A Polygenic Risk Score Derived From Episodic Memory Weighted Genetic Variants Is Associated With Cognitive Decline in Preclinical Alzheimer’s Disease

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Studies of Alzheimer’s disease risk-weighted polygenic risk scores (PRSs) for cognitive performance have reported inconsistent associations. This inconsistency is particularly evident when PRSs are assessed independent of APOE genotype. As such, the development and assessment of phenotype-specific weightings to derive PRSs for cognitive decline in preclinical AD is warranted. To this end a episodic memory-weighted PRS (emPRS) was derived and assessed against decline in cognitive performance in 226 healthy cognitively normal older adults with high brain Aβ-amyloid burden participants from the Australian Imaging, Biomarkers and Lifestyle (AIBL) study. The effect size for decline in a verbal episodic memory was determined individually for 27 genetic variants in a reference sample (n = 151). These were then summed to generate an emPRS either including APOE (emPRS<sub>SAPOE</sub>) or excluding APOE (emPRS<sub>SAPOE</sub>). Resultant emPRS were then evaluated, in a test sample (n = 75), against decline in global cognition, verbal episodic memory and a pre-Alzheimer’s cognitive composite (AIBL-PACC) over 7.5 years. The mean (SD) age of the 226 participants was 72.2 (6.6) years and 116 (51.3%) were female. Reference and test samples did not differ significantly demographically. Whilst no association of emPRSs were observed with baseline cognition, the emPRS<sub>SAPOE</sub> was associated with longitudinal global cognition (−0.237, P = 0.0002), verbal episodic memory (−0.259, P = 0.00003) and the AIBL-PACC (−0.381, P = 0.02). The emPRS<sub>SAPOE</sub> was also associated with global cognition (−0.169, P = 0.021) and verbal episodic memory (−0.208, P = 0.004). Stratification by
INTRODUCTION

An improved understanding of the extended preclinical phase of Alzheimer’s disease (AD), has seen an increased focus on early disease intervention (Sperling et al., 2014). As a result, importance has been placed on investigating potential factors that could underpin the significant variability in cognitive decline between individuals in this early stage of the disease. Accumulation of $\beta$-amyloid ($\beta$A) occurs up to 20 years prior to symptom onset (Villemagne et al., 2013). In addition, abnormally high neocortical $\beta$A in cognitively normal (CN) older adults is associated with an increased risk for cognitive decline and development of AD (Villemagne et al., 2011). Despite this, levels of $\beta$A alone do not track well with progressive cognitive decline and there is strong convergent evidence that variable rates of decline in the preclinical stages of AD may be influenced by genetic factors (Lim et al., 2015a,b; Porter et al., 2018a,c). Identification of genetic factors that contribute to accelerated rates of cognitive decline in at risk individuals will be of significant importance, through an increased understanding of potential mechanisms of preclinical decline and the identification of individuals most suitable for intervention trials.

One method frequently investigated for use as a predictor of cognitive performance and decline employs polygenic risk scores (PRSs). These are typically focused on AD risk associated genes identified through genome wide association studies (GWAS). Once identified, these genetic variants are weighted by their respective effect sizes and summed. The resulting scores have then been used for the analysis of associations with clinical and pathological variables including: measures of clinical classification (Biffi et al., 2010; Rodriguez-Rodriguez et al., 2013; Chauhan et al., 2015; Escott-Price et al., 2015, 2017; Sleegers et al., 2015; Chouraki et al., 2016; Mormino et al., 2016; Desikan et al., 2017; Lacour et al., 2017), disease progression, and fluid (Sabuncu et al., 2012; Martiskainen et al., 2015; Sleegers et al., 2015; Louwersheimer et al., 2016) and imaging (Biffi et al., 2010; Sabuncu et al., 2012; Chauhan et al., 2015; Habes et al., 2016; Harrison et al., 2016; Lupton et al., 2016; Mormino et al., 2016; Foley et al., 2017) biomarkers. However, inconsistent findings have been reported when investigating associations of PRSs with cognition. Almost equally, studies have observed significant associations with cognitive performance (Sabuncu et al., 2012; Carraquillo et al., 2015; Andrews et al., 2016; Louwersheimer et al., 2016; Marden et al., 2016; Mormino et al., 2016) or an absence of association (Gui et al., 2014; Harrison et al., 2016; Bressler et al., 2017; Darst et al., 2017).

