression and cognitive decline

	Model 1		Model 2	
	β (SE)	P	β (SE)	P
Global WMH progression	-0.146(0.043)	0.001*	-0.150(0.045)	0.001*
Cholinergic WMH progression	-0.342(0.161)	0.035*	-0.350(0.168)	0.038*

Abbreviations: WMH = white matter hyperintensity.
Model 1 is adjusted for baseline MMSE, age, sex, education years, follow-up years, and interval time between cognition assessment and MRI; Model 2 is additionally adjusted for vascular risk factors, including current smokers, current alcohol drinkers, hypertension, diabetes, and hyperlipidemia, based on Model 1. * P < 0.05.

Table 2. Association between global and cholinergic WMH progression and cognitive decline after adjustment for atrophy of brain structures

	β (SE)	P	Attenuation
Cholinergic WMH progression	-0.350(0.168)	0.038*	-
Cholinergic WMH progression, adjusted for amygdala atrophy	-0.323(0.168)	0.056	7.71%
Cholinergic WMH progression, adjusted for hippocampus atrophy	-0.314 (0.173)	0.071	10.29%
Cholinergic WMH progression, adjusted for thalamus atrophy	-0.297(0.175)	0.090	15.14%
Cholinergic WMH progression, adjusted for striatum atrophy	-0.255(0.171)	0.138	27.14%

Adjusted for baseline MMSE, age, sex, education years, follow-up years, interval time between cognition assessment and MRI, and vascular risk factors.

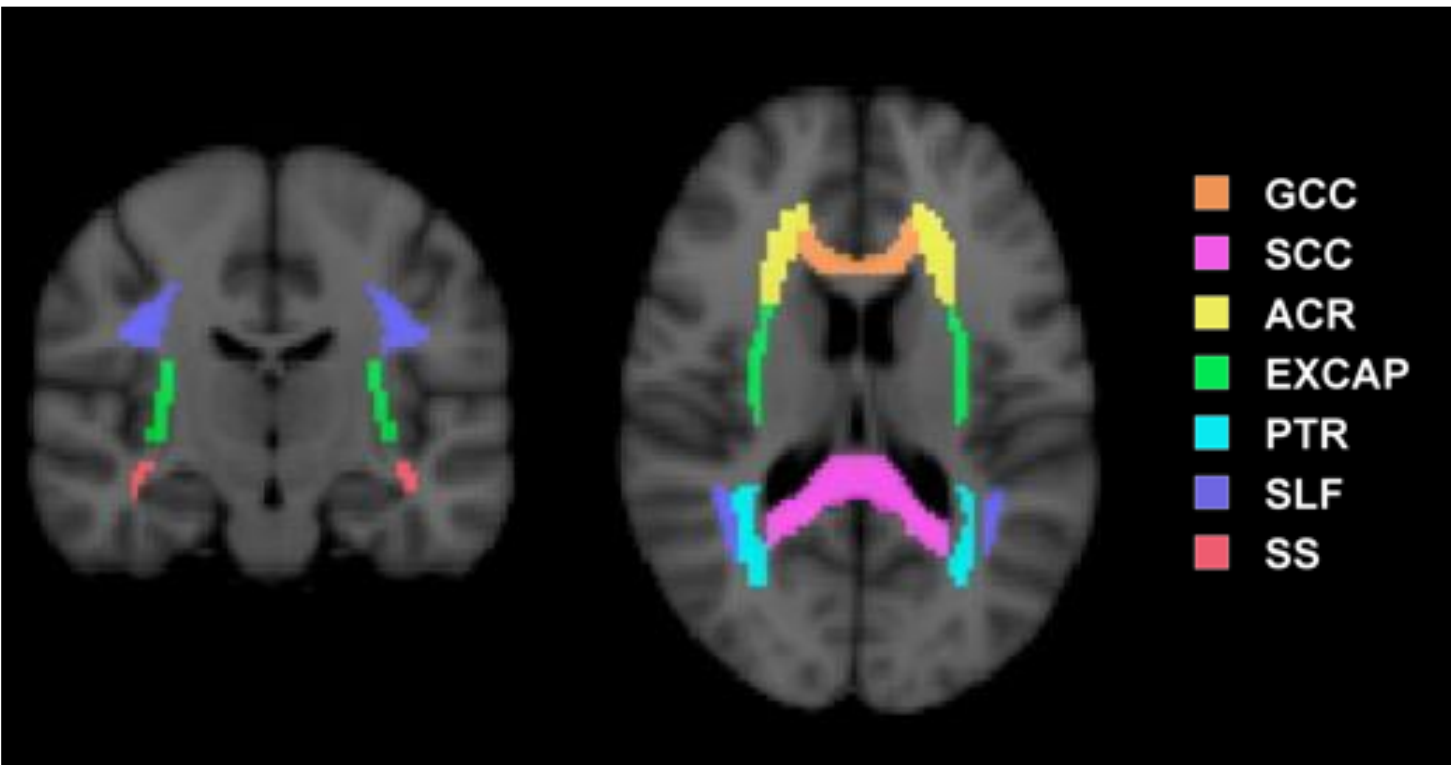


Figure 1. The cholinergic pathways in this study consist of seven white matter tracts.

