

Machine Learning To Identify Dimensions Of Memory Self-awareness In MCI: Associations With AD Biomarkers And Progression



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- Data-driven clustering identified distinct memory awareness phenotypes in mild cognitive impairment
- Phenotypes characterized by high informant-reported decline showed higher CSF phosphorylated tau and lower amyloid-β, and higher PET amyloid centiloid levels
- Loss of self-awareness was associated with substantially increased risk of progression to Alzheimer’s disease dementia
- Heightened but uncorroborated concern (‘worried well’) was not associated with increased biomarker burden and predicted lower progression risk
- Multidimensional assessment of self-awareness may improve biological staging and risk stratification in prodromal Alzheimer’s disease

INTRODUCTION

Artificial intelligence offers new tools to refine measurement of changes in Alzheimer’s disease (AD) and improve risk stratification. Self-awareness of memory decline is a hallmark of AD, but traditional questionnaires obscure item-level differences between heightened awareness and unawareness¹. Early AD also shows substantial heterogeneity in self-awareness, rarely considered in prognosis^{2,3}. Here, we examine dimensions of self-awareness not captured by traditional methods and their relationship to AD progression heterogeneity.

- Objectives:**
1. Classify self-awareness heterogeneity in MCI by identifying distinct phenotypes
 2. Examine cross-sectional associations between phenotypes and AD biomarkers (CSF and PET amyloid/tau)
 3. Examine associations between baseline phenotype and progression from MCI to AD

METHODS

Memory Self-Awareness Measurement
Memory self-awareness was assessed using the memory section of the Everyday Cognition (ECog) questionnaire⁴. Participants and study partners rated memory abilities relative to 10 years earlier (e.g., remember shopping items, repeat stories) on a 4-point scale, with higher scores indicating greater decline. Unawareness (participant > partner) and heightened awareness (partner > participant) sub-scores were calculated¹.

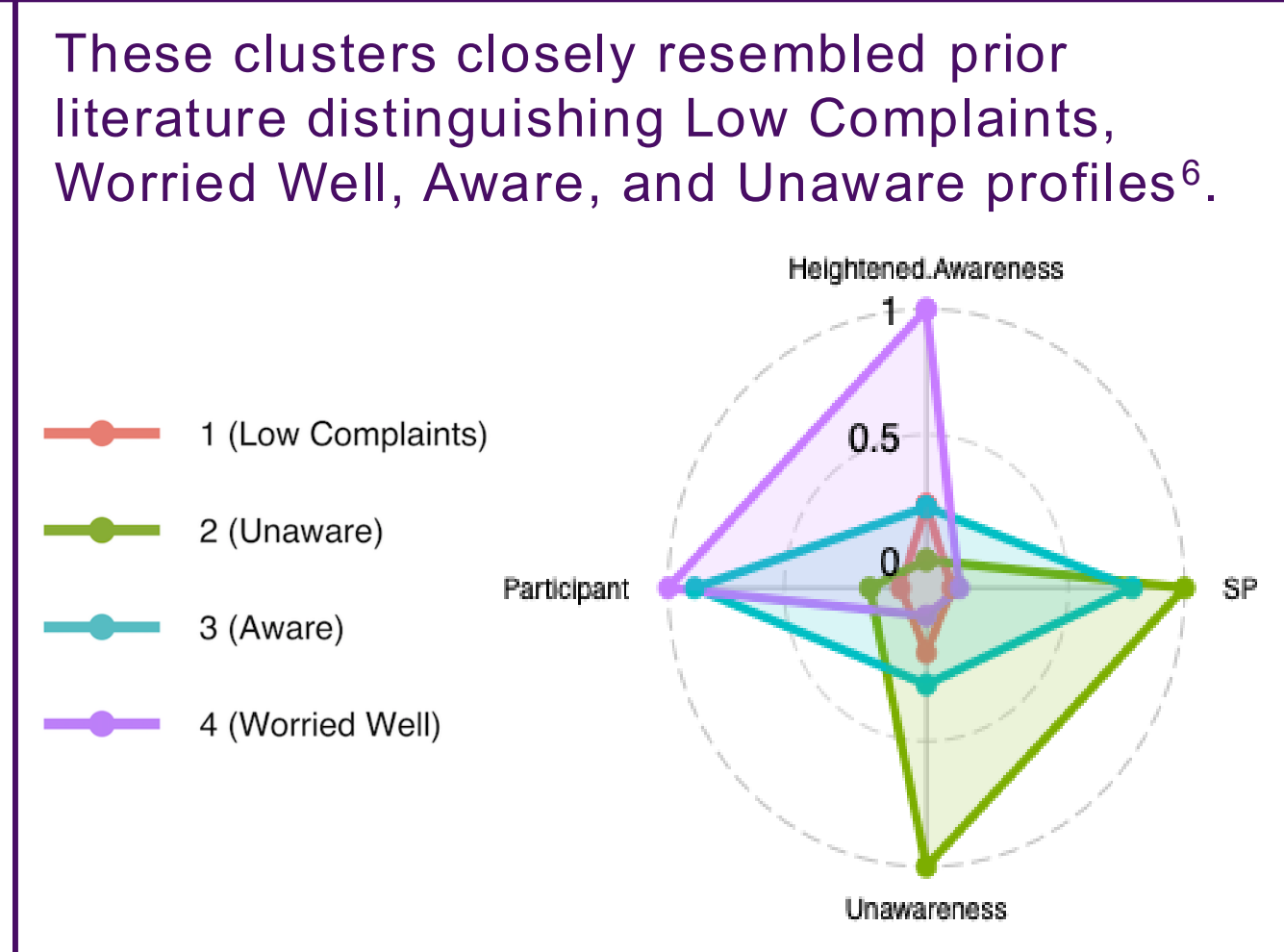
Clustering of Awareness Phenotypes
K-means clustering was applied to four features: unawareness sub-score, heightened awareness sub-score, mean participant complaints, and mean partner complaints.