We have previously reported that while an AD risk weighted PRS was associated with cognitive decline (Porter et al., 2018b), the association was only observed in carriers of the apolipoprotein E (APOE) $\varepsilon 4$ allele. This is consistent with other studies which have reported no association with cognition when APOE was removed from the calculation of a PRS (Carraquillo et al., 2015; Andrews et al., 2016). In addition to being the strongest known genetic risk factor for the development of AD, the $\varepsilon 4$ allele of APOE has previously been associated with cross-sectional and longitudinal cognitive performance (Lim et al., 2015b). Of particular interest, carriage of APOE $\varepsilon 4$ in CN older adults at risk for AD (determined by $\beta$A brain imaging) is associated with accelerated decline in multiple cognitive domains (Lim et al., 2015b).

In addition to APOE, a number of genetic variants with no or limited association with AD risk have been independently associated with cognitive performance in diseased, at risk and healthy populations. The genes containing these variants have roles in promotion of neuronal survival (BDNF; Brain Derived Neurotropic Factor; (Lim et al., 2015a), synaptic plasticity (KIBRA; Kidney and Brain expressed protein; (Tracy et al., 2016; Porter et al., 2018a), regulation of dopamine availability (COMT; Catechol-O-methyltransferase; Sheldrick et al., 2008), longevity (KL; Klotho; Arking et al., 2002), inflammation (CSMD1; CUB and Sushi Multiple Domain 1; Kraus et al., 2006) and amyloid precursor protein (APP) processing (SPON1; Spodin 1; Ho and Sudhof, 2004). In addition to the independent association of these genes with cognitive performance, we have also recently reported on the utility of combining these cognition-associated genetic variants for assessing longitudinal cognition (Porter et al., 2018c). As identified above there is also a significant body of literature combining GWAS derived AD risk associated genetic variants, typically within a core set of 21 genes, into PRSs that have previously been associated with the clinical classification of AD and disease phenotypes, albeit with inconsistency of association with cognition. However, there are few studies that have investigated the combination of AD risk and cognition associated variants. This is likely due the possible dilution of the effects of the cognition associated genetic variants when their weak AD risk weightings are applied (Andrews et al., 2016).

Reasons for the inconsistency of studies investigating PRSs may be twofold. First, cognition has significant inter-individual variability, particularly in the elderly, which works to increase the difficulty of predicting rates of cognitive decline. Second, late disease stage methods of weighting, such as AD risk,
may not be suitable for predicting cognitive decline at early preclinical stages. As such, a cognitive phenotype, such as verbal episodic memory, may be more appropriate as it is typically observed to precede decline in executive function by 4–8 years and between 7 and 10 years before other domains (Elias et al., 2000; Grober et al., 2008; Derby et al., 2013). The hypothesis of this study was therefore: through combining individually weighted AD risk and cognitive decline associated genetic variants, by endophenotype effect-sizes, a PRS can be derived with utility for prediction of preclinical rates of cognitive decline. Further, by focusing on CN older adults with high levels of neocortical Aβ, population heterogeneity, and so cognitive performance variability, is reduced. To test this hypothesis, the study undertook a targeted approach to the development and assessment of utility of a novel episodic memory-weighted PRS (emPRS), by weighting each genetic variant by its effect on decline in verbal episodic memory, in CN older adults with high neocortical Aβ burden.

