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Degree of cognitive impairment does not signify early versus late MCI: Confirmation based on Alzheimer's disease polygenic risk

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Abstract

Degree of memory impairment is often used to infer early versus late amnestic mild cognitive impairment (aMCI). Previously, 318 Alzheimer's Disease Neuroimaging Initiative participants with aMCI – determined by a single memory test – were divided based on Rey Auditory Verbal Learning Task (AVLT) delayed recall: AVLT-impaired (n=225) and AVLT-normal (n=93). Equally consistent with differential progression or differential diagnosis, the AVLT-impaired group had more abnormal Alzheimer's disease (AD) biomarkers, more neurodegeneration over time, and were more likely to develop AD. In the present study, higher AD polygenic risk scores were associated with increased odds of being AVLT-impaired (OR=1.8, P<0.001). Thus, impairment severity does not necessarily reflect early versus late aMCI because disease progression cannot alter polygenic risk. What is presumed to be earlier MCI is likely a heterogeneous category that includes excess false-positive diagnoses. The additional cognitive test improved diagnostic precision by reducing those false positives. Impairment severity may reflect differences in underlying disease risk but, based on cross-sectional data alone, it cannot be used to infer early versus late MCI status.

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[1]Data used in preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). As such, the investigators within the ADNI contributed to the design and implementation of ADNI and/or provided data but did not participate in analysis or writing of this report. A complete listing of ADNI investigators can be found at: http://adni.loni.usc.edu/wp-content/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf

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Alzheimer's disease (AD); mild cognitive impairment (MCI); polygenic risk scores (PRS); diagnostic criteria

1 INTRODUCTION

Mild cognitive impairment (MCI) is a heterogenous condition, and it is important to reduce false positive diagnoses that may be applied to those not on the Alzheimer's disease (AD) continuum. Vuoksimaa et al. (2018) assessed Alzheimer's Disease Neuroimaging Initiative (ADNI) participants with amnestic MCI (aMCI). The cognitive criterion for aMCI in ADNI is impairment on Wechsler Logical Memory delayed recall. Modifying the criteria to also require impairment on Rey Auditory Verbal Learning Task (AVLT) delayed recall was associated with more abnormal AD biomarkers and substantially increased progression to AD. The most common explanation is that impairment on the additional test is simply identifying individuals further along on the disease trajectory who have been subject to more cognitive decline and accumulation of pathology—sometimes referred to as early versus late MCI. However, those results are equally consistent with an alternative possibility that the AVLT-normal group contains excess false positives who were simply at lower underlying disease risk and therefore less likely to progress. Put another way, we ask the question: Does this represent different disease stage or differential diagnosis?

Genetic information can provide a key piece of evidence to distinguish between these possibilities. If the groups differ because one has progressed further than the other along the disease trajectory, they should not differ in their genetic risk for AD. If, on the other hand, the AVLT-normal group contains excess false positives, they should have lower AD genetic risk. To address this issue, we build on the findings of Vuoksimaa et al. (2018) by testing for group differences on an AD polygenic risk score.

2 MATERIAL AND METHODS

2.1 Participants

Data used in the preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). The ADNI was launched in 2003 as a public-private partnership, led by Principal Investigator Michael W. Weiner, MD. The primary goal of ADNI has been to test whether serial magnetic resonance imaging (MRI), positron emission tomography (PET), other biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of MCI and early AD.

The present study included 318 participants from the ADNI-1 who fulfilled criteria for aMCI at baseline, had AVLT data, and had good quality genotyping data. This represents a subset of the individuals included in our previous analysis (Vuoksimaa et al., 2018). Demographic characteristics included: age, sex, education, and American National Adult Reading Test (ANART) scores (a measure of estimated premorbid cognitive ability).

Procedures were approved by the Institutional Review Board of participating institutions. Informed consent was obtained from all participants.

2.2 Mild cognitive impairment subtypes

As described previously (Vuoksimaa et al., 2018), ADNI participants were diagnosed with aMCI according to Petersen (Petersen et al., 2010) criteria: ≥1.5 SDs below the education-adjusted mean on Wechsler Logical Memory Story A delayed recall; subjective memory complaint; Clinical Dementia Rating Scale score of 0.5, and Mini-Mental State Exam score ≥24. We then categorized these baseline aMCI cases based on whether they were also impaired on AVLT delayed recall, defined by a cut-off of 1 SD below normative means: AVLT-normal (scaled score ≥8) and AVLT-impaired (scaled score ≤7).

