Investigating Relationships Between Glutamate and Dopamine Synthesis Capacity in Healthy Older Adults: A Multimodal MRS and PET Investigation

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Background

What is MRS?

Magnetic Resonance Spectroscopy (MRS) is a non-invasive MRI technique that measures brain metabolite concentrations in vivo — including glutamate, GABA, NAA, and others — providing a window into neurochemical factors linked to cognition and aging

Neurochemistry & Cognitive Aging

Working memory (WM) declines are among the most consistent cognitive changes in healthy aging. Converging evidence links WM variation to alterations in cortical excitatory/inhibitory balance and dopaminergic signaling in frontostriatal circuits[2, 3]

Lower prefrontal glutamate→ **greater WM forgetting rates**[5]

Prefrontal GABA/Glx **correlates with WM scores** in older adults[6]

Dopamine Synthesis Capacity

The PET tracer [^{18}F]fluoro-L-m-tyrosine (FMT) measures dopamine synthesis capacity (K_i). In older adults, synthesis capacity may be upregulated as a compensatory mechanism even as receptors/transporters decline[4]

Neurometabolites Measured

Single Voxel MRS - PRESS Sequence - Osprey Pipeline

Glx
Glutamate + glutamine

Primary excitatory neurotransmitter; drives corticostriatal signaling and modulates dopamine synthesis capacity.

tNAA
NAA + NAAG

Marker of neuronal integrity and viability; declines with age and neurodegeneration, correlates with cognitive performance[8].

Cr
Total creatine

Reflects cellular energy metabolism; used as an internal reference for metabolite quantification in MRS analyses.

tCho
Total choline-containing compounds

Index of membrane turnover and myelination; positively associated with years of education in the present sample.

Lactate
Anaerobic metabolite

Indicator of anaerobic glycolysis and oxidative stress in neural tissue.

mI
Myo-inositol

Glial marker; elevated in neuroinflammation[7]. Positively linked to DA synthesis

Asc
Ascorbate (Vitamin C)

Antioxidant; protects against oxidative stress[9]. Positively linked to DA synthesis

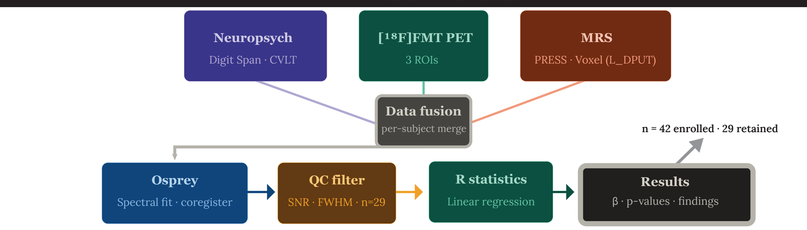
Hypotheses

1. Putamen Glx will be positively associated with [^{18}F]FMT K_i

2. Both Glx and [^{18}F]FMT K_i will jointly predict Digit Span Backward performance

3. Regional specificity: dorsal vs. ventral striatal subregions may show distinct neurochemical–dopamine coupling profiles

Methods



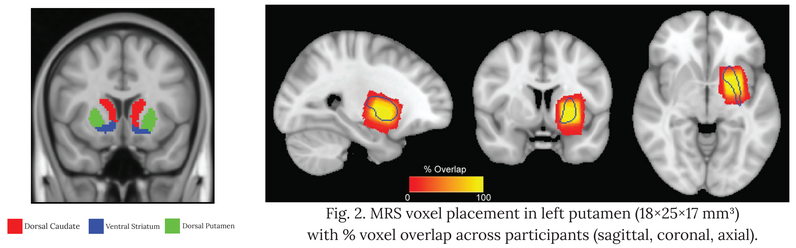


Fig. 2. MRS voxel placement in left putamen (18×25×17 mm³) with % voxel overlap across participants (sagittal, coronal, axial).

MRS Acquisition: PRESS sequence - Processed with Osprey[10]: spectral alignment, coregistration, tissue segmentation, metabolite quantification.

QC: Spectra with FWHM <0.01 ppm or SNR <3 excluded; voxel placement verified manually. 29/42 participants retained.

[^{18}F]FMT PET: Participants injected with ~2.5 mCi [18F]FMT; 90-min dynamic acquisition. Patlak graphical analysis with posterior cerebellar reference region; partial volume correction applied. ROIs: left dorsal putamen (L_DPUT), dorsal caudate (L_DCA), ventral striatum (L_VST).

Statistical Models: Linear regression predicting [^{18}F]FMT K_i and Digit Span Backward, covarying age, sex, and years of education. Each metabolite entered separately.