CSF and PET Biomarkers
Baseline CSF p-tau181 and amyloid-β1–42 were measured via Roche Elecsys immunoassays⁵. In a subsample, PET amyloid centiloids, entorhinal tau (SUVR), and inferior temporal tau (SUVR) were measured.

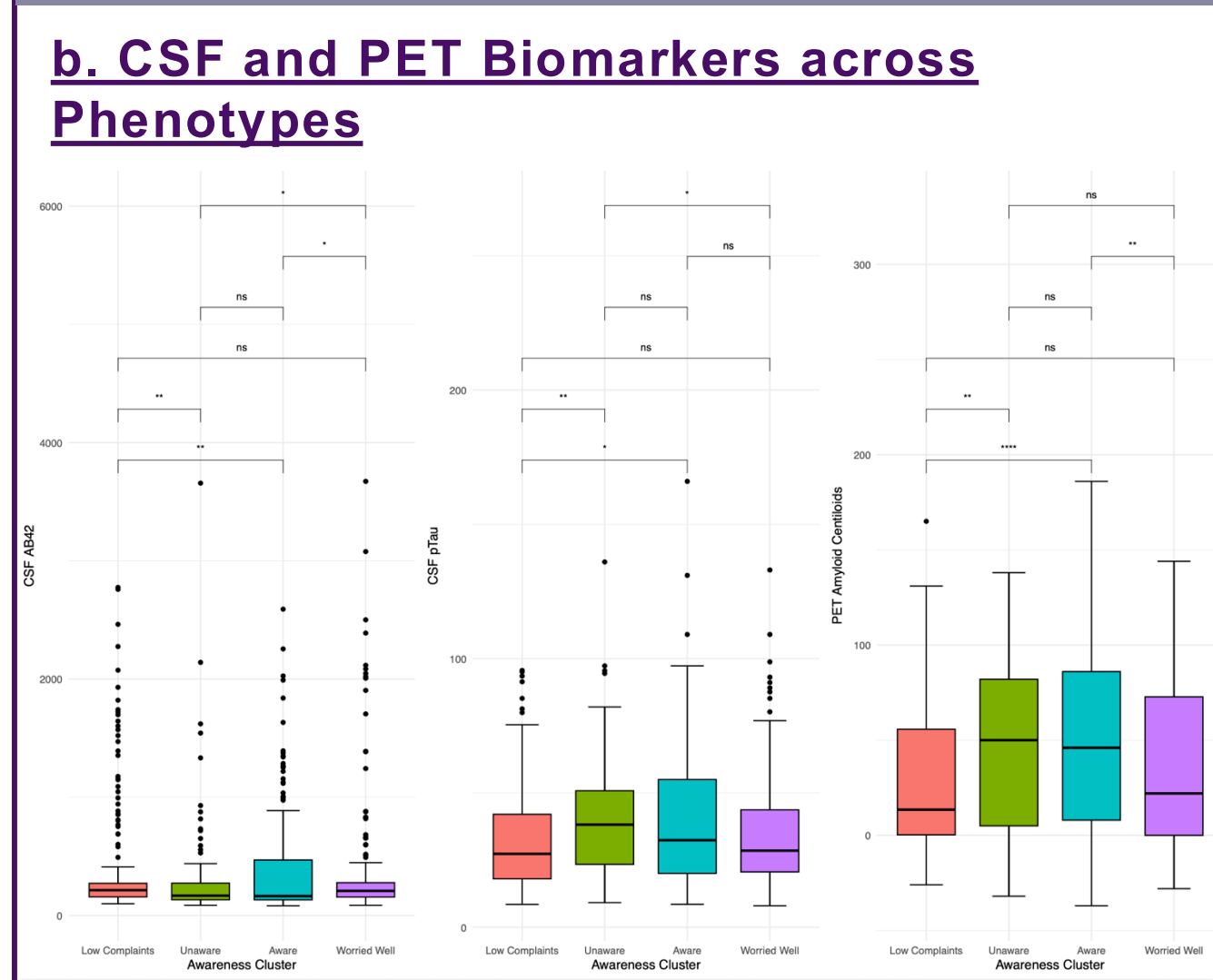
Statistical Analyses
Cross-sectional group differences in biomarkers were tested with Kruskal-Wallis and post hoc Wilcoxon Rank Sum tests, with FDR correction. Progression from MCI to AD dementia was examined using Cox proportional hazards models, adjusting for age, sex, MMSE, and education.