These tracts are divided into three classes, i.e., commissural (GCC and SCC), association (EXCAP, SLF, and SS), and projection (ACR and PTR) tracts. Abbreviation: GCC, genu of corpus callosum; SCC, splenium of corpus callosum; ACR, anterior corona radiata; EXCAP, external capsule; PTR, posterior thalamic radiation; SLF, superior longitudinal fasciculus; SS, sagittal stratum.

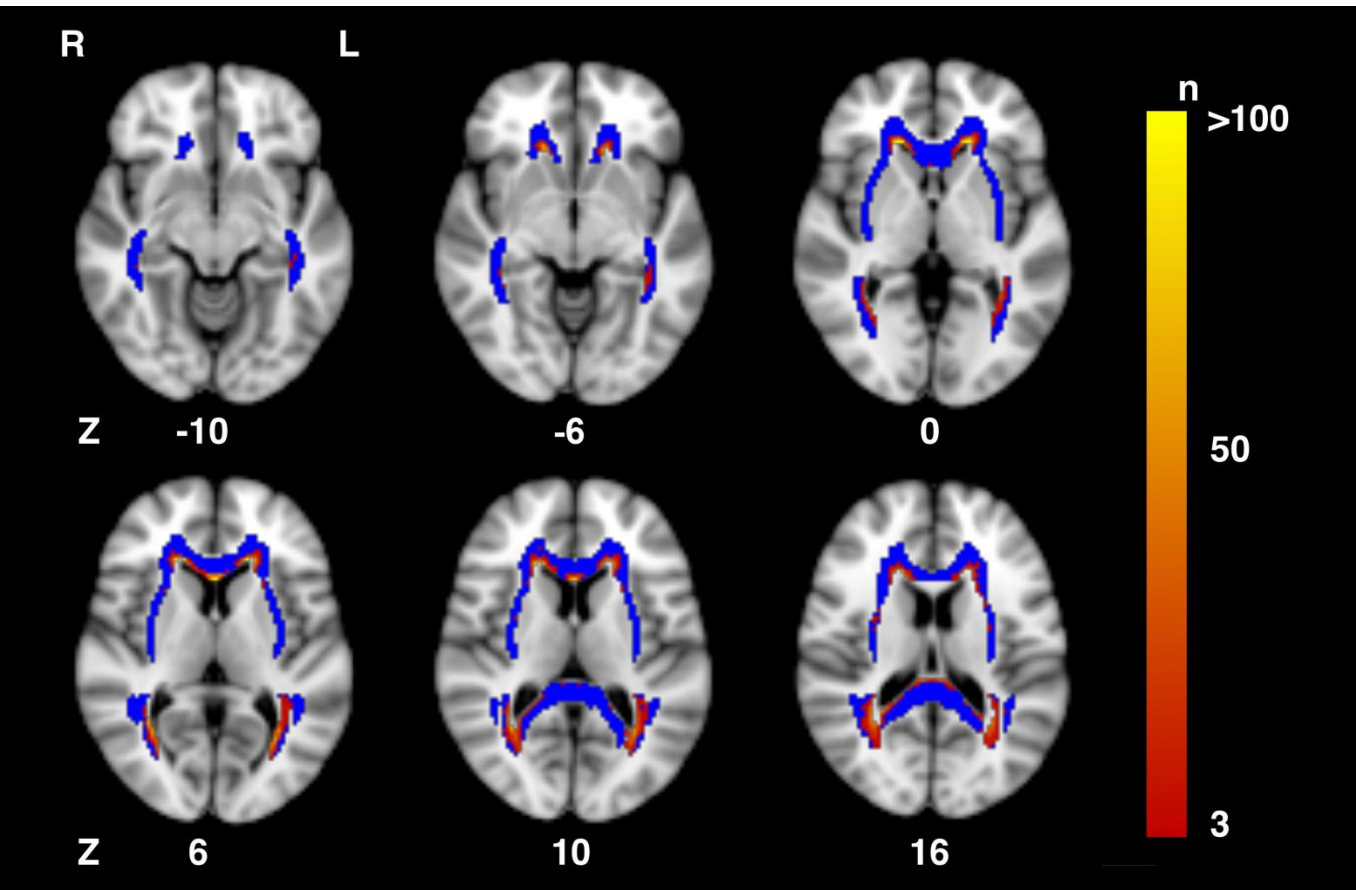


Figure 2. The distribution of WMH progression within the cholinergic pathways.