Relationships between cerebrovascular health and tau PET uptake are associated with global cognition

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Introduction

Emerging evidence demonstrates a role for vascular dysfunction as a significant contributor to Alzheimer's pathophysiology[1-3], in addition to amyloid and tau

Associations between vascular dysfunction and tau pathology, and their effects on cognition remain poorly understood

To better understand these associations, we conducted analyses comparing brain tau PET and vascular dysfunction (cerebral blood flow deficits and pericyte injury) in discovery (USC) and replication (ADNI) cohorts

Aim

Investigate the relationships between tau (measured by [^{18}F]flortaucipir (FTP) PET) and vascular dysfunction (measured by arterial spin labeled (ASL) MRI and CSF sPDGFRβ) on cognition, as well as the influence of amyloid burden on these associations

Methods

Subject characteristics

	USC (n=68)			ADNI (n=138)		
Diagnostic group	CN (n=19)	MCI-risk (n=43)	MCI (n=6)	CN (n=73)	MCI (n=45)	AD (n=20)
Age (yr)[c]	62.7 ± 9.1	66.6 ± 6.9	68.7 ± 5.5	72.7 ± 6.6	74.3 ± 7.5	76.6 ± 7.3
Sex[c]	16 F (84%)	30 (70%)	4 F (67%)	39 F (53%)	18 (40%)	6 (29%)
Global GM CBF[c]	40.4 ± 6.4	41.0 ± 8.6	40.1 ± 14	48.3 ± 11	43.5 ± 11	40.7 ± 16[a]
Education (yrs)	16.9 ± 1.6	16.9 ± 2.5	15.5 ± 2.5	16.8 ± 2.4	16.6 ± 2.7	16.0 ± 2.6
APOE4 carrier*	11 (61%)	11 (26%)[a]	4 (67%)[b]	24 (34%)	11 (27%)	8 (44%)
MoCA	28.3 ± 1.5	26.5 ± 2.5[a]	20.3 ± 4.2[a,b]	25.8 ± 2.6	23.2 ± 3.2[a]	17.8 ± 4.4[a,b]
Amyloid (centiloids)	13.1 ± 15	17.1 ± 26	59.6 ± 44	20.9 ± 30	31.9 ± 44	89.7 ± 35[a,b]
Braak I/II FTP SUVR	1.15 ± 0.1	1.19 ± 0.1	1.54 ± 0.3[a,b]	1.19 ± 0.1	1.22 ± 0.2	1.40 ± 0.2
Braak III/IV FTP SUVR	1.13 ± 0.1	1.13 ± 0.1	1.52 ± 0.4[a,b]	1.13 ± 0.1	1.19 ± 0.2	1.50 ± 0.3[a,b]
Injected dose – FTP (mCi)[c]	10.5 ± 0.4	10.6 ± 1.5	10.4 ± 0.6	10.1 ± 0.8	10.2 ± 0.5	10.4 ± 0.3[a,b]

*Missing data for 10 participants

PET acquisition

All PET scans were acquired on a Siemens PET/CT scanner. Participants received an IV injection of tracer outside the scan room.
FBB/FBP – 4 x 5 minute frames of data were acquired starting 90 (FBB) and 50 (FBP) minutes post-injection.
FTP – 6 x 5 minute frames were acquired starting ~75 minutes post-injection.

MR acquisition

USC cohort: MR images were acquired on a Siemens 3T Prisma scanner. Structural MPRAGE images were acquired with the following parameters: TR=2400ms, TE=2.2ms, slice thickness=1.2mm
Pseudo-continuous arterial spin labeled (pCASL) images were acquired with the following parameters: TR=4300ms, TE=36.7ms, slice thickness=2.5mm, PLD=2000ms.
ADNI cohort: MR images were acquired according to the ADNI3 imaging protocol.

Data processing

Motion-corrected, mean PET and pCASL images were moved into a subject- and cohort-specific template space, created using Advanced Normalization Tools (ANTs). Cerebellar gray matter (FBB) and inferior cerebellar gray matter (FTP) were used as reference regions for the PET data. A modified level 3 CL calibration was performed to convert FBB and FBP SUVR to the same scale[4].
Cerebral blood flow (CBF) was quantified using methods recommended in Alsop et al[5]. Global mean CBF was extracted using a probabilistic gray matter map and used as a normalization factor for each CBF image[6].