2.3 Polygenic risk scores

Genotyping was done using the Illumina Human610-Quad BeadChip (Illumina, San Diego, CA) (Saykin et al., 2010) and imputed using the 1,000 Genomes Phase 3 EUR data as a reference panel (The 1000 Genomes Project Consortium, 2015). The AD-PRS was computed with PRSice-2 (Choi and O'Reilly, 2019) using summary data of an AD GWAS meta-analysis (Lambert et al., 2013). We excluded rare SNPs (MAF<1%) and SNPs with poor imputation quality (R2<0.5) from the calculation. SNPs were trimmed for linkage disequilibrium (LD) (r^2 threshold of 0.2 in a 500 kb window) based on LD patterns in the 1000 Genomes EUR cohort. Scores were calculated from SNPs based on a P-value threshold of P<0.50, as this has been shown to provide optimal case-control discrimination in previous studies (Escott-Price et al., 2017; Escott-Price et al., 2015; Logue et al., 2019). An additional "No *APOE*" version of the AD-PRS was calculated excluding the region of LD surrounding the *APOE* gene. *APOE* was directly genotyped at participant enrollment and we coded *APOE*-ε4+ versus *APOE*-ε4-.

2.4 Statistical analysis

Group differences on demographic characteristics were analyzed with t- and χ^2-tests. Logistic regression models tested whether AD-PRS scores were associated with odds of being in the AVLT-impaired MCI group. To determine whether the effect of the AD-PRS was driven by the *APOE* gene, an additional model was run using the "No *APOE*" AD-PRS and a covariate indicating presence/absence of the *APOE*-ε4 allele. Models additionally controlled for age and the first 10 genetic principal components to control for population stratification. Analyses were conducted with R version 3.5 (R Core Team, 2017).

3 RESULTS

There were no significant between-group differences for sex, education, or ANART, but the AVLT-normal MCI group was significantly older than the AVLT-impaired MCI group (77 vs. 74 years; P<0.001; Table 1).

Despite the older age of the AVLT-normal group, individuals with higher AD-PRSs were significantly more likely to be in the AVLT-impaired group (OR=1.80, P<0.001; Table 2). *APOE*-ε4+ carriers were more likely to be in the AVLT-impaired group (OR=2.14,

P=0.006). Individuals with higher "NoAPOE" AD-PRSs were still significantly more likely to be in the AVLT-impaired group (OR=1.71, *P*<0.001; Table 2) after controlling for *APOE*-ε4+ status.

4 DISCUSSION

As shown previously, modifying the ADNI criteria for aMCI by requiring impairment on an additional memory test resulted in a higher rate of progression to AD, more pathological levels of amyloid and tau, and more neurodegeneration over time (Vuoksimaa et al., 2018). The difference between the aMCI AVLT-impaired and aMCI AVLT-normal subgroups initially appears to be consistent with the concept of staging, similar to the introduction of early and late MCI diagnoses in ADNI-2 (Aisen et al., 2010). Early versus late MCI in ADNI is determined by magnitude of impairment on a single test, whereas here the groups were classified by impairment on one versus two tests. The early versus late MCI distinction in ADNI is not a formal diagnostic subcategory. What is most relevant is that the classification assesses the extent of impairment, and the most common interpretations of these distinctions have been based on the notion that the more cognitively impaired group is at a later stage of the same disease trajectory compared to those with less impairment. Anecdotally, we have found that, by far, colleagues most often take this viewpoint in accounting for the greater pathology and progression to AD in the more impaired group. However, the current findings indicate that the distinction between early and late MCI groups reflects some excess false positives in the early MCI group.

