Polygenic scores generated from cerebrospinal fluid biomarkers instead of magnetic resonance imaging volumetrics may be better predictors for hippocampal volume in Alzheimer's disease

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Background

Recent National Institutes on Aging guidelines for Alzheimer's disease (AD) research reflect growing trends in the field to better understand biological factors of AD, by utilizing a biomarker-based framework referred to as ATN (A=amyloid, T=tau, N=neurodegeneration) to classify individuals as having, or at risk for having, AD. Biomarkers that reliably reflect biological disease processes and have a genetic association with disease are referred to as endophenotypes. Genome-wide association studies (GWAS) of endophenotypes are a powerful tool for understanding disease biology, and polygenic scores (PGS) combine the effects of multiple variants from GWAS to predict traits which can help predict whether someone is at risk for a disease trait or help study relationships between different biomarkers. The goal of this study was to construct PGS from AD endophenotypes and test them against a measure of hippocampal volume (HV) in the Wisconsin Alzheimer's Disease Research Center (WADRC) and the Wisconsin Registry for Alzheimer's Prevention (WRAP) to:

1) determine how much variance in HV can be explained by the PGS

2) identify potential pleiotropic effects between HV and CSF biomarkers.

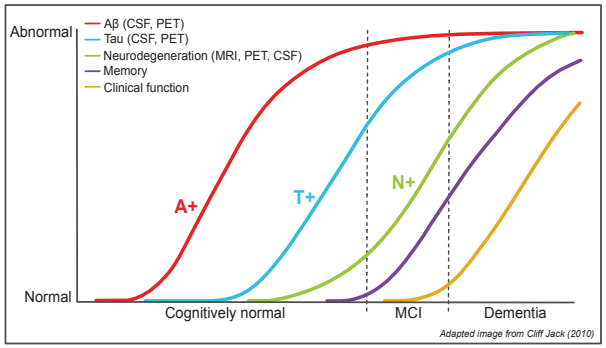

Figure 1. Changes in AD biomarkers begin decades before clinical onset. If we can identify polygenic scores that can predict these changes we can identify individuals at-risk without the use of expensive or invasive methods and well before any changes begin to manifest.

Methods

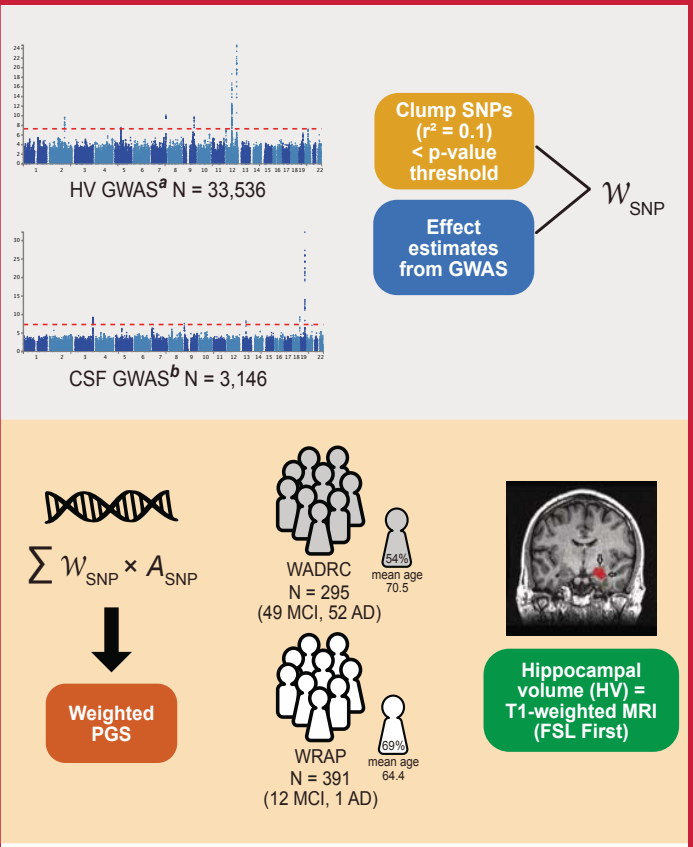

Figure 2. Weighted PGS for each trait were calculated using estimates from large GWAS (w_{SNP}) times the number of effect alleles (A_{SNP}) for each participant. PGS were regressed against intracranial volume-normalized HV (residual method), correcting for age, sex, scanner, head coil, and 4 principal components (PCs) for population structure.

Results

Preliminary analyses using PRSice2 suggested the best-fit HV-based PGS included all clumped SNPs ($P \leq 1$) but the best-fit CSF-based PGS included only genome-wide significant SNPs ($P \leq 5\times10^{-8}$). The PGS associations were very different between WADRC and WRAP (Figure 3). After 10,000 permutations (randomly shuffling the phenotypes), only the associations in WADRC between HV and $PGS_{t\text{-}tau}$ and $PGS_{A\beta}$ had empirical $P < 0.05$. We tested the top CSF GWAS SNPs for association with HV in our samples (Table 1).

Figure 3. R^2 for each PGS (represented by the colored bars) in regressions against the combined normalized HV after correcting for age, sex, scanner, head coil, and 4 PCs. *P*-values (before permutation) are reported on top of the bars. Asterisks (*) label the results with empirical $P < 0.05$ after 10,000 permutations.

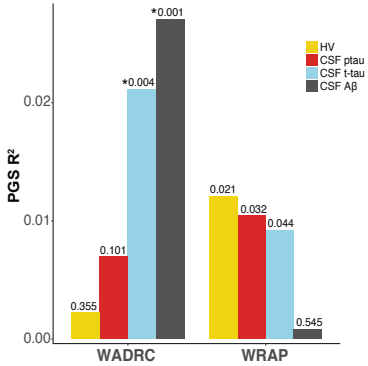

Table 1. Top CSF GWAS SNP associations with HV

SNP	WADRC β (SE)	WADRC *P*	WRAP β (SE)	WRAP *P*
rs35055419 [C]	-7.27 (80.1)	0.9277	**151.5 (53.0)**	**0.0045**
rs9527039 [C]	1.33 (152.2)	0.9930	**-254.3 (104.3)**	**0.0152**
rs429358 [C]	**-309.5 (86.6)**	**0.0004**	-57.2 (67.6)	0.3979

Associations with P < 0.05 are bolded. Results shown are after correcting for age, sex, scanner, head coil, and 4 PCs for population structure.

Conclusions

- PGS generated from a large general population GWAS of HV were associated with HV measured in WRAP but not WADRC
- PGS generated from AD CSF endophenotypes explained more of the variance in HV in WADRC than the HV-based PGS; however, this may be explained by the shared strong association with *APOE* genotype
- The WRAP cohort is younger, has more cognitively healthy participants, and more females than WADRC. Further analyses will be necessary to determine which cohort differences explain these incongruous observations
- Future work will determine the predictive power of different biomarker PGS in classifying individuals within the ATN framework

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[a] The ENIGMA-CHARGE consortia provided summary statistics from HV GWAS (Hibar et al, 2017, *Nat Commun*). [b] CSF GWAS summary statistics were provided by the Cruchaga lab at the Knight ADRC (Deming et al, 2017, *Acta Neuropathol*). We'd like to express our appreciation to all of the studies' participants and their families, without whom this research would not be possible.