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Erlangen Score Predicts Cognitive and Neuroimaging Progression in Mild Cognitive Impairment Stage of Alzheimer's Disease

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Abstract.
Background: To alleviate the interpretation of the core Alzheimer's disease (AD) cerebrospinal fluid (CSF) biomarkers, amyloid β_{1-42} ($A\beta_{42}$), total tau (*T*-tau), and phosphorylated tau (*P*-tau), the Erlangen Score (ES) interpretation algorithm has been proposed.
Objective: In this study, we aim to assess the predictive properties of the ES algorithm on cognitive and neuroimaging outcomes in mild cognitive impairment (MCI).
Methods: All MCI subjects with an available baseline CSF sample from ADNI-1 were included ($n = 193$), and assigned an ES between 0 and 4 based on their baseline CSF biomarker profile. Structural magnetic resonance imaging brain scans and MMSE and ADAS-Cog scores were collected at up to 7 times in follow-up examinations.
Results: We observed strong and significant correlations between the ES at baseline and neuroimaging and cognitive results with patients with neurochemically probable AD (ES = 4) progressing significantly ($p \leq 0.01$) faster than those with a neurochemically improbable AD (ES = 0 or 1), and the subjects with neurochemically possible AD (ES = 2 or 3) in-between these two groups.

[1]Data used in preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (http://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 (also available as Supplemental Material).

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Conclusion: This study further demonstrates the utility of the ES algorithm as a as a tool in predicting cognitive and imaging progression in MCI patients.

Keywords: $A\beta_{1–42}$, Alzheimer's disease, biomarkers, cerebrospinal fluid, Erlangen score, *P*-tau, *T*-tau

INTRODUCTION

The importance of cerebrospinal fluid (CSF) biomarkers of Alzheimer's disease (AD) as an aid for diagnostic decisions and a measure of disease progression is growing, both in research and in the clinical setting [1–3]. Reaching early and dependable diagnosis and prognosis for patients with memory complaints and other cognitive symptoms is likely key to be able to in time administer future treatments minimizing irreparable damage to the central nervous system [4]. A well-established panel of CSF biomarkers might be able to provide needed support in this task. The four most prominent and widely used biomarkers to date reflect different aspects of AD pathology: deposition of amyloid plaques leading to decreased concentrations of CSF amyloid $\beta_{1–42}$ ($A\beta_{42}$) and/or decreased $A\beta_{42/40}$ ratio; neuronal degeneration as reflected by total tau (*T*-tau); and neurofibrillary tangle formation correlated to phosphorylated tau (*P*-tau) [5, 6]. However, inter-laboratory differences in biomarkers assays, analytical procedures and pre-analytical sample collection protocols have made it hard to establish laboratory-independent cutoff values [7]. This leads to difficulties in comparing CSF results between centers, and even within a given center if a measurement method and/or preanalytical handling protocol are changed. To alleviate the interpretation of laboratory analysis results in AD, the Erlangen Score (ES) interpretation algorithm has previously been proposed [8]. The ES categorizes subjects into five ordinal categories with scores from 0 to 4 based on their CSF biomarker profile in relation to cutoff values that are given laboratory-specific. This approach reflects reality closer than the dichotomization into normal or pathologic biomarker status used in other studies [9, 10]. The ES algorithm has previously been validated in pre-dementia subjects in two multicenter studies, and its utility was supported by strong associations to the development of AD dementia [11–13]. However, the relation of the ES to cognitive and neuroradiological measures of the disease progression in mild cognitive impairment (MCI) stage of AD has never been investigated.

Therefore, in this study we aimed to assess the validity of the ES algorithm as a tool for predicting cognitive and imaging progression in MCI. We hypothesized that a higher score would be associated with faster disease progression.