There appears to be an inherent inconsistency in the aMCI AVLT-normal classification. This inconsistency is reflected in the fact that, if an individual performs normally on the AVLT, it ought to raise serious concerns as to whether they truly have aMCI (i.e., truly have memory impairment). In these analyses, individuals diagnosed as aMCI who had normal performance on the AVLT had significantly lower genetic risk for AD compared with those in the AVLT-impaired MCI group. If they simply happened to be enrolled at different points along their trajectories, there would be no reason for the groups to differ with respect to genetic risk. Although accurate diagnosis can be compromised by ascertainment bias (Storandt and Morris, 2010), this form of ascertainment bias seems unlikely since these ADNI participants were not selected on the basis of AD genetic risk. The significant AD-PRS difference suggests that, rather than representing individuals from the same risk population who are at different points in the disease trajectory, the AVLT-impaired and AVLT-normal groups were drawn from two different risk populations. In other words, the AVLT-normal group likely contains more false positives who are not on the AD continuum and/or who are unlikely to develop dementia.

Although cross-sectionally we cannot definitively determine where on the disease trajectory AVLT-impaired individuals fall, we can be more confident that they are experiencing true cognitive impairment. This is consistent with neuropsychological studies which show that determining impairment based on a single test results in excess false positives (Bondi et al., 2014; Edmonds et al., 2015; Jak et al., 2009; Kremen et al., 2014). Incorporating multiple tests has been shown to reduce the number of reversions from MCI to cognitively normal, providing strong evidence that, in these cases, the original diagnoses were false positives

(Bondi et al., 2014; Edmonds et al., 2015). Evidence of longitudinal decline is necessary to definitively determine disease staging and rule out false positives that can arise from ascertainment bias (Edmonds et al., 2015; Edmonds et al., 2016; Storandt and Morris, 2010). For example, it is not possible to distinguish decline from longstanding low performance. However, diagnoses are often based only on the current assessment, so it is important to identify approaches that can reduce misclassification. Our group has found that a composite or factor score of multiple memory tests greatly increases prediction of future decline compared to any single test (Gustavson et al., 2020). We note that in clinical work and in screening of individuals into drug trials, the balance in cost-effectiveness has to be taken into consideration. While we believe that the cost of acquiring a comprehensive battery of memory tests is worth the increased sensitivity, our results demonstrate that even one additional memory test is valuable.

It is worth noting that the PRS excluding the APOE region was significantly associated with group even after controlling for APOE-ε4 status. This is consistent with findings that the PRS adds significant information above and beyond the APOE genotype (Escott-Price et al., 2015; Logue et al., 2019). A substantial number of APOE-ε4 carriers do not develop AD, and vice versa. That is, non-carriers may still be at risk, and some carriers are at lower risk than others. This result thus underscores the importance of more comprehensively assessing genetic risk for AD, which is a highly polygenic disease. The AD-PRS may include risk genes with pleiotropic effects, and thus may not be entirely specific to AD. However, those with lower AD-PRS should be at lower risk for both AD and any other genetically associated pathology. Put another way, many risk factors for AD are not specific to the disease, but individuals not exposed to that risk factor (or in this case, individuals who do not carry risk alleles) will still have a lower likelihood of developing AD. Moreover, PRSs are still considered useful in assessing risk for the corresponding condition despite the fact that common brain disorders exhibit a high degree of shared genetic influences (Brainstorm et al., 2018).

Another way to reduce false positives and increase diagnostic certainty is in assessing AD-related biomarkers of amyloid or tau. Moscoso et al. (2019) found that, when restricting to those with abnormal amyloid, individuals with greater episodic memory impairment did appear to be in a later stage of MCI. Our results are consistent with this finding in that, when only a single timepoint is available, requiring additional memory tests, evidence of genetic risk, or abnormal biomarkers provides important context to reduce false positives when inferring disease staging. Indeed, by restricting their sample to amyloid-positive subjects, Moscoso et al. minimized the potential for false positives in the early MCI group.

Our results have two main implications. First, a small amount of additional memory testing provides a time- and cost-effective method of improving accuracy for the diagnosis of MCI due to AD. Better identification of those who are likely to decline versus remain stable may help patients and families anticipate potential changes in daily functioning. It may also facilitate more sensitive clinical trials by enriching samples for individuals on the AD continuum (i.e., with abnormal AD biomarkers) and those likely to demonstrate cognitive decline within the study timeframe. Second, because genotype information remains constant, it can provide valuable additional context for interpreting group differences. AD-PRSs

determined MCI sub-groups with differential risk of disease. Without such genetic information, it is not possible to differentiate early versus late MCI on the basis of cross-sectional data.

