

Imaging Cholinergic Integrity in Alzheimer’s Disease Using a Novel M4 Muscarinic PET Tracer, ¹¹C-MK6884: Comparison with ¹⁸F-FDG

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Background

- Alzheimer’s disease (AD) is characterized by progressive cholinergic neuron loss, contributing to cognitive decline and motivating acetylcholinesterase therapy.
- While ¹⁸F-FDG PET captures global synaptic dysfunction, it does not directly measure neurotransmitter-specific changes.
- ¹¹C-MK-6884 is a novel PET tracer targeting M4 muscarinic receptors, enabling *in vivo* assessment of cholinergic synaptic integrity¹.

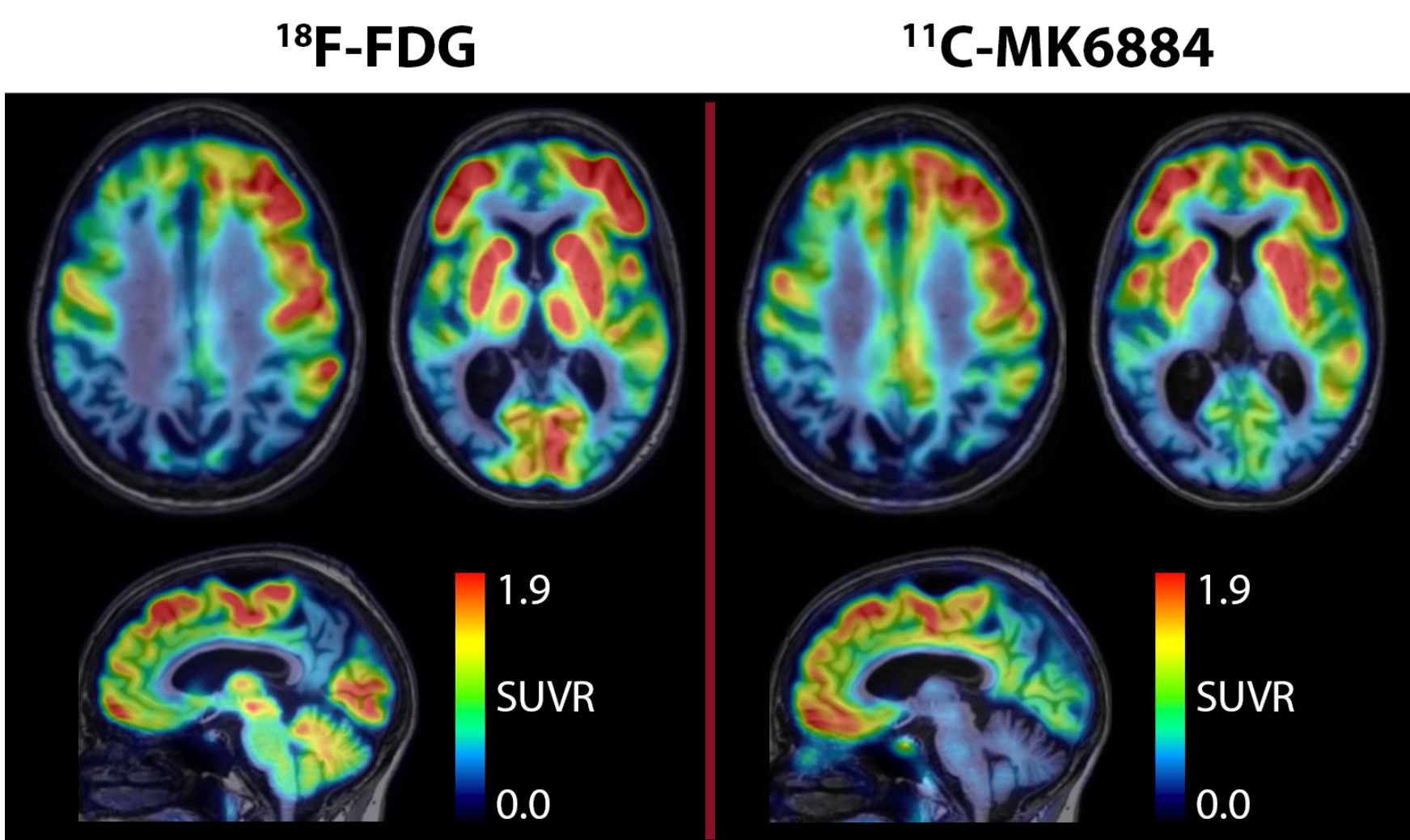
Objective: Using muscarinic receptor imaging, determine the brain topography of cholinergic loss in AD and its association with ¹⁸F-FDG PET and cognitive performance in AD.

