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Normative Brain Metabolite Reference Values and Age-Related Changes in Healthy Elderly Korean Adults

Junghyeon Park, M.D.[1], Hyeong Hun Lee, Ph.D.[2], Young-Ah Choi, M.D., Ph.D.[1], Seungho Hong M.D.[1], Si Won Yang, M.D.[1], Min Wook Kim, M.D., Ph.D.[1]

[1]Department of Rehabilitation Medicine, Incheon St. Mary's Hospital, College of Medicine, The Catholic University of Korea
[2]R&D Center, METLiT Inc, Seoul, Republic of Korea

Purpose

Proton magnetic resonance spectroscopy (^{1}H-MRS) enables non-invasive quantification of brain metabolite concentrations and is widely used to evaluate metabolic changes in stroke, traumatic brain injury, and cognitive decline. Accurate detection of metabolic abnormalities requires age- and region-specific normative references; however, multi-regional data for elderly Korean adults remain scarce. This study aimed to establish normative brain metabolite references in healthy elderly Korean adults using deep learning-based ^{1}H-MRS and to characterize regional distribution differences and age-related changes.

Methods

Twenty healthy elderly adults (11M/9F; mean age 70.6 ± 9.1 years; range 56–84) underwent single-voxel ^{1}H-MRS at 3T in the dorsal anterior cingulate cortex (DACC), posterior cingulate cortex (PCC), and occipital cortex (OC) using short TE (35 ms) PRESS. Twenty-one metabolites were quantified by the DL model; 14 with reliable quantification were selected for analysis and normalized to total creatine (tCr). Regional comparisons used Kruskal–Wallis tests with Bonferroni correction; age correlations used Spearman's ρ; sex differences were assessed by Mann–Whitney U tests. Sensitivity analyses after outlier removal verified robustness.

Results

Sixty MRS spectra (20 subjects×3 regions) were analyzed. Nine of 14 metabolites showed significant regional differences; five key metabolites are shown in Table 1. NAA/tCr and GABA/tCr were highest in OC, while mI/tCr and tCho/tCr were highest in DACC, demonstrating region-specific distribution patterns consistent with known cytoarchitectural characteristics. In exploratory (uncorrected) analyses, four metabolites showed negative age correlations in PCC: Asp/tCr (ρ=−0.638, p=.003), GSH/tCr (ρ=−0.542, p=.014), tNAA/tCr (ρ=−0.496, p=.026), and Gln/tCr (ρ=−0.473, p=.035), suggesting progressive neuronal integrity loss, reduced antioxidant defense, and altered glutamate–glutamine cycling with aging in this default mode network (DMN) hub (Table 2, Figure 1). In DACC, Glc/tCr showed a positive age correlation (ρ=+0.529, p=.017), potentially reflecting impaired glucose utilization.
However, none of these associations survived Benjamini–Hochberg FDR correction (all pFDR > 0.10); findings are therefore exploratory and require confirmation in larger cohorts. No metabolite showed a significant age correlation in OC (all p>.10), indicating metabolic stability across the 56–84 age range. No significant sex differences were observed.

Table 1. Comparison of key brain metabolite ratios to total creatine (tCr) across three brain regions in healthy elderly Korean adults (n=20).

Metabolite	DACC (mean ± SD)	PCC (mean ± SD)	OC (mean ± SD)	H	p
NAA/tCr	1.332±0.312	1.426±0.190	1.637±0.320	9.42	.009**
GABA/tCr	0.179±0.067	0.167±0.046	0.252±0.072	15.87	<.001***
mI/tCr	1.173±0.198	1.026±0.155	1.014±0.179	9.34	.009**
tCho/tCr	0.523±0.251	0.394±0.124	0.337±0.184	7.45	.024*
tNAA/tCr	1.439±0.235	1.537±0.167	1.739±0.278	13.04	.001**

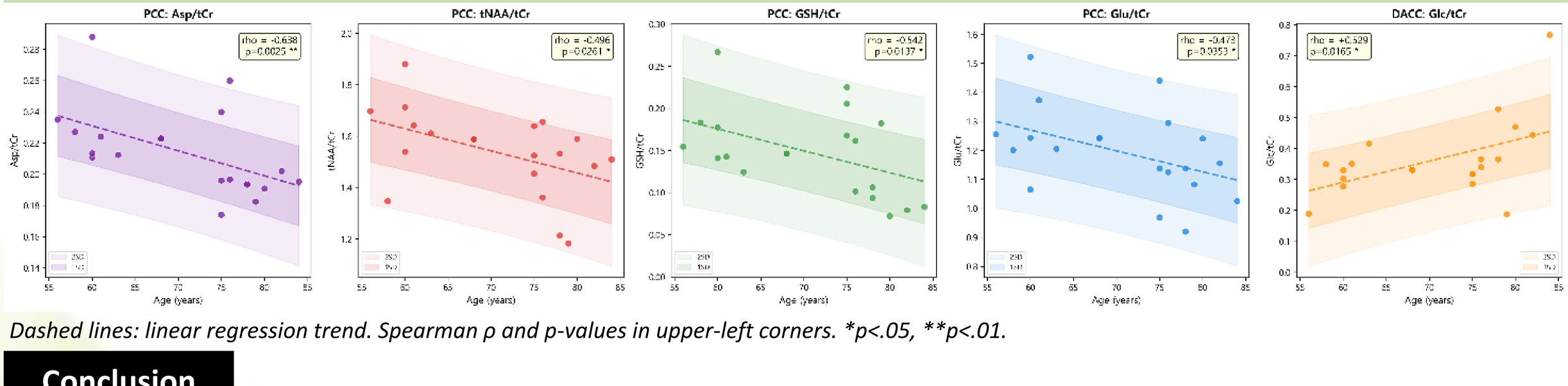
**p<.05, **p<.01, ***p<.001 (Kruskal–Wallis test with Bonferroni correction)*

Table 2. Brain metabolites showing statistically significant correlations with age, assessed by Spearman's rank correlation (ρ).

Region	Metabolite	ρ	p	Interpretation
PCC	Asp/tCr	−0.638	.003**	Neurotransmitter substrate decline
PCC	GSH/tCr	−0.542	.014*	Reduced antioxidant defense
PCC	tNAA/tCr	−0.496	.026*	Neuronal integrity loss
PCC	Gln/tCr	−0.473	.035*	Glu–Gln cycle alteration
DACC	Glc/tCr	+0.529	.017*	Impaired glucose utilization

**p<.05, **p<.01; OC: no significant correlations (all p>.10)*

Figure 1. Scatter plots showing brain metabolites with significant age correlations.



*Dashed lines: linear regression trend. Spearman ρ and p-values in upper-left corners. *p<.05, **p<.01.*

Conclusion

This study established multi-regional normative brain metabolite references for healthy elderly Korean adults using deep learning-based ^{1}H-MRS. Key metabolites showed region-specific distributions consistent with prior literature. In PCC, a core DMN hub, age-dependent decreases in Asp, tNAA, GSH, and Gln were suggested in exploratory analyses, highlighting the potential need for region-specific age consideration in cognitive rehabilitation assessments; confirmation in larger cohorts is warranted. OC demonstrated metabolic stability, supporting its use as a stable reference region without age correction. These normative data provide a benchmark for evaluating brain metabolic changes in stroke, traumatic brain injury, and cognitive decline.