Statistical analysis

We conducted voxelwise analyses to assess relationships between CBF and FTP PET uptake in a University of Southern California (USC) discovery cohort, the results of which were used to mask replication analyses in an independent Alzheimer's Disease Neuroimaging Initiative (ADNI) cohort. Secondary, gray matter- masked analyses were performed on the replication dataset. A voxelwise threshold of p<0.001 and an FDR-corrected cluster-level threshold of p<0.05 was used to determine significance for all voxelwise analyses. Regions showing significant CBF-tau associations were used as regions of interest for subsequent GLM analyses. We tested whether CBF/sPDGFRβ – tau relationships differed based on performance on the Montreal Cognitive Assessment (MoCA), a measure of global cognition, or as a function of amyloid burden by assessing MoCA*CBF and amyloid*CBF interaction effects in parallel models. Age, sex, education, diagnosis, amyloid burden, and gray matter volume were included as covariates.

[^{18}F]FTP-CBF Associations: Discovery and Replication

CBF and tau are negatively correlated in discovery and replication analyses.

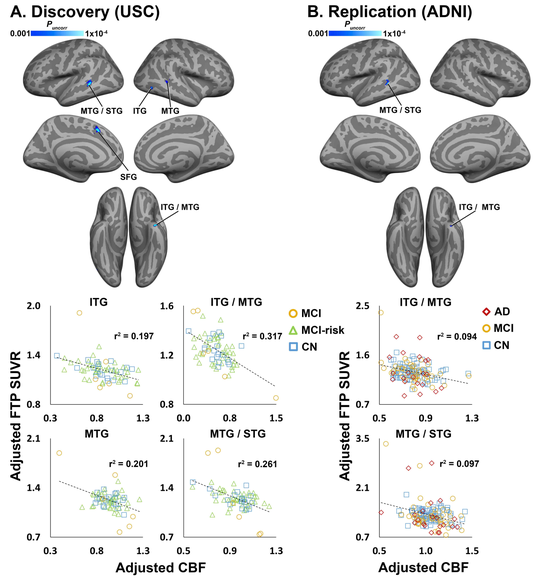

Figure 1. A) Clusters shown in blue colorscale depict significant negative correlations between CBF (normalized by global gray matter CBF) and FTP SUVR in the discovery cohort (n=68). B) Blue clusters show significant CBF-tau correlations in the ADNI replication cohort (n=138), masked with significant results from the discovery analysis (A). All analyses were covaried for age, sex, diagnosis, and amyloid CL. For visualization purposes, average values from selected significant clusters were extracted, adjusted for covariates, and plotted below each analysis.

GM-Masked Analyses: ADNI cohort

CBF and tau are negatively correlated in secondary, gray-matter masked ADNI analyses

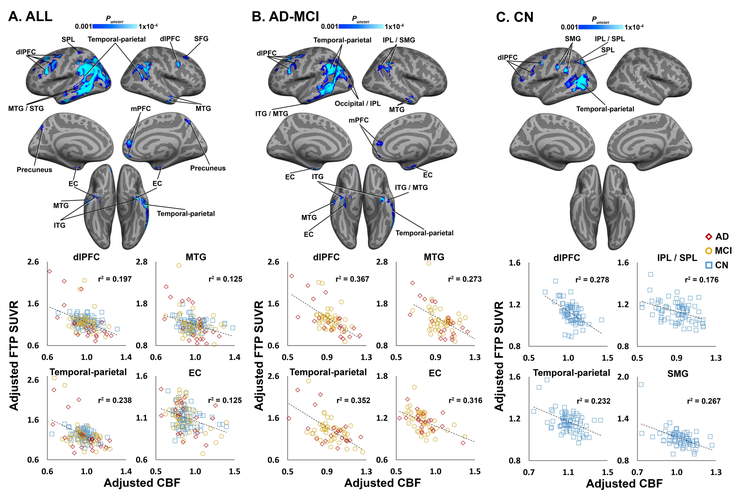

Figure 2. A) Clusters shown in blue colorscale depict significant negative correlations between CBF (normalized by global gray matter CBF) and FTP SUVR across the whole group (n=138). B) Blue clusters show significant CBF-tau correlations in the ADNI AD-MCI subgroup (n=65). C) Significant negative CBF-tau correlations in the ADNI CN subgroup (n=73). All analyses were covaried for age, sex, and amyloid CL (and diagnosis in A and B).