METHODS

Data used in the preparation of this article were obtained from the Alzheimer's disease Neuroimaging Initiative (ADNI) database (http://adni.loni.usc.edu). ADNI was launched in 2003 by the National Institute on Aging (NIA), the National Institute of Biomedical Imaging and Bioengineering (NIBIB), the Food and Drug Administration (FDA), private pharmaceutical companies and non-profit organizations as a $60 million, 5-year public-private partnership. 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 Principal Investigator of this initiative is Michael W. Weiner, MD, VA Medical Center and University of California – San Francisco. ADNI is the result of efforts of many co-investigators from a broad range of academic institutions and private corporations, and subjects have been recruited from over 50 sites across the U.S. and Canada. The initial goal of ADNI was to recruit 800 subjects but ADNI has been followed by ADNI-GO and ADNI-2. To date these three protocols have recruited over 1,500 adults, ages 55 to 90, to participate in the research, consisting of cognitively normal older individuals, people with early or late MCI, and people with early AD. The follow up duration of each group is specified in the protocols for ADNI-1, ADNI-2, and ADNI-GO. Subjects originally recruited for ADNI-1 and ADNI-GO had the option to be followed in ADNI-2. For up-to-date information, see http://www.adni-info.org, where inclusion/exclusion criteria are also described in detail.

Subjects

Our study population consisted of all MCI subjects with available baseline CSF samples from ADNI-1 ($n = 193$). Briefly, all subjects included in ADNI-1 were between the ages of 55 and 90 years, had completed at least 6 years of education, were fluent in Spanish or English, and were free of any significant neurologic disease other than AD. The MCI group had Mini-Mental State Examination (MMSE) score $\geq$24, objective memory loss as shown on scores on delayed recall of the Wechsler Memory Scale Logical Memory II (>1 standard deviations below the normal mean), Clinical Dementia Rating scale 0.5, preserved activities of daily living, and absence of dementia.

Erlangen score

All study subjects were assigned an ES between 0 and 4 based on their CSF biomarker profile with a macro written in Microsoft Excel. The detailed protocol for the ES can be found elsewhere [8]. Briefly, a CSF profile with all biomarkers normal is scored 0 points; a pattern with only slight alterations in one biomarker group (either Aβ or Tau, but not both) results in the score of 1; alterations in amyloid β pathology (in this particular study, decreased $A\beta_{1–42}$ concentrations) or tau metabolism (increased concentrations of *T*-tau and/or *P*-tau) but not in both is scored 2 points; a result with clear alterations in one biomarkers' group (either Aβ or Tau) accompanied by marginal alterations in the other group is scored 3 points; clear alterations in both Aβ and *T*-tau/*P*-tau result in 4 points. A simplified rendition of the interpretation algorithm used to translate the biomarker profiles of each subject is described elsewhere. Eventually, the subjects with the score of 0-1 are defined as "neurochemically improbable AD", the subjects with the score of 2-3 are defined as "neurochemically possible AD", and the subjects with the score of 4 are defined as "neurochemically probable AD".

CSF measurements

CSF collection, processing, and storage procedures have been described previously [14]. CSF $A\beta_{42}$, *T*-tau, and *P*-tau were measured using the multiplex xMAP Luminex platform (Luminex Corp, Austin, TX, USA) with the INNOBIA AlzBio3 kit (Fujirebio, Ghent, Belgium). The reference ranges used for the calculations of the scores were taken directly from the previous study [14], and applied for this study without further modifications: 192 pg/mL for $A\beta_{1–42}$, 93 pg/mL for *T*-tau, and 23 pg/mL for *P*-tau. The border zones, defining "slight alterations", were set as the concentrations within the range of 173–192 pg/mL for $A\beta_{1–42}$, within 93–102 pg/mL for *T*-tau, and within 23–25 pg/mL for *P*-tau.

Magnetic resonance imaging

Structural magnetic resonance imaging brain scans were acquired using 1.5 Tesla MRI scanners (up to 7 time points: screening, and 6, 12, 18, 24, 36 and 48 months) with a standardized protocol including T1-weighted MRI scans using a sagittal volumetric magnetization prepared rapid gradient echo (MP-RAGE) sequence [15]. In brief, automated volume measures were performed with FreeSurfer software package (http://surfer.nmr.mgh.harvard.edu/fswiki) [16, 17]. We used averaged volume measurements for the right and left hippocampi for this study.

Cognitive assessments

Overall cognition was assessed by the MMSE and the Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog) tests at up to 7 time points (screening, and at 6, 12, 18, 24, 36 and 48 months after the baseline assessment).