Methods

- Eight participants with AD underwent ¹¹C-MK6884 M4 receptor and ¹⁸F-FDG metabolism PET.

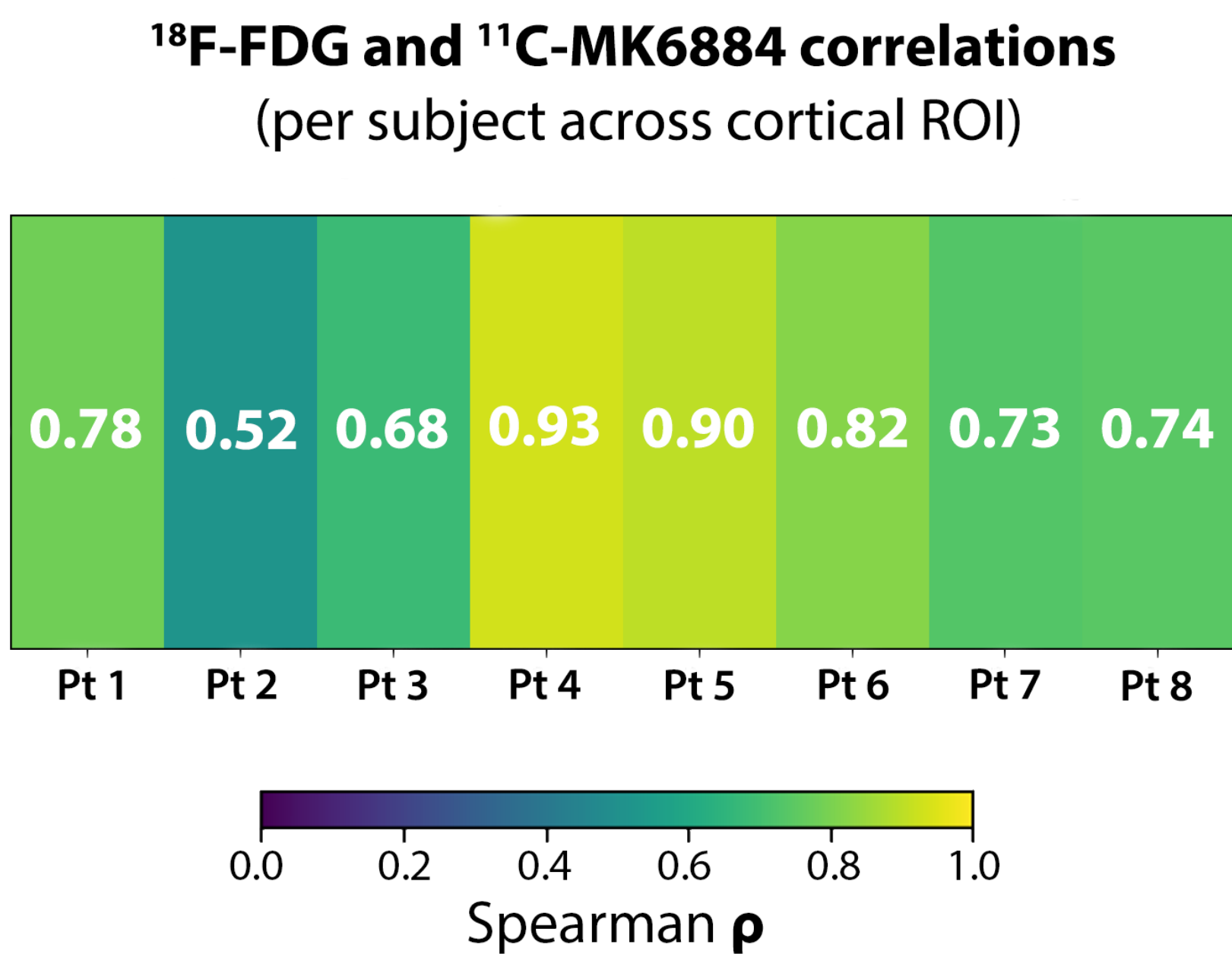
Demographics	AD Participants
N	8
Women/Men	4/4
Age, years (mean±SD)	68.9 ± 6.4
Years of Education (mean±SD)	15 ± 1.85
MMSE (mean±SD)	15.88 ± 4.79 / 30
DemTect (mean±SD)	3.75 ± 3.28 / 18
Clock Drawing Test (mean±SD)	6.00 ± 3.38 / 14
Ace – Naming (mean±SD)	9.13 ± 3.60 / 12

