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Background:

- Parental history of dementia confers an increased risk of dementia in offspring, yet the underlying pathways of this intergenerational risk transmission remain poorly understood
- One potential pathway is through cerebrovascular health including blood brain barrier (BBB) dysfunction
- Prior work points to sex-specific patterns in maternal versus paternal transmission of dementia risk to offspring
- We used a novel MR-based method, termed diffusion prepared pseudo continuous arterial spin labelling (DP-pCASL), to quantitate regional BBB intracellular water exchange rate (kw) and test its relationship with parental history of dementia in the midlife adult children (Offspring Study) of older, community-dwelling adults from the Washington Heights Inwood Columbia Aging Project (WHICAP)

Methods:

- One hundred forty two midlife adults (55±10.6 mean±SD age, 68% women, 73% Latinx, 15% Black, and 11% White individuals) from the Offspring Study received DP-pCASL MR imaging
- Parental dementia status was determined prospectively by consensus diagnosis
- Mixed-effect models tested the association of parental history of dementia with medial temporal lobe blood brain barrier function in 1:1 propensity score matched and inverse probability weighting groups (based on age, sex, and years of education)
- Covariates include offspring intracranial volume, age, years of education, hypertension status, diabetes status, and random effect of family
- Both propensity score matching (n=50/142 matched) and inverse probability weighting (n=97/142 weighted) achieved adequate covariate balance (<0.1 SD tolerance)

	No Parental Dementia (N=106)	Parental Dementia Diagnosis (N=36)	Combined (N=142)
Offspring Age (years)			
Mean (SD)	53.3 (10.1)	60.0 (10.7)	55.0 (10.6)
Median [Min, Max]	55.1 [30.1, 77.0]	61.8 [29.1, 79.0]	56.1 [29.1, 79.0]
Offspring Sex/Gender			
Men	34 (32.1%)	12 (33.3%)	46 (32.4%)
Women	72 (67.9%)	24 (66.7%)	96 (67.6%)
Offspring Race and Ethnicity			
White/Non-Hispanic	14 (13.2%)	2 (5.6%)	16 (11.3%)
Black/Non-Hispanic	19 (17.9%)	2 (5.6%)	21 (14.8%)
Hispanic	72 (67.9%)	32 (88.9%)	104 (73.2%)
Other	0 (0%)	0 (0%)	0 (0%)
Offspring Education (years)			
Mean (SD)	13.7 (3.41)	12.8 (3.00)	13.5 (3.33)
Median [Min, Max]	14.0 [2.00, 20.0]	13.0 [4.00, 19.0]	14.0 [2.00, 20.0]
Offspring Hypertension Status			
No	78 (73.6%)	22 (61.1%)	100 (70.4%)
Yes	28 (26.4%)	14 (38.9%)	42 (29.6%)
Offspring Diabetes Status			
No	93 (87.7%)	32 (88.9%)	125 (88.0%)
Yes	13 (12.3%)	4 (11.1%)	17 (12.0%)

Table 1: Demographics of BBB MRI cohort by parental history of dementia groups

Results:

