

Decreased functional connectivity is associated with increased levels of CSF soluble-PDGFR β , a marker of blood brain barrier breakdown, in older adults

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INTRODUCTION

- Cerebrovascular dysfunction and vascular pathology are associated with Alzheimer's disease (AD)¹ along with decreased functional connectivity (FC) in DMN regions²
- BBB breakdown has already been observed in DMN regions at early stages of AD (MCI)³

In this study, CSF sPDGFR β is used as a direct marker for BBB breakdown to examine extent vascular damage can have on FC among DMN regions

METHODS

All participants were recruited through USC, Alzheimer's Disease Research Center (ADRC) in LA, CA

•89 participants were included based: 1. T1-weighted MPRAGE scan 2. resting state functional magnetic resonance imaging (rsfMRI) scan 3. cerebrospinal fluid (CSF) biomarker data 90 days from scan date

•Meso Scale Discovery (MSD) human multiplex assay used to determine CSF levels of sPDGFR β in CSF (ng/mL). Standard curves generated using recombinant human PDGFR β

•rsfMRI images were preprocessed in CONN-toolbox v20b⁴. Preprocessing consisted of motion correction, spatial normalization, coregistration of structural and functional images to the MNI template, smoothing with a 5mm FWHM Gaussian kernel, and band-pass filtering of 0.009–0.1 Hz

•Mean BOLD signal time course was extracted from ROIs predefined by the Harvard-Oxford atlas and resting state networks⁵. Pearson's correlation coefficients were calculated for all pairwise comparisons between ROIs areas.

RESULTS

DEMOGRAPHICS

	CDR=0 (N=67)	CDR>0 (N=22)	Mean (S.D.) N=89
MRI age	64.57 (10.43)	65.5 (15.43)	64.83 (11.73)
Sex (m/f)	31/36	11/11	41/48
APOE4 status (noncarrier/carrier)	37/30	11/11	48/41
CDR (0/.5/1/3)	n/a	n/a	66/18/3/1
sPDGFR β (ng/mL)	695.99 (347.30)	704.96 (369.54)	685.63 (351.72)
Averaged FC among DMN regions	0.06 (.07)	0.05(.07)	0.12 (0.07)