MATERIALS AND METHODS

Study Participants

Data is reported on 232 CN older adults enrolled in the Australian Imaging Biomarkers and Lifestyle (AIBL) Study of Ageing. The AIBL Study is a prospective longitudinal study of aging, the study design, enrolment process, neuropsychological assessments, and diagnostic criteria have been previously described (Ellis et al., 2009). Briefly, a participant was classified by a clinical review panel (Ellis et al., 2009), blinded to Aβ-amyloid status, as CN if they did not meet the clinical criteria for diagnosis of mild cognitive impairment (MCI) (Winblad et al., 2004) or dementia (McKhann et al., 1984). Ethics approval was granted for the study by each member institution, including Austin Health, Edith Cowan University, Hollywood Private Hospital, and St Vincent’s Health. All participants provided informed written consent.

Cognitive Measures

The AIBL neuropsychological test battery consists of the Mini-Mental State Examination (MMSE), Clock Drawing Test, California Verbal Learning Test-Second edition (CVLT-II), Logical Memory I and II (LMI; LMII; Story A only), D-KEFS verbal fluency, a 30-item version of the Boston Naming Test (BNT), Wechsler Test of Adult Reading (WTAR), Digit Span and Digit Symbol-Coding subtests of the Wechsler Adult Intelligence Scale-Third edition (WAIS-III), the Stroop task (Victoria version), and the Rey Complex Figure Test (RCFT) (Ellis et al., 2009). Test results were used in combination to calculate cognitive composite scores, as previously described (Donohue et al., 2014; Burnham et al., 2015, 2016). Specifically, in this study these composite scores included a measure of global cognition (CDR sum of boxes (CDRSB), MMSE, LMII, CVLT-II recognition false positives (CVLT-II FP) and Clock) and verbal episodic memory (CDRSB, LMII, CVLT-II FP) (Burnham et al., 2015), in addition to a composite of tests shown to be sensitive to decline in preclinical AD [AIBL-pre-Alzheimer’s cognitive composite (PACC); CVLT-II-LDFR, LMII, MMSE, WAIS-III PS-CL] (Donohue et al., 2014; Burnham et al., 2016). The calculation of the aforementioned composites involved corrections for age, sex, years of education, premorbid IQ [WTAR-estimated WAIS-III Full Scale Intelligence Quotient (FSIQ)] and depressive symptoms [Geriatric Depression Scale (GDS)] (Donohue et al., 2014). The AIBL-PACC did not include an age correction, however, this was included as a covariate in subsequent analyses. 7.5 years of cognitive assessment data was utilized with collections occurring at 0, 18, 36, 54, 72, and 90 months.

Amyloid Imaging

All participants were imaged for neocortical Aβ by positron emission tomography (PET) using one of the following radiolabelled tracers: 11C-Pittsburgh Compound B (PiB), 18F-florbetapir or 18F-flutemetamol, as previously described (Rowe et al., 2010; Vandenberghe et al., 2010; Clark et al., 2011). CapAIBL™, a web-based, freely available software, was used to generate PET standardized uptake value (SUV) ratios (SUVR) for all tracers without the requirement for magnetic resonance imaging (Bourgeat et al., 2015). Target-region to reference-region SUVRs were calculated by the summation and normalization of SUVs to brain regions specific to each tracer [PiB (cerebellar cortex), florbetapir (whole cerebellum), flutemetamol (pons)]. All participants included in this study were classified as having a high Aβ (Aβhigh) burden at any time point, as determined by tracer specific thresholds of ≥1.4, ≥1.05 and ≥0.55 for PiB, florbetapir and flutemetamol respectively.