Results

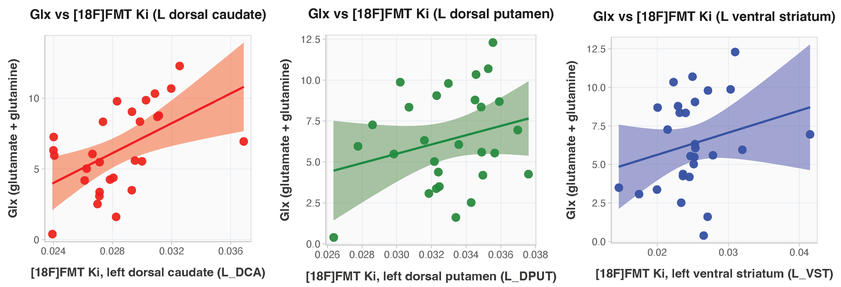


Figure 2. Associations between putamen Glx (glutamate + glutamine) concentration and [^{18}F]FMT Ki (dopamine synthesis capacity) across three left-hemisphere striatal regions of interest: left dorsal caudate (L_DCA), left dorsal putamen (L_DPUT), and left ventral striatum (L_VST). Regression lines with 95% confidence intervals are shown. A significant positive association was observed in the left dorsal caudate (β = 530.07, p = 0.008), with a positive but non-significant trend in the left dorsal putamen (β = 284.01, p = 0.24). Each data point represents one participant (n = 29).

Key Findings

Region	Metabolite	β	p-value	Finding
L Dorsal Caudate	Glx	530.07	**0.008** *	↑Glx → ↑DA synthesis
L Dorsal Putamen	Glx	284.01	0.24 (trend)	Positive trend
L Ventral Striatum	myo-Inositol	282.41	**0.0004** **	Glial coupling
L Ventral Striatum	Ascorbate	148.61	**0.002** *	Antioxidant coupling
L Dorsal Putamen	NAAG (age)	0.047	**0.015** †	↑NAAG with age
WM (Backwards DigitSpan)	FMT K_i (D_PUT)	410.48	0.054 (trend)	↑Ki→ ↑Digit Span

(p < 0.05 ** p < 0.001 † age-metabolite association All models covaried age, sex, years of education)

Table 1. Summary of key regression findings examining associations between putamen neurometabolites and dopamine synthesis capacity, working memory, and age. Each model included age, sex, and years of education as covariates. Significant associations (p < 0.05) are bolded. * p < 0.05; ** p < 0.001; † age-metabolite association.

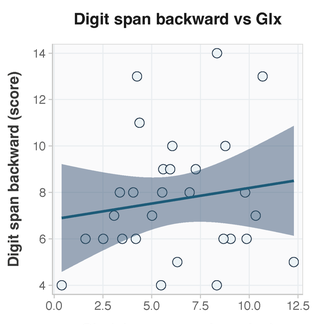


Figure 3. Association between putamen Glx (glutamate + glutamine) concentration and Digit Span Backward performance (n = 29). The regression line with 95% confidence interval indicates a positive but non-significant trend (β = 0.126, p = 0.595)

Discussion

Glx–Dopamine Coupling Preserved in Aging

The significant positive association between FMT in the DPUT and Glx in the DCA extends prior work in young adults by Lorenz et al. (2015) into an older adult population, suggesting that glutamate–dopamine coupling in dorsal striatum may be preserved across the lifespan[11]. Cortical glutamatergic projections provide the primary excitatory input to striatal medium spiny neurons, which are heavily modulated by dopaminergic inputs from the substantia nigra[12] — creating a functional intersection supporting motor control, reinforcement learning, and cognition.

Consistency Across Dorsal Striatum

Positive Glx–dopamine associations were not observed in the dorsal putamen and caudate, regions that share patterns of cortical connectivity and dopaminergic innervation from the substantia nigra[12]. The positive relationship for dopamine warrants further investigation in larger samples.

Working Memory

Glx did not directly predict WM scores. FMT Ki in the DPUT showed a trending association with WM scores that was not statistically significant (β = 410.48, p = 0.054). The current sample (n = 28) was underpowered to detect modest neurochemical–WM associations; future work with larger cohorts is needed to clarify this relationship.

Key takeaway: Glutamate–dopamine neurochemical coupling in dorsal striatum appears preserved in healthy aging. Individual differences in this coupling may contribute to variability in cognitive aging trajectories and represents a promising target for future investigation.

Future Directions

Larger cohort: Expand to full study sample to achieve power for detecting WM and motor performance associations

Longitudinal follow-up: Examine whether Glx–dopamine coupling strength predicts cognitive or motor decline over time

Functional connectivity (AFNI): Analyze whole-brain connectivity seeded from neurometabolite levels to characterize distributed network correlates

Motor outcomes: Extend analyses to grip strength and fine motor tasks, leveraging the putamen's central role in motor control

Clinical translation: Test whether striatal neurometabolite profiles predict vulnerability to neurodegeneration or cognitive impairment

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