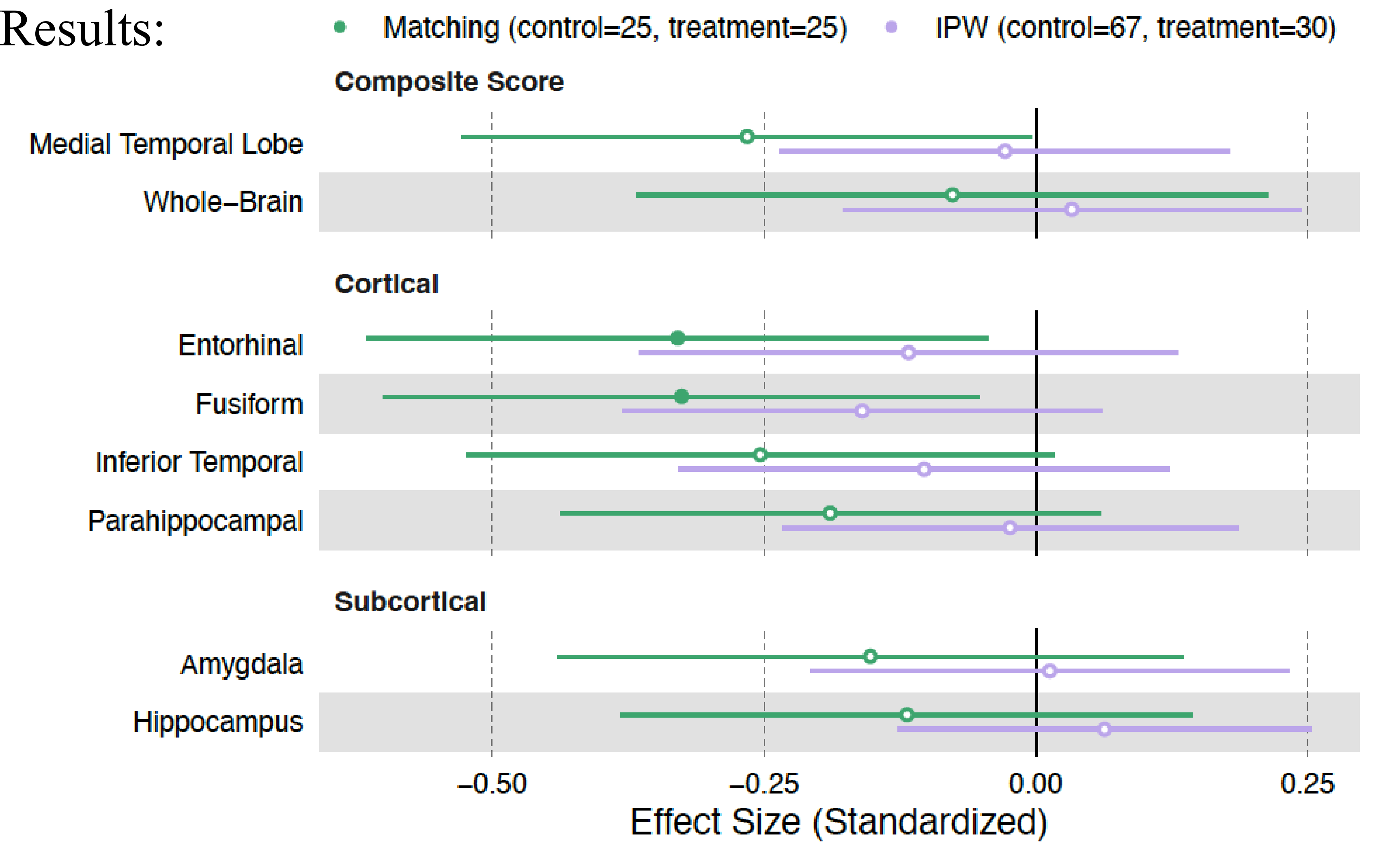


Figure 1: Forest plot showing the effect sizes of the relationship of parental history of dementia with regional blood brain barrier function in the medial temporal lobe. Green bars represent propensity score matched groups and purple bars represent inverse probability weighted groups. Filled and open circles represent significant and non-significant associations, respectively.