SNP Selection and Genotyping

A thorough literature review was conducted in PubMed and 27 single nucleotide polymorphisms (SNPs) were selected based on a priori evidence of associations with either AD risk or cognitive performance (or both; Table 1). Of these, 21 variants had previously been associated with the clinical classification of AD and disease phenotypes. The remaining six variants had previously been associated with cross-sectional and longitudinal cognitive phenotypes in cognitively normal and/or demented individuals. QIAamp DNA Blood Maxi Kits (Qiagen, Hilden, Germany) were used for the extraction of DNA from 5 mL of whole blood. TaqMan® assays with the TaqMan® GTXpress™ Master Mix (Life Technologies) were used to genotype APOE (rs7412, assay ID: C___904973_10; rs429358, assay ID: C___3084793_20; Life Technologies, Carlsbad, CA, United States) on a QuantStudio 12K Flex™ Real-Time-PCR system (Applied Biosystems, Foster City, CA, United States). QIAamp and TaqMan® kits detailed above were used following manufacturer’s instructions. Genotype information for the additional SNPs included in the PRS were extracted from a genome-wide SNP array conducted on the Illumina OmniExpressHumanExome+ BeadChip with subsequent imputation using impute2 ver2.3, with the 1000 genome reference panel (2015 release). Complete SNP information was available for the 232 individuals included in
the study. However, 6 samples were excluded from further analysis due to homozygosity of KL-VS variant, which has been reported to confer phenotypic risk not in a gene dosage dependent fashion (Arking et al., 2003). Analysis of all SNPs was performed using the dominant model of minor allele (Table 1).

**Statistical Analysis**

RStudio (RStudio Team 2015) Version 0.98.1103 for Macintosh was used for all statistical analyses (RStudio Team, 2015). 226 Aβ42+ CN older adults were randomly split using the "sample" function of the R “base” package, creating the reference (n = 151) and test (n = 75) samples sets. Means/counts and standard deviations/percentages for demographic variables for the reference and test groups were then determined. To ensure the reference and test samples were not significantly different in demographic measures analysis of covariance (ANOVA; age, premorbid IQ, depressive symptoms) and chi-squared tests (gender, years of education, APOE ε4+ve) were performed.

Calculation of an individual's emPRS was by the summation of each SNP's effect size for the risk allele, if the risk allele is present. This can be represented as emPRS = Σ RAi(di), where n is each individual SNP, RA is the presence (1) or absence (0) of risk allele of n, and d is the calculated effect size for the risk allele of n. To calculate d, changes in verbal episodic memory performance for individual participants in the reference sample (n = 151) were calculated for each SNP using random intercepts linear mixed effects (LME) models, as implemented in the “nlme” package in R, in a dominant model for the minor allele. The resultant mean and standard deviation of the β-coefficient, for the verbal episodic memory slopes, were used to determine the effect sizes for all SNPs (Table 1) using the “effsize” package in R. The resultant effect sizes were then used to assign the risk genotype for each variant. Individual sample emPRSs were then calculated by summing the effect sizes if the assigned risk genotypes were present. We have previously reported that the utility of PRS for prediction of cognitive decline are dependent on the inclusion of APOE genotype in their construction (Porter et al., 2018b). As such we wished to determine whether the utility of the emPRS defined in this study was likewise dependent on the inclusion of APOE. To this end each individual in the test sample had two emPRSs calculated. The first included APOE (emPRSAPOE) whilst the second excluded APOE (emPRSCAPOE).

Random intercepts LME models were used to assess associations between both emPRSAPOE and emPRSCAPOE and cognitive performance in the test sample (n = 75). Modeling was