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Verification

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3. The data contained in the manuscript being submitted have not been previously published, have not been submitted elsewhere and will not be submitted elsewhere while under consideration at Neurobiology of Aging.

4. All participants provided informed consent and the study was approved by local Institutional Review Boards at ADNI participating institutions.

5. All authors have reviewed the contents of the manuscript being submitted, approve of its contents and validate the accuracy of the data.

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Highlights

- Degree of impairment defines early vs late MCI and implies disease progression.
- Early vs late MCI reflects Alzheimer's polygenic risk, but not disease progression.
- Early MCI diagnoses are likely associated with increased false positive diagnoses.
- Just one additional memory test significantly reduces false positive MCI diagnoses.
- Cross-sectional data cannot determine disease progression (early vs late MCI).

Table 1.

Sample characteristics of MCI sub-groups based on the Rey Auditory Verbal Learning Test (AVLT).

Descriptive statistics at baseline of AVLT-normal (MCI AVLT+) versus AVLT-impaired (MCI AVLT−) mild cognitive impairment groups. Mean (SD) presented for continuous variables, count (%) presented for categorical variables. P-values are based on chi-square tests for categorical variables and t-tests for continuous variables. ANART = American National Adult Reading Test (number of correct words).

	AVLT-normal	AVLT-impaired	p
n	93	225	
Age	77.02 (6.96)	73.97 (7.21)	0.001
Gender (male)	62 (66.7%)	149 (66.2%)	1.000
Education (years)	15.84 (2.91)	15.60 (2.94)	0.517
ANART	36.80 (9.66)	36.28 (9.24)	0.655
AVLT trial 1	4.78 (1.73)	3.92 (1.47)	<0.001
AVLT trial 5	9.87 (2.70)	6.48 (1.87)	<0.001
AVLT trials 1-5	38.38 (10.32)	27.44 (6.46)	<0.001
AVLT delayed	6.89 (3.03)	1.08 (1.32)	<0.001

Table 2.

Association of Alzheimer's disease polygenic risk score with MCI sub-groups based on the Rey Auditory Verbal Learning Test (AVLT).

Full regression results of logistic regression models. Odds ratios represent the odds of being in the AVLT-impaired group compared to the AVLT-normal group. The table on the left displays results from the model including the full Alzheimer's disease polygenic risk score (AD-PRS). The table on the right displays results from the "No *APOE*" Ad-PRS which excludes SNPs in the region of the *APOE* gene as well as a separate variable coding for the presence versus absence of the directly genotyped *APOE*-ε4+ allele. Both models included age and the first ten genetic principal components (PC) as covariates.

Predictors	Odds Ratios	95 % CI	p
AD-PRS	1.80	1.35 – 2.38	<0.001
Age	0.66	0.50 – 0.87	0.003
PC 1	1.30	1.00 – 1.68	0.05
PC 2	1.16	0.89 – 1.52	0.281
PC 3	0.96	0.70 – 1.32	0.803
PC 4	0.97	0.71 – 1.32	0.844
PC 5	0.92	0.71 – 1.20	0.544
PC 6	1.03	0.79 – 1.33	0.839
PC 7	1.00	0.77 – 1.29	0.97
PC 8	0.81	0.63 – 1.05	0.12
PC 9	0.80	0.61 – 1.04	0.099
PC 10	1.19	0.91 – 1.56	0.199

Predictors	Odds Ratios	95% CI	p
AD-PRS No *APOE*	1.71	1.28 – 2.28	<0.001
APOE-ε4+	2.14	1.24 – 3.69	0.006
Age	0.68	0.52 – 0.91	0.008
PC 1	1.20	0.92 – 1.57	0.184
PC 2	1.17	0.89 – 1.55	0.26
PC 3	0.98	0.71 – 1.35	0.881
PC 4	0.97	0.71 – 1.32	0.836
PC 5	0.92	0.71 – 1.21	0.557
PC 6	1.00	0.77 – 1.31	0.983
PC 7	0.99	0.76 – 1.28	0.914
PC 8	0.82	0.63 – 1.07	0.139
PC 9	0.79	0.60 – 1.03	0.086
PC 10	1.20	0.91 – 1.58	0.191