Statistical analysis

If not stated otherwise, the results of continuous variables are presented as means and standard deviations (std. dev.) or as medians and inter-quartile ranges (IQR). ANOVA and χ^2 statistics were used to test differences in age and sex distribution, baseline measurements of hippocampal and whole brain volumes, and baseline MMSE and ADAS-Cog scores between the study groups. Generalized estimating equation (GEE) was used to discern statistical differences between ES groups in the development of MMSE scores, ADAS-Cog scores, hippocampal volumes and whole brain volumes over time. The interaction term of ES*month from baseline was used to test modifying effects of the ES on the effect of the observation time. All longitudinal changes in MMSE, ADAS-Cog scores, whole brain volumes, and hippocampal volumes were normalized to a percentage change in relation to their baseline values. Statistical significance was determined at the $p < 0.05$ level. All statistics, charts, and tables were generated with SPSS version 22 (IBM, New York, USA).

Ethics

All CSF samples analyzed in this study were collected in accordance with regional ethical guidelines as well as the ethical standards of the Helsinki Declaration of 1975.

RESULTS

Demographics of the study cohort

Demographics and the baseline measures of the metrics analyzed in this study are presented in Table 1. There were no significant differences in age between the groups. There were significant differences in the sex distribution between the groups ($p = 0.02$). The group with neurochemically improbable AD (ES = 0 or 1) had 26% female subjects, the group with neurochemically possible AD (ES = 2 or 3) had 18% female subjects, and the group with neurochemically probable AD (ES = 4) had 40% female subjects.

Subjects in the neurochemically improbable AD group had significantly larger hippocampal volumes at baseline compared to the neurochemically possible (mean diff = 718 mm^3, $p = 0.03$) and the neurochemically probable (mean diff = 777 mm^3, $p \leq 0.01$) AD groups. There were no significant differences in hippocampal volumes between the neurochemically possible and probable groups ($p = 1.0$).

The neurochemically improbable AD subjects also had significantly larger whole brain volumes at baseline compared to those with neurochemically probable AD (mean diff = 6.9E5 mm^3, $p < 0.01$) but not compared to the subjects with neurochemically possible AD ($p = 1.0$). The neurochemically possible group and the neurochemically probable group did not significantly differ in baseline whole brain volumes ($p = 0.11$).

The neurochemically improbable AD group registered lower ADAS-Cog scores at baseline compared to the neurochemically possible AD (mean diff = 5.5, $p < 0.01$) and the neurochemically probable AD (mean diff = 5.5, $p < 0.01$) groups. No significant differences in ADAS-Cog scores between the neurochemically possible and probable AD groups could be found ($p = 1.0$).

The neurochemically improbable AD group presented slightly higher MMSE scores than the neurochemically possible AD (mean diff = 1.0, $p = 0.04$) but not the neurochemically probable group ($p = 0.20$). There were, again, no significant

Table 1
Demographics and the cognitive and neuroimaging results. M/F, number of the male/female subjects; Mdn., median; IQR, inter-quartile range; Std. dev., standard deviation; MMSE, mini-mental state examination; ADAS-Cog, Alzheimer's Disease Assessment Scale-cognitive subscale; E3, $*10^3$; E6, $*10^6$. All measures were collected at the baseline

Erlangen score	Sex	Age (y)		MMSE (points)		ADAS-Cog (points)		Whole brain volume (mm3)		Hippocampal volumes (mm3)	
	M/F	Mean (Std.dev.)	Mdn (IQR)	Mean (Std.dev.)	Mdn (IQR)	Mean (Std.dev.)	Mdn (IQR)	Mean (Std.dev.)	Mdn (IQR)	Mean (Std.dev.)	Mdn (IQR)
0-1	12/35	73.8 (7.9)	74 (67.5–80.4)	27.4 (1.7)	28 (26–29)	14.8 (5.4)	15.8 (11.3–17.3)	1.05E6 (.12E6)	1.05E6 (0.98E6–1.08E6)	6.98E3 (1.28E3)	7.20E3 (6.05E3–7.68E3)
2-3	6/28	76.8 (7.5)	77.2 (73.9–80.9)	26.4 (1.9)	26 (25–28)	20.3 (6.2)	19.9 (15.7–24.7)	1.04E6 (0.12E6)	1.07E6 (0.96E6–1.13E6)	6.26E3 (1.28E3)	6.50E3 (5.34E3–7.11E3)
4	45/67	78.1 (7.1)	79.1 (70.3–85.9)	26.9 (1.8)	27 (25–28)	20.3 (6.0)	21 (16.3–24.3)	0.99E6 (0.10E6)	0.98E6 (0.92E6–1.05E6)	6.20E3 (0.87E3)	6.11E3 (5.57E3–6.75E3)