**TABLE 1 | Single nucleotide polymorphisms (SNP) information.**

| Gene | SNP | Chromosome | Position | Minor allele | Risk genotype | AIBL Effect Size d (95% CI) |
|------|-----|------------|----------|--------------|---------------|-----------------------------|
| APOE | rs7412 rs429358 | 19 | 44008822 | ε4 | ε4+ | 0.472 (0.14 – 0.80) |
| CR1  | rs3818361 | 1 | 20786116 | A | G/G | 0.109 (0.24 – 0.46) |
| BIN1 | rs744373 | 2 | 12717039 | G | A/A | 0.003 (0.32 – 0.33) |
| INPP5D | rs35349669 | 2 | 23315983 | T | T+ | 0.152 (0.20 – 0.50) |
| KIBRA | rs17070145 | 5 | 168413786 | C | C/C | 0.097 (0.22 – 0.42) |
| MEF2C | rs190982 | 5 | 88927603 | G | A/A | 0.278 (0.07 – 0.62) |
| HLA cluster | rs9271192 | 6 | 32610753 | C | C+ | 0.256 (0.07 – 0.58) |
| CD2AP | rs9049407 | 6 | 7485642 | C | C+ | 0.114 (0.21 – 0.43) |
| NME8 | rs2718058 | 7 | 37801932 | G | G+ | 0.041 (0.28 – 0.36) |
| ZCWPW1 | rs1476679 | 7 | 100406823 | C | T/T | 0.149 (0.17 – 0.47) |
| EPHA1 | rs11767557 | 7 | 143412046 | C | T/T | 0.061 (0.27 – 0.39) |
| CSMD1 | rs2740931 | 8 | 4022021 | A | A/A | 0.201 (0.16 – 0.56) |
| CLU | rs11336000 | 8 | 27607002 | T | T+ | 0.078 (0.25 – 0.40) |
| PTK2B | rs28834970 | 8 | 27337604 | C | C+ | 0.030 (0.30 – 0.36) |
| SPON1 | rs11023139 | 11 | 14202800 | A | A+ | 0.045 (0.44 – 0.53) |
| BDNF | rs6265 | 11 | 27658369 | Met | Met+ | 0.143 (0.20 – 0.49) |
| CELF1 | rs10838725 | 11 | 47536319 | C | C+ | 0.103 (0.22 – 0.42) |
| MS4A6A | rs610932 | 11 | 60171834 | T | T+ | 0.167 (0.18 – 0.52) |
| PICALM | rs3651179 | 11 | 86157598 | T | C/C | 0.098 (0.23 – 0.42) |
| SORL1 | rs11218343 | 11 | 12158547 | C | T/T | 0.214 (0.68 – 1.10) |
| KL | rs9536314 | 13 | 33054001 | VS | VS+ | 0.160 (0.20 – 0.52) |
| FERMT2 | rs17125944 | 14 | 52935911 | C | C+ | 0.277 (0.15 – 0.71) |
| SLC24A4 | rs10498633 | 14 | 92460680 | T | T+ | 0.110 (0.21 – 0.43) |
| ABCA7 | rs3764650 | 19 | 1046521 | G | G+ | 0.062 (0.34 – 0.47) |
| CD33 | rs3865444 | 19 | 51224706 | A | A+ | 0.082 (0.24 – 0.40) |
| CASS4 | rs7274581 | 20 | 56443204 | C | T/T | 0.080 (0.36 – 0.52) |
| COMT | rs4680 | 22 | 19063748 | Met | Met+ | 0.098 (0.26 – 0.45) |

Location and risk information on the 27 genetic variants included in the calculation of the PRS. Minor alleles for SNPs based on published 1000 Genomes Phase 3 European allele frequencies (Genomes Project et al., 2015). Effect sizes [Cohen’s d and 95% Confidence Interval (CI)] are presented with their accompanying risk genotype as per calculation in AIBL. SNP, single nucleotide polymorphism; AIBL, Australian Imaging, Biomarkers and Lifestyle Study of Aging.
again performed using the “nlme” R package. For all analyses, the cognitive composite scores were included as dependent variables, emPRS × Time interactions as fixed factors, and participant baseline scores as random factors. Additionally, those analyses investigating associations with AIBL-PACC performance included age as a covariate. Further, the test sample was then stratified based on the number of APOE ε4 alleles carried, and the model described above was used to determine associations of the emPRSAPAPE in each group. All models were graphically represented as baseline or change in composite score given emPRS, with error shading signifying emPRS dependent standard error.