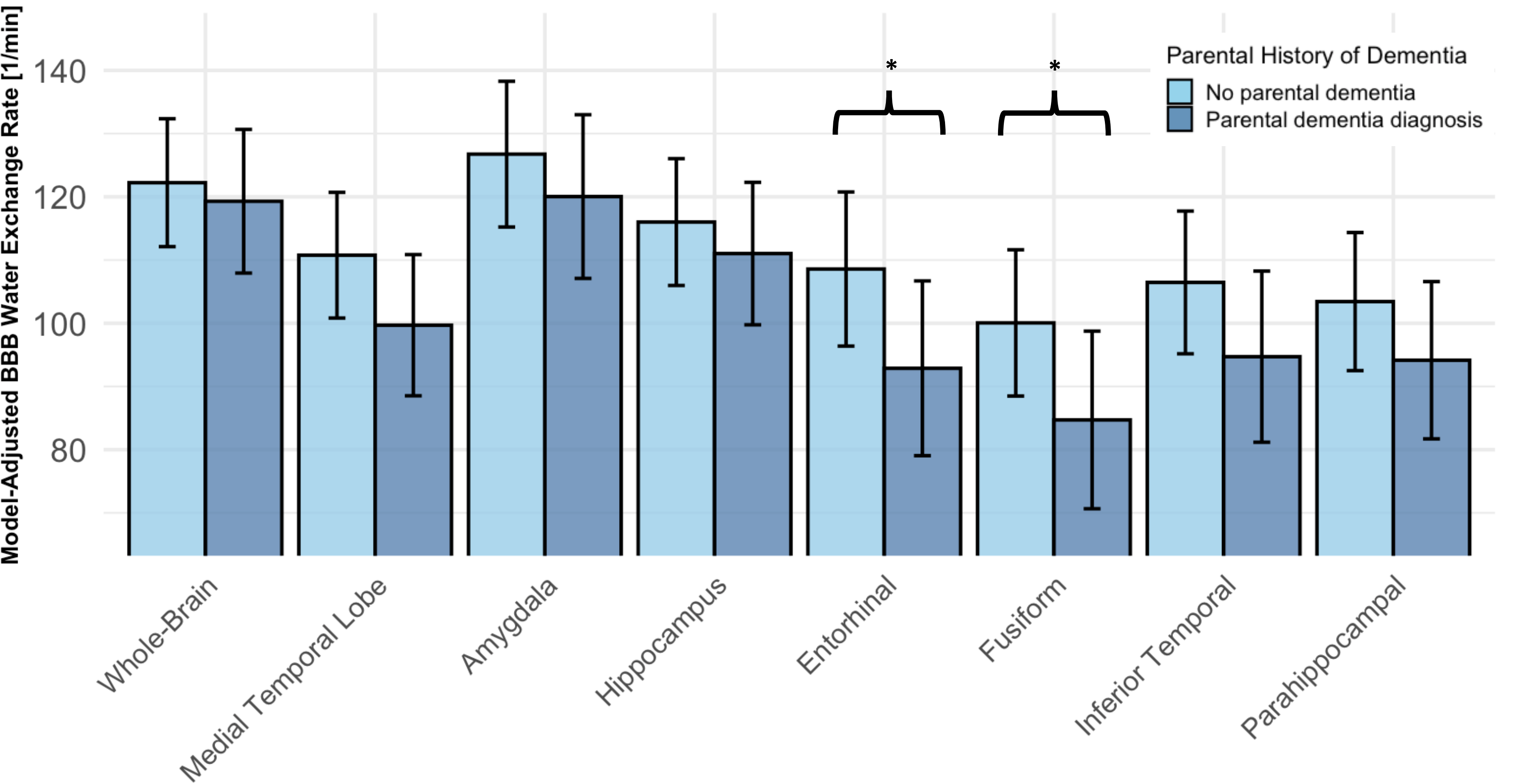


Figure 2: Model-adjusted BBB function by parental history of dementia of propensity-scored matched groups

Conclusions:

- Parental history of dementia is associated with a midlife cerebrovascular profile that reflects BBB dysfunction (lower kw) in the entorhinal cortex and fusiform gyrus
- Effect estimates showed some sensitivity to matching parameters and methods
- These findings support the hypothesis that one pathway though which parental history of dementia may increase offspring dementia risk is through endogenous cerebrovascular factors that may affect neurodegeneration in midlife