Table 2
Participants at follow-up times

Follow-up		Baseline	6 months	12 months	18 months	24 months	30 months	36 months	42 months	48 months	54 months
Erlangen	0 or 1	47	45	43	40	36	33	30	21	6	3
score	2 or 3	34	33	31	29	27	27	22	10	5	3
	4	112	108	106	98	91	81	75	36	16	10

differences between the neurochemically possible and probable AD groups ($p = 0.64$).

Longitudinal changes in cognitive measures in the MCI group

Follow-up times and number of participants at each point of follow-up is presented in Table 2. The number of included patients decreased over time, but remained over 65% until the follow-up at 42 months where the number of included patients dropped to 35%. At 48 months 14%, and at 54 months 8% of the original study participants were included.

MMSE scores declined significantly faster in the subjects with neurochemically possible AD ($B = –0.20$, $p = 0.03$) and with neurochemically probable AD ($B = –0.36$, $p < 0.01$) compared to the subjects with neurochemically improbable AD (Fig. 1A). There was a nonsignificant tendency towards faster decline in the MMSE score in neurochemically probable subjects compared to neurochemically possible subjects ($B = –0.16$, $p = 0.10$).

Subjects with neurochemically probable AD also increased faster in ADAS-Cog scores as compared to the subjects with improbable AD ($B = 0.71$, $p = 0.01$, Fig. 1B). We did not observe differences in ADAS-Cog scores increase between the neurochemically possible AD subjects compared to the neurochemically improbable AD subjects ($B = 0.10$, $p = 0.76$). There was, however a significant difference in decline between the neurochemically probable and neurochemically possible AD subjects ($B = 0.60$, $p = 0.02$).

Longitudinal changes in brain structure in MCI

Whole brain volumes decreased faster in subjects with neurochemically possible AD ($B = –0.032$, $p = 0.03$) and neurochemically probable AD ($B = –0.066$, $p < 0.01$) as compared to subjects with neurochemically improbable AD (Fig. 1C). Whole brain volumes also decreased faster in subjects with neurochemically probable AD ($B = –0.034$, $p = 0.01$) as compared to subjects with neurochemically possible AD.

Hippocampal volumes declined faster in patients with neurochemically possible AD ($B = –0.084$, $p < 0.01$), and neurochemically probable AD ($B = –0.20$, $p < 0.01$) compared to the subjects with neurochemically improbable AD (Fig. 1D). This was also true for subjects with neurochemically probable AD ($B = –0.117$, $p < 0.01$) as compared to subjects with neurochemically possible AD.

DISCUSSION

In this study, we examined the utility of the ES as a globally implementable composite AD biomarker evaluation algorithm to predict cognitive and brain imaging decline in MCI stage of AD. In a well-suited study cohort of MCI patients with very little differences in explanatory variables like age and MMSE at baseline, we found that a higher ES predicted a faster disease progression in MCI patients; the subjects with higher ES showed a faster reduction of the whole brain and the hippocampal volumes, as well as faster decrease in MMSE, and a faster increase in ADAS-Cog scores.

In all disease progress measures selected for this study there were clear and statistically significant distinctions between patients with neurochemically improbable AD (ES of 0-1) and those with neurochemically probable AD (ES of 4), and for most measures also between the subjects with neurochemically improbable AD and those with neurochemically possible AD (ES = 2 or 3). Expectedly, subjects with ES 2-3 exhibited disease developing patterns in between those with the scores score 0-1 and 4. Here, the differences between the groups were statistically weaker, probably at least partly due to the low number of subjects with ES 2 and 3 ($n = 27$ and $n = 7$, respectively). However, their statistical parameters in the GEE models as well as visual indications in the Loess regressions in Fig. 1 corroborate them being part of a continuum between the higher subject count groups of neurochemically improbable AD and neurochemically probable (ES = 4) AD. An interesting feature of the differences in the time-dependent correlations of the cognitive and the structural measures and ES, is that the neurochemically improbable AD and the