RESULTS

SNP Information,PRS Calculation and Demographics

A total of 27 SNPs were identified and selected for inclusion into the current emPRSs. Effect sizes were calculated for the selected SNPs, based on their discriminatory effect on decline in verbal episodic memory in the reference cohort. These are represented with corresponding 95% confidence intervals in Table 1. The effect sizes ranged from APOE, with the largest effect size (d = 0.472), to BIN1 with the smallest (d = 0.003). These effect sizes were then used for weighting each SNP in the calculated emPRS in the test cohort. No significant differences were identified between the reference (n = 151) and test (n = 75) samples for the baseline demographic measures (Table 2).

emPRSAPAPE and emPRSΛAPOE Are Associated With Longitudinal Cognition in Aβhigh CN Older Adults

No significant associations were observed between emPRSAPAPE or emPRSΛAPOE and performance at baseline for global cognition (emPRSAPAPE: −0.172, p = 0.655; emPRSΛAPOE: 0.098, p = 0.836), verbal episodic memory (emPRSAPAPE: −0.144, p = 0.706; emPRSΛAPOE: 0.125, p = 0.791) or the AIBL-PACC (emPRSAPAPE: 0.143, p = 0.892; emPRSΛAPOE: 0.786, p = 0.541) (Figures 1, 2). The emPRSΛAPOE was significantly associated with longitudinal cognitive performance as measured by global cognition (−0.237, p = 0.0002), verbal episodic memory (−0.259, p = 0.0003) and the AIBL-PACC (−0.381, p = 0.020) (Figure 1). Specifically, in the test cohort, as the emPRSΛAPOE increased the rate of decline in cognitive outcomes worsened.

To assess whether these associations were dependent upon the inclusion of APOE in the calculation, the emPRS was calculated excluding APOE. This derived emPRS, emPRSΛAPOE, was likewise observed to be significantly associated with longitudinal global cognition (−0.169, p = 0.021) and verbal episodic memory (−0.208, p = 0.004) performance, albeit to a reduced extent (Figure 2). However, it was no longer associated with decline on the AIBL-PACC (−0.152, p = 0.420). As was the case when investigating emPRSΛAPOE, an increase in emPRSΛAPOE was significantly associated with a concomitant increased rate of cognitive decline.

emPRSΛAPOE Is Associated With Longitudinal Cognition in Aβhigh CN Older Adults, When Stratified by APOE ε4 Carriage

After stratification of the test sample into groups based on the carriage of the APOE ε4 allele, association between the emPRSΛAPOE and cognition was evaluated separately. Significant associations between the emPRSΛAPOE and longitudinal measures of verbal episodic memory and global cognition were observed irrespective of APOE ε4 status (Table 3). However, the emPRSΛAPOE association with decline in the AIBL-PACC was limited to APOE ε4 carriers. Finally, no associations were observed in any groups when investigating baseline levels of cognition.