- Standardized uptake value ratios (SUVRs) were calculated for 32 cortical and subcortical regions for both tracers.
- For ¹¹C-MK6884, SUVRs were derived from 5–15 min frames using the whole cerebellum as reference. For ¹⁸F-FDG, SUVRs from 40–60 min frames were calculated using the pons as reference. SUVRs were z-scored across participants.
- Mixed-effects models (subject random intercepts, ROI fixed effects) estimated ¹¹C-MK6884/¹⁸F-FDG differences with 95% confidence intervals.
- A temporal meta-ROI, defined a priori as the bilateral temporal cortex, hippocampus, and amygdala, was used to examine associations between regional M4 signal and cognitive performance.
- Cognitive performance was assessed with a neuropsychological battery covering memory, language, executive function, and social cognition, summarized as a composite z-score.
- Partial Pearson correlations (adjusted for age and education) evaluated associations between regional SUVRs and cognition.



Representative PET images from a **single subject** comparing ¹⁸F-FDG and ¹¹C-MK6884 across matched axial and sagittal slices

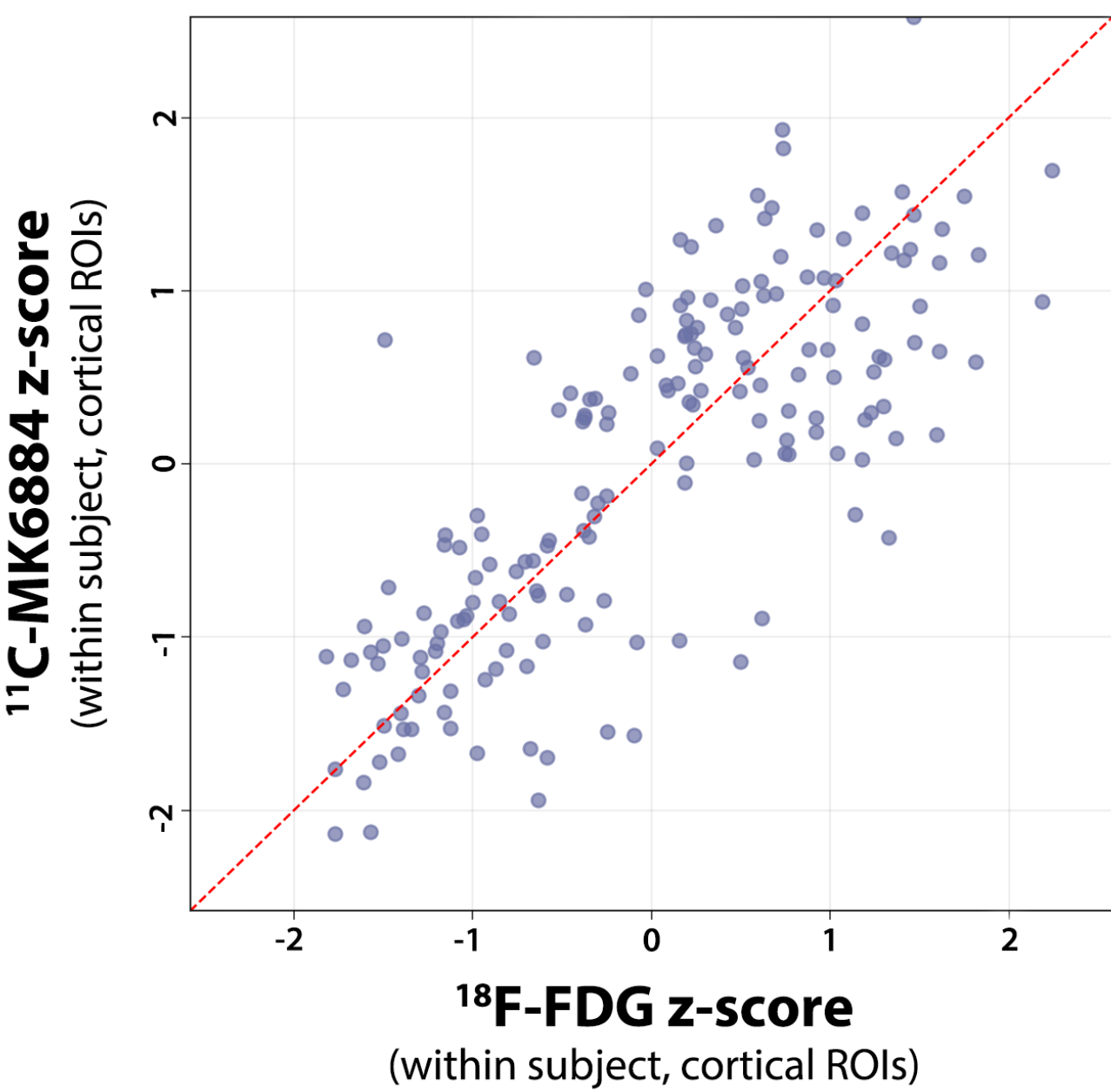
Minimal ¹¹C-MK6884 binding in cerebellum and thalamus is consistent with low M4 receptor density in those structures



Heat map showing subject-level Spearman correlations between ¹⁸F-FDG and ¹¹C-MK6884 across cortical ROIs, strongest in subjects 4–5