TABLE 1: DEMOGRAPHICS TABLE. Cohort characteristics used in analysis

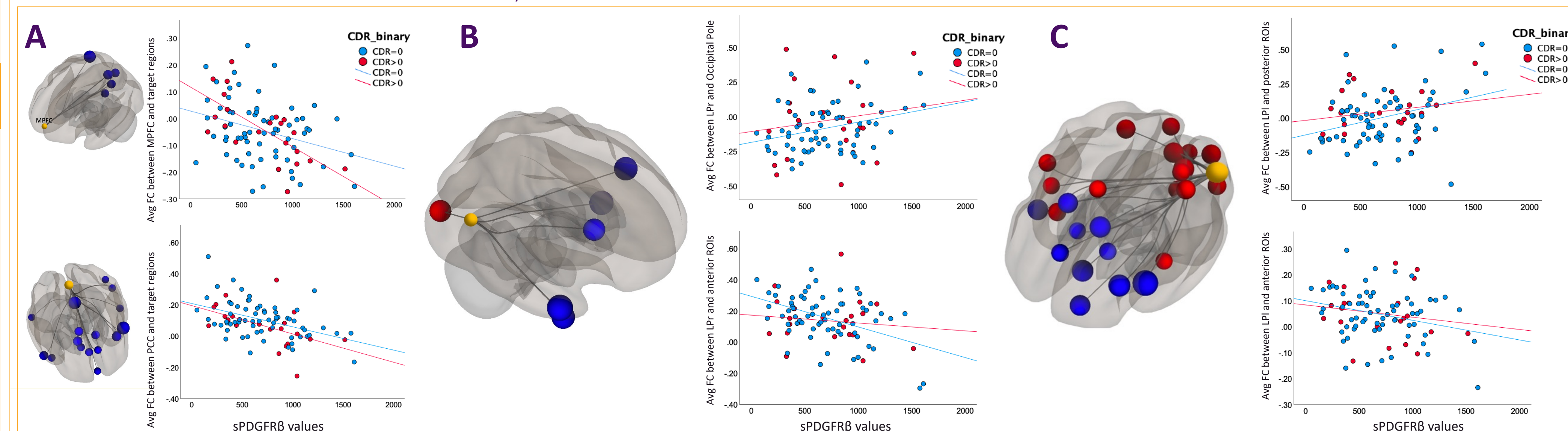
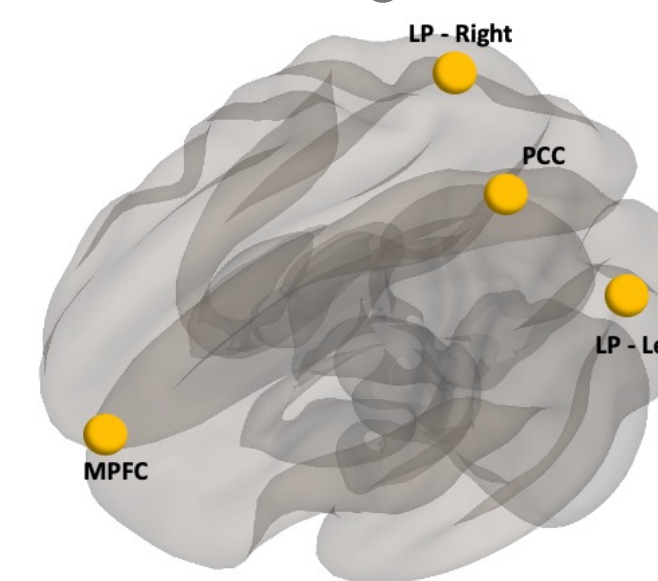


FIGURE 2: Significant pairwise correlations between DMN regions and other ROIs that correlate with sPDGFR β . Panel A shows decreased FC between DMN seed regions medial prefrontal cortex and posterior cingulate cortex and ROIs within the parietal and frontal lobe are correlated with increased CSF sPDGFR β values. Patients with CDR scores 0.5 and above show a more marked decrease. Panels B and C uses bilateral parietal areas as seed region. When brain regions were split anteriorly and posteriorly we saw different relationships with sPDGFR β values. FC between seed regions and anterior regions correlated negatively to increased BBB breakdown and posterior regions correlated positively to BBB breakdown.

INCREASED SPDGFR β VALUES (BBB BREAKDOWN) CORRELATED WITH LOWER FUNCTIONAL CONNECTIVITY BETWEEN DEFAULT MODE NETWORK REGIONS AND OTHER BRAIN REGIONS

Seed Regions Used



Target Regions

FP (Frontal Pole)	toMTG (Middle Temporal Gyrus, temporooccipital)	PC (Cingulate Gyrus, posterior division)
IC (Insular Cortex)	aITG (Inferior Temporal Gyrus, anterior division)	Precuneus (Precuneus Cortex)
SFG (Superior Frontal Gyrus)	MidFG (Middle Frontal Gyrus)	Cuneal (Cuneal Cortex)
IFG tri (Inferior Frontal Gyrus, posterior division)	IFG oper (Inferior Frontal Gyrus, pars opercularis)	Forb (Frontal Orbital Cortex)
PreCG (Precentral Gyrus)	TP (Temporal Pole)	aPaHC (Parahippocampal Gyrus, anterior division)
aSTG (Superior Temporal Gyrus, anterior division)	pSTG (Superior Temporal Gyrus, posterior division)	PostCG (Postcentral Gyrus)
pSTG (Superior Temporal Gyrus, posterior division)	aMTG (Middle Temporal Gyrus, anterior division)	SPL (Superior Parietal Lobule)
pMTG (Middle Temporal Gyrus, posterior division)		AG (Angular Gyrus)
		atlas.MedFC (Frontal Medial Cortex)
		SMA (Supplementary Motor Cortex)
		PaCIG (Paracingulate Gyrus)
		AC (Cingulate Gyrus, anterior division)
		OP (Occipital Pole)
		Thalamus
		Caudate
		Putamen
		Hippocampus
		Amygdala
		Accumbens