DISCUSSION

This study describes a emPRS developed by weighting AD risk and cognition associated genetic variants by their effect on decline in verbal episodic memory in a cohort defined in terms of pre-clinical AD by reference to neocortical Aβ PET imaging. The emPRSs were calculated in the test sample by the summation of gene variant effect sizes calculated with respect to decline in episodic memory in the reference sample. In the test sample no associations were observed between the emPRSs and baseline levels of cognition, however, associations with longitudinal performance were statistically significant. The emPRSΛAPOE was significantly associated with decline in global
FIGURE 1 | Association between emPRS\textsuperscript{APOE} and baseline and longitudinal change in cognition in Aβ\textsubscript{high} CN older adults. Association between emPRS\textsuperscript{APOE} and baseline (A,C,E) and longitudinal change (B,D,F) in composite measures of cognition including a statistically driven global composite (A,B), verbal episodic memory composite (C,D), and Pre-Alzheimer’s Cognitive Composite (AIBL-PACC; E,F) in cognitively normal (CN) older adults with high Aβ (Aβ\textsubscript{high}; n = 75). AIBL-PACC controlled for age. Shaded regions represent emPRS dependent standard error. emPRS\textsuperscript{APOE}, cognition polygenic risk score with APOE genotype.
FIGURE 2 | Association between emPRS\textsuperscript{S\textsuperscript{APOE}} and baseline and longitudinal change in cognition in A\textsubscript{\beta\textsuperscript{high}} CN older adults. Association between emPRS\textsuperscript{S\textsuperscript{APOE}} and baseline (A,C,E) and longitudinal change (B,D,F) in composite measures of cognition including a statistically driven global composite (A,B), verbal episodic memory composite (C,D), and Pre-Alzheimer’s Cognitive Composite (AIBL-PACC; E,F) in cognitively normal (CN) older adults with high A\textsubscript{\beta}\textsuperscript{high} (n = 75). AIBL-PACC controlled for age. Shaded regions represent emPRS dependent standard error. emPRS\textsuperscript{S\textsuperscript{APOE}}, cognition weighted polygenic risk score without APOE genotype.
cognition, verbal episodic memory and the AIBL-PACC (Table 3 and Figure 1). While these associations were strongest when APOE was included they were not dependent on the inclusion of APOE ε4, as associations with verbal episodic memory and global cognition were still observed in the emPRSAPOE (Table 3 and Figure 2). Further evidence that the score developed was not purely dependent on APOE was provided when the participants were stratified by carriage of the APOEε4 allele. AIBL-PACC controlled for age. emPRSAPOE, cognition weighted polygenic risk score without APOE genotype.

| APOEε4 non-carrier (n = 41) | α      | P   | β      | P   |
|-----------------------------|--------|-----|--------|-----|
| Global                      | 0.210  | 0.619 | −0.145 | 0.044 |
| Verbal Episodic Memory      | 0.242  | 0.575 | −0.185 | 0.011 |
| AIBL-PACC                   | 0.531  | 0.708 | 0.086  | 0.645 |

| APOEε4 carrier (n = 34) | α      | P   | β      | P   |
|-------------------------|--------|-----|--------|-----|
| Global                  | 0.032  | 0.972 | −0.329 | 0.028 |
| Verbal Episodic Memory  | 0.047  | 0.958 | −0.383 | 0.013 |
| AIBL-PACC               | 1.477  | 0.522 | −0.821 | 0.034 |

Mean slopes for models assessing the association between emPRS and baseline (α) and longitudinal (β) change in cognitive composite measures in all cognitively normal (CN) older adults with high Aβ (Aβ40; n = 75), and by carriage of the APOEε4 allele. AIBL-PACC controlled for age. emPRSAPOE, cognition weighted polygenic risk score without APOE genotype.

That in the previous study it was over a shorter duration (4.5 years) and used a learning/working memory composite derived from the online Cogstate Brief Battery (Lim et al., 2015b). In this study there was no obvious disparity in the calculated effect sizes between the a priori cognition associated variants or GWAS-derived AD risk variants. This lack of disparity supports both our notion of phenotype-specific effect size driven PRSs, as well as the importance of combining both cognition and AD risk associated variants. In addition, after excluding APOE, the variants with the 3 largest effect sizes in this study were rs190982 [Myocyte-specific enhancer factor 2C (MEF2C)], rs9271192 (HLA cluster), and rs17125944 [Fermitin family homolog 2 (FERMT2)]. While these variants were included due to their previous associations with AD risk, they have been associated (albeit inconsistently) with cognitive performance and/or decline. In one study, MEF2C was associated with general cognitive function whilst neither FERMT2 or genes in the HLA cluster were associated (Davies et al., 2015). In a further study, analysis of the same variants in the current study revealed a trend toward association of MEF2C (rs190982) whilst the HLA cluster (rs9271192), and FERMT2 (rs17125944) were not significant (Nettiksimmons et al., 2016). However, in the same study aggregate associations of SNPs within the MEF2C and HLA loci were associated with cognitive decline (Nettiksimmons et al., 2016). The protein products of these genes do have functions in neuronal homeostasis and plasticity that would indicate they could be associated with maintaining cognitive functioning. MEF2C is reported to be involved in neurogenesis (Li et al., 2008), whilst its deletion in the CNS of mice impairs hippocampal-dependent learning and memory (Barbosa et al., 2008) and peripheral mRNA expression has been reported to correlate with memory performance in a Japanese sample (Sao et al., 2017). The HLA cluster has important roles in the immune response, and FERMT2 maintains cellular structures including neuronal cells.