MoCA X CBF interactions

Participants with low global cognition show stronger relationships between CBF/sPDGFRβ and tau

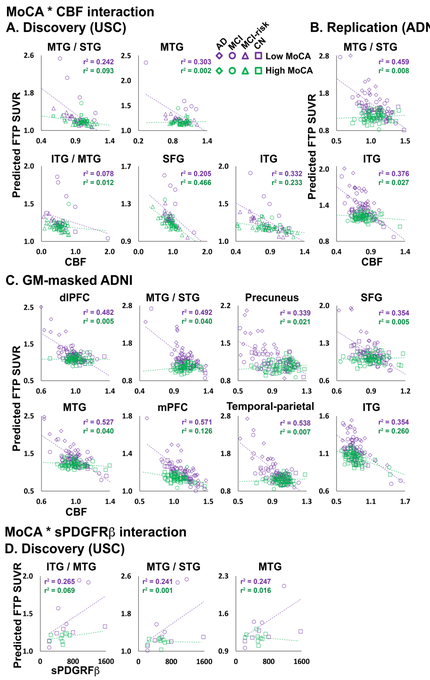

Figure 3. MoCA*CBF interaction effects on FTP SUVR in discovery (A), replication (B), and secondary GM-masked ADNI (C) analyses. MoCA*sPDGFRβ interaction effects on FTP SUVR from discovery analysis ROIs (D). Average CBF and FTP from significant clusters in the voxelwise analysis, or CSF sPDGFRβ, were entered into GLMs.

Amyloid X CBF interactions

Participants with high amyloid burden show stronger relationships between CBF/sPDGFRβ and tau

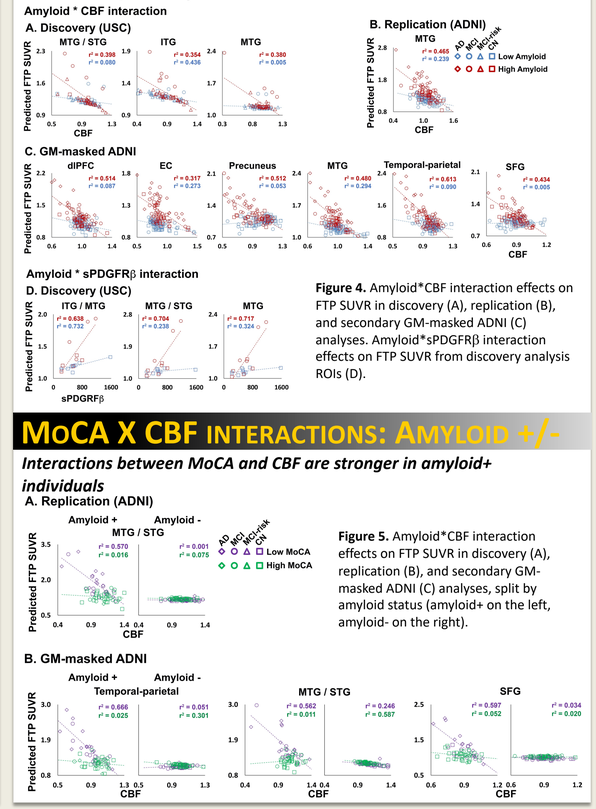

Figure 4. Amyloid*CBF interaction effects on FTP SUVR in discovery (A), replication (B), and secondary GM-masked ADNI (C) analyses. Amyloid*sPDGFRβ interaction effects on FTP SUVR from discovery analysis ROIs (D).

MoCA X CBF interactions: Amyloid +/-

Interactions between MoCA and CBF are stronger in amyloid+ individuals

Figure 5. Amyloid*CBF interaction effects on FTP SUVR in discovery (A), replication (B), and secondary GM-masked ADNI (C) analyses, split by amyloid status (amyloid+ on the left, amyloid- on the right).

Conclusions

- Two indices of impaired vascular health (decreased CBF and elevated CSF sPDGFRβ) are negatively correlated with [^{18}F]FTP binding in regions known to accumulate tau throughout the progression of Alzheimer's Disease, in two independent cohorts
- Linear relationships between CBF/sPDGFRβ and tau PET binding had steeper slopes as a function of poorer global cognition
- Linear CBF/sPDGFRβ – tau PET associations had steeper slopes in participants with higher amyloid burden
- MoCA*CBF/sPDGFRβ interactions on tau PET appeared to be driven by amyloid positivity

We provided evidence of associations between elevated tau PET signal and vascular dysfunction, reflected by decreased CBF and increased CSF sPDGFRβ, two independent measures of impaired vascular health

References & Acknowledgements

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R01 AG046928
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