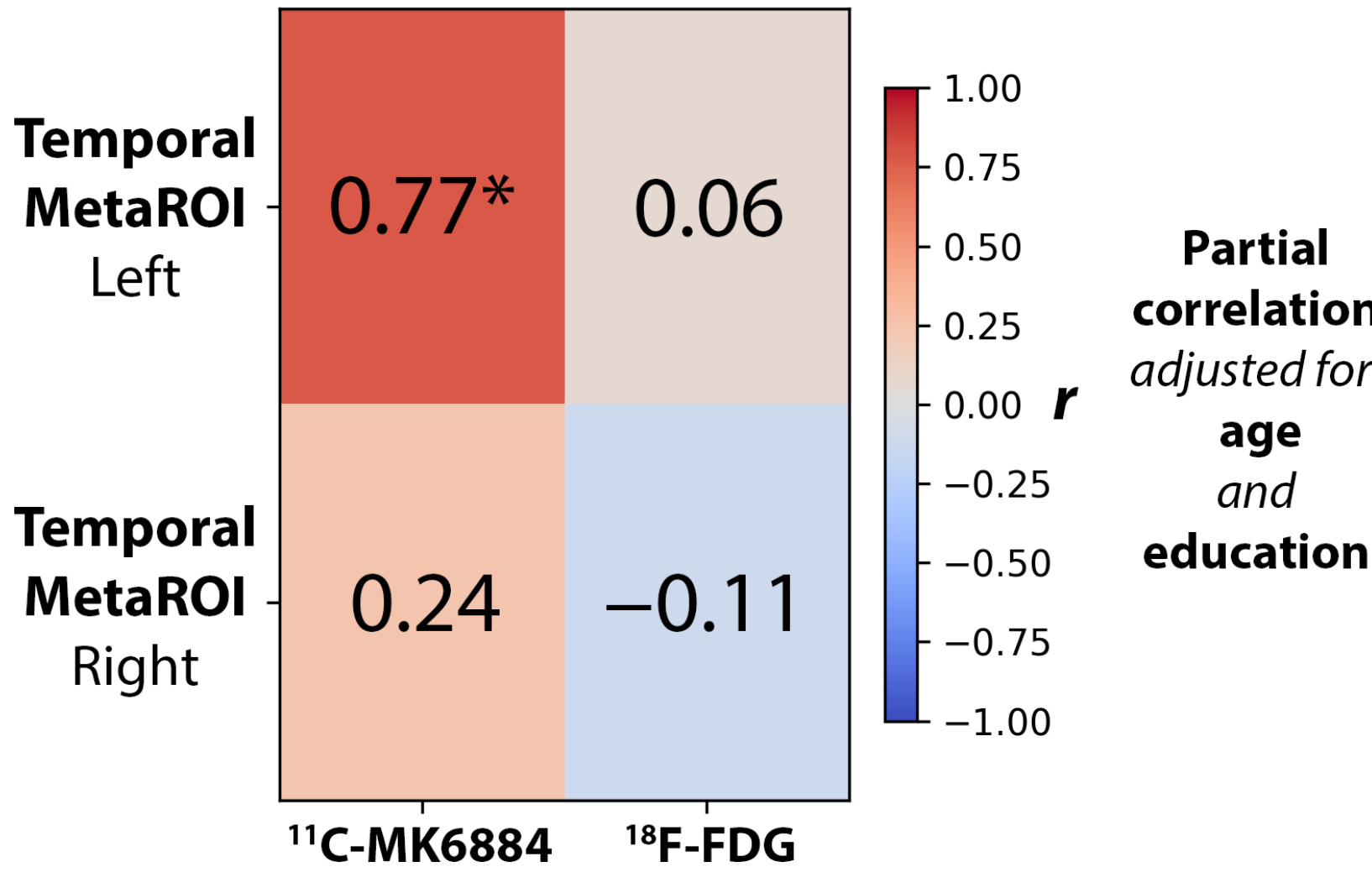
Results

¹⁸F-FDG and ¹¹C-MK-6884 correlations (group comparison across cortical ROIs)