RESULTS

a. Phenotypes and Demographic Overview
We identified four distinct self-awareness phenotypes (Figure 1). **Low Complaints:** low scores across all measures. **Unaware:** high unawareness and partner complaints, but low heightened awareness and participant complaints. **Aware:** low unawareness and heightened awareness with high complaints from both participant and partner. **Worried Well:** high heightened awareness and participant complaints not corroborated by the partner. The clustering showed good fit and moderate separation (DBI = 0.936, silhouette mean = 0.381).



	Low Complaint	Worried Well	Aware	Unaware	p
N	184	153	171	82	
N (PET)	34	29	36	15	
Age	71.6 (7.4)	71.1 (7.8)	72.4 (7.4)	73.6 (7.3)	.04
Female, %	43	47	43	39	ns
Education, y	16.3 (2.4)	16.3 (2.7)	16.0 (2.8)	16.1 (2.6)	ns
MMSE	28.5 (1.6)	28.0 (1.8)	27.7 (2.1)	27.3 (2.5)	< .001
Progression, %	8.2	5.2	20	29	< .001

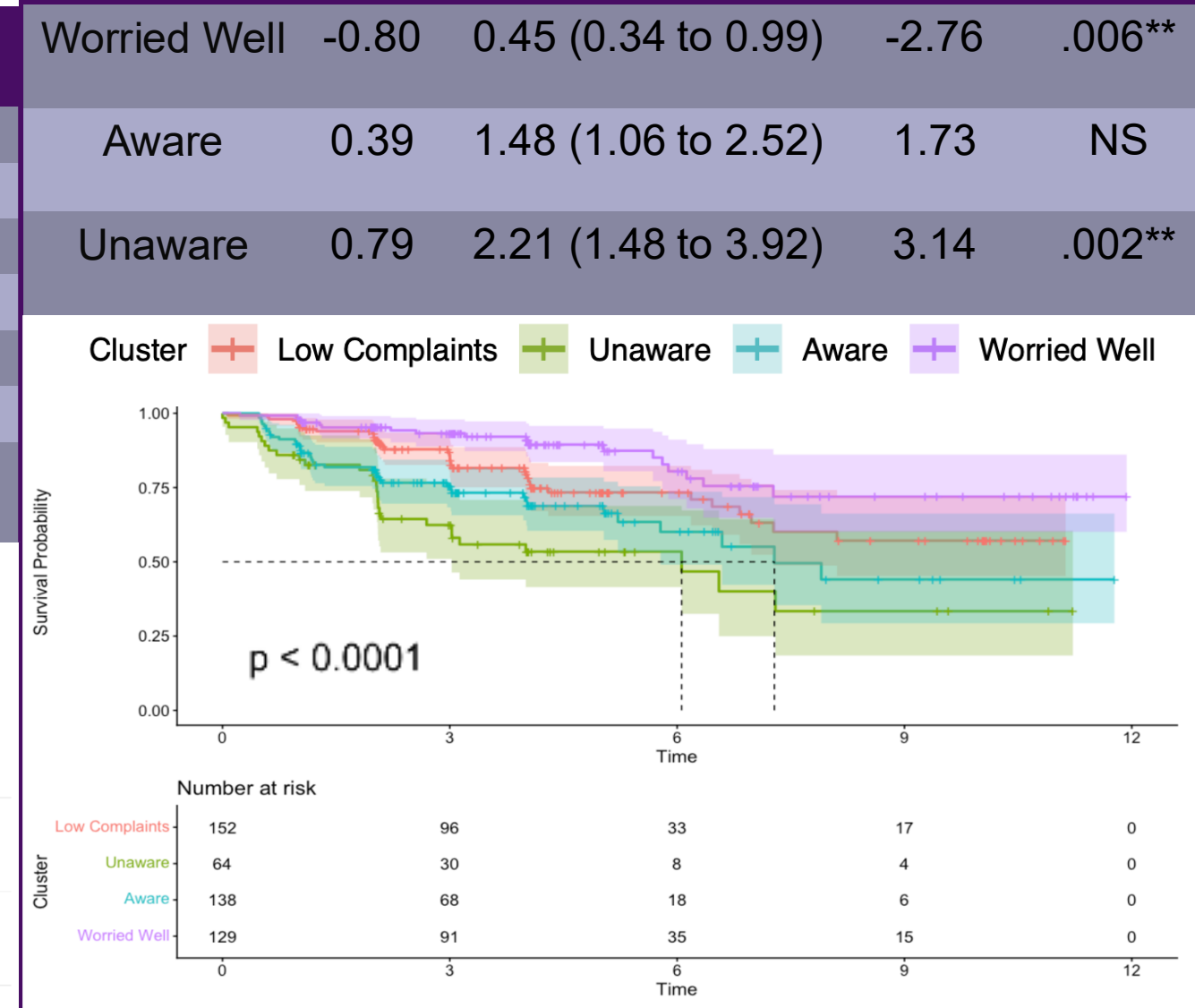


Kruskal–Wallis tests showed main effects for CSF Aβ1–42, p-tau, and PET amyloid centiloids, though no main effect of PET tau. The Unaware phenotype had the lowest Aβ1–42 **(A)** highest p-tau **(B)** and amyloid centiloids **(C)**, followed by the Aware phenotype. Low Complaints and Worried Well showed significantly lower pathology ($p < 0.02$).

c. Phenotypes and Progression to AD

- Using Low Complaints as reference: Worried Well showed 55% lower progression risk and Unaware showed 121% higher risk.

Phenotype	b	HR (95% CI)	z	p-value
Worried Well	-0.80	0.45 (0.34 to 0.99)	-2.76	.006**
Aware	0.39	1.48 (1.06 to 2.52)	1.73	NS
Unaware	0.79	2.21 (1.48 to 3.92)	3.14	.002**



CONCLUSIONS

Clustering uncovered novel phenotypes with clinical value beyond traditional methods, identifying unawareness as a significant risk factor for progression independent of cognitive impairment and biomarker burden.

However, the sample was mostly non-Hispanic White, and moderate cluster separation suggests these phenotypes may exist along a continuum rather than as fully discrete categories.

By integrating behavioral measures with biomarker and progression data, this framework illustrates the potential of unsupervised learning to enhance precision phenotyping in AD. Such approaches lay the groundwork for future models that incorporate multimodal data to better predict outcomes and inform risk stratification for personalized care.

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