FIGURE 1: SEED AND TARGET REGIONS. Panel A shows DMN seed regions that were selected (medial prefrontal cortex, posterior cingulate cortex and bilateral parietal brain regions) Panel B lists target regions. Significance was set at p<.05 for correlation with sPDGFR β

CONCLUSIONS

- BBB breakdown may be linked to impaired functional connectivity in brain regions that experience early pathology

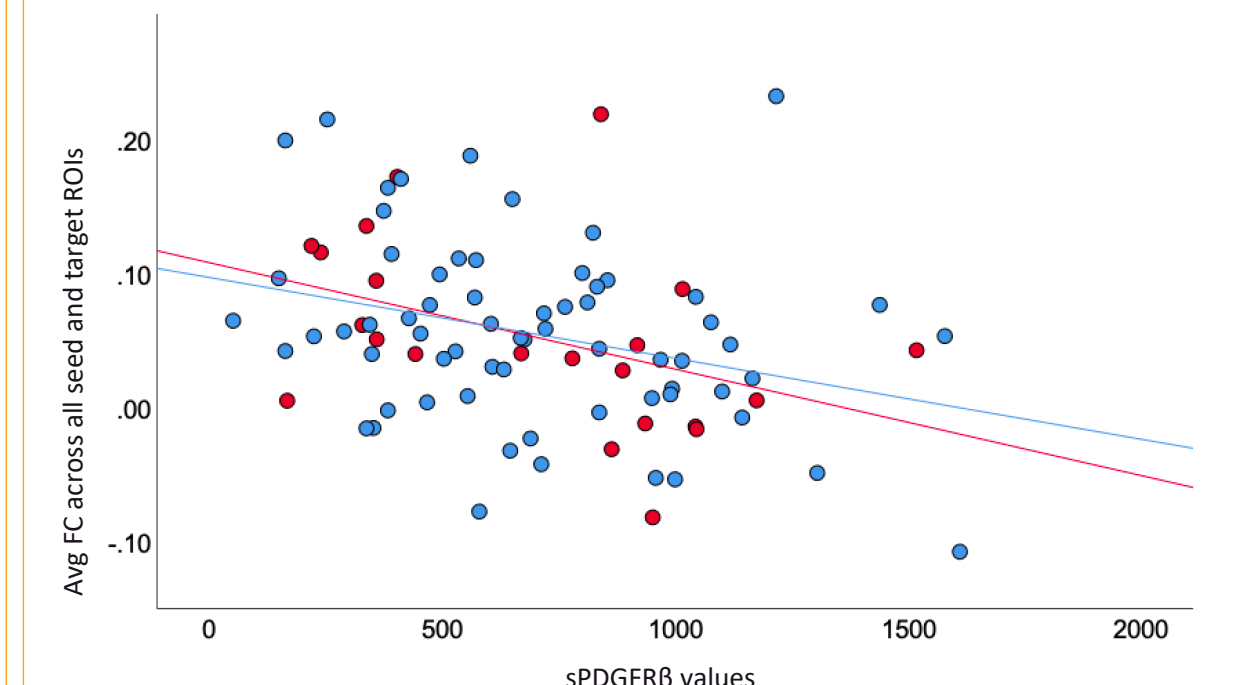


FIGURE 3: Averaged FC across all significant pairwise connections between seed regions show decreased FC is associated with increased sPDGFR β

- Dissociation between anterior and posterior brain regions correlating with increased sPDGFR β values

REFERENCES

- ¹Barisano et al., 2022 ⁴Whitefield-Gabrieli and Nieto-Castanon, 2012
²Jones et al., 2011 ⁵Shen et al., 2013
³Montagne et al., 2016

CONTACT

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