It is acknowledged that the current study has several limitations. First, AIBL study participants generally have higher levels of education, which may not be representative of the broader community (Ellis et al., 2009). Second, the current study represents a majority Caucasian population and results may differ based on ethnicity. Finally, small sample sizes in the resulting reference and test cohorts may have influenced the results reported. This is evidenced by differences in the risk alleles of certain SNPs observed in this study, compared with those previously reported. In addition to these limitations, several strengths of the AIBL study may impact replication studies. Firstly, the calculation of effect sizes for PRS weighting a combined group measure of verbal episodic memory performance over 7.5 years was utilized. It is possible that studies of shorter duration could yield differing results. Second, the use of a composite measure of verbal episodic memory is a further strength of the study, the same or comparable neuropsychological tests are likely to be required to calculate appropriate cognitive composite scores for validation purposes. For this reason, the replication of the methods and results reported here in large, comparably comprehensive studies are warranted to validate the clinical utility of this emPRS.
CONCLUSION

The study detailed above describes a \textit{emPRS} for the prediction of rates of cognitive decline in cognitively normal older adults at risk for AD. It shows that the \textit{emPRS} is able to predict rates of cognitive decline in domains typically affected in the preclinical stages of AD. Further, this is the first \textit{PRS} calculated with a conservative number of genetic variants to be associated with longitudinal cognition in the absence of APOE. The reported \textit{emPRS} has utility in those individuals carrying no or one copy of the APOE ε4 allele. The results presented here provide evidence which support the further evaluation and use of endophenotype weightings in \textit{PRS} development rather than the standard AD risk weightings that demonstrate inconsistent utility. The methodology and results should be validated in similarly well-characterized cohorts with comparable phenotypic and longitudinal data.

DATA AVAILABILITY STATEMENT

All data and samples used in this study are derived from the Australian Imaging, Biomarkers and Lifestyle (AIBL) Study of Ageing. AIBL data can be accessed through an Expression of Interest procedure, for more information please see https://aibl.csiro.au/awd.

AUTHOR CONTRIBUTIONS

TP contributed to acquisition of genetic data, statistical analysis, interpretation of findings, and drafting the manuscript. SB contributed to specific study concept and design, study supervision, statistical analysis, interpretation of findings, and revising the manuscript. GS and PM contributed to AIBL study design, obtaining funding, interpretation of findings, and revising the manuscript. YL contributed to interpretation of findings and revising the manuscript. LM and MP contributed to acquisition of genetic data. DA, CM, CR, and RM contributed to AIBL study design, obtaining funding, and revising the manuscript. SR-S and KT contributed to revising the manuscript. DG and GV contributed to current study concept and design, obtaining funding, study supervision, acquisition of data, interpretation of findings, and revising the manuscript. SL contributed to current study concept and design, obtaining funding, study supervision, acquisition of data, interpretation of findings, and drafting of the manuscript. All authors read and approved the final manuscript.

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Conflict of Interest Statement: CM is an advisor to Prana Biotechnology Ltd., and a consultant to Eli Lilly. PM is a full-time employee of CogState Ltd. YL reports serving as a scientific consultant to CogState Ltd., Biogen, and Lundbeck. CR has served on scientific advisory boards for Bayer Pharma, Elan Corporation, GE Healthcare, and AstraZeneca, has received speaker honoraria from Bayer Pharma and GE Healthcare, and has received research support from Bayer Pharma, GE Healthcare, Piramal Lifesciences and Avid Radiopharmaceuticals. VV served as a consultant for Bayer Pharma, and received research support from a NEDO grant from Japan.

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