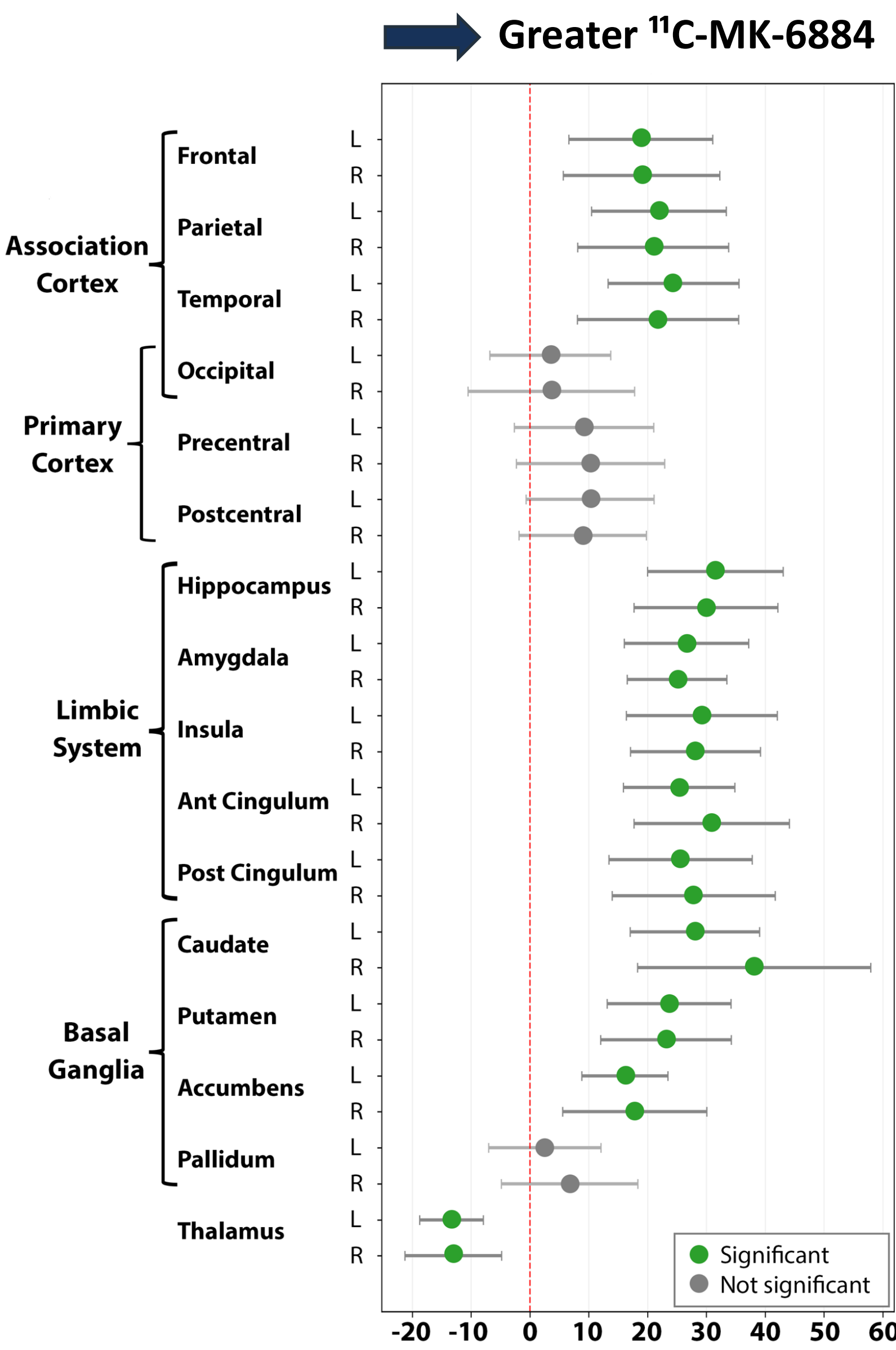
Z-normalized scatterplot illustrates a near-linear relationship across ROIs within subjects

Cognitive Composite (Z scores)



Partial correlations with cognition were significant only for ¹¹C-MK6884, stronger and near-linear in the left hemisphere, with no significant associations for ¹⁸F-FDG

¹¹C-MK6884 vs ¹⁸F-FDG % Differences



Compared with ¹⁸F-FDG, ¹¹C-MK6884 exhibited higher SUVRs in most regions, with the greatest differences in cingulate, temporal, insular, limbic, and striatal areas

Thalamic and cerebellar ¹¹C-MK6884 uptake was lower, and no differences were observed in primary cortical regions

Conclusions

- ¹¹C-MK6884 and ¹⁸F-FDG PET correlate strongly across cortical regions, yet ¹¹C-MK6884 highlights cholinergic-specific elevations in temporal, cingulate, and striatal areas, which align with cognition, suggesting complementary roles for muscarinic receptor and metabolic imaging in AD.
- The strong concordance between ¹¹C-MK6884 and ¹⁸F-FDG supports M4 PET as a marker of synaptic dysfunction and neurodegeneration, with potential advantages over FDG PET including a stable cerebellar reference region and possibly reduced sensitivity to metabolic confounds.

References

Li *et al.* The PET tracer [¹¹C]MK-6884 quantifies M4 muscarinic receptor in rhesus monkeys and patients with Alzheimer's disease. *Science translational medicine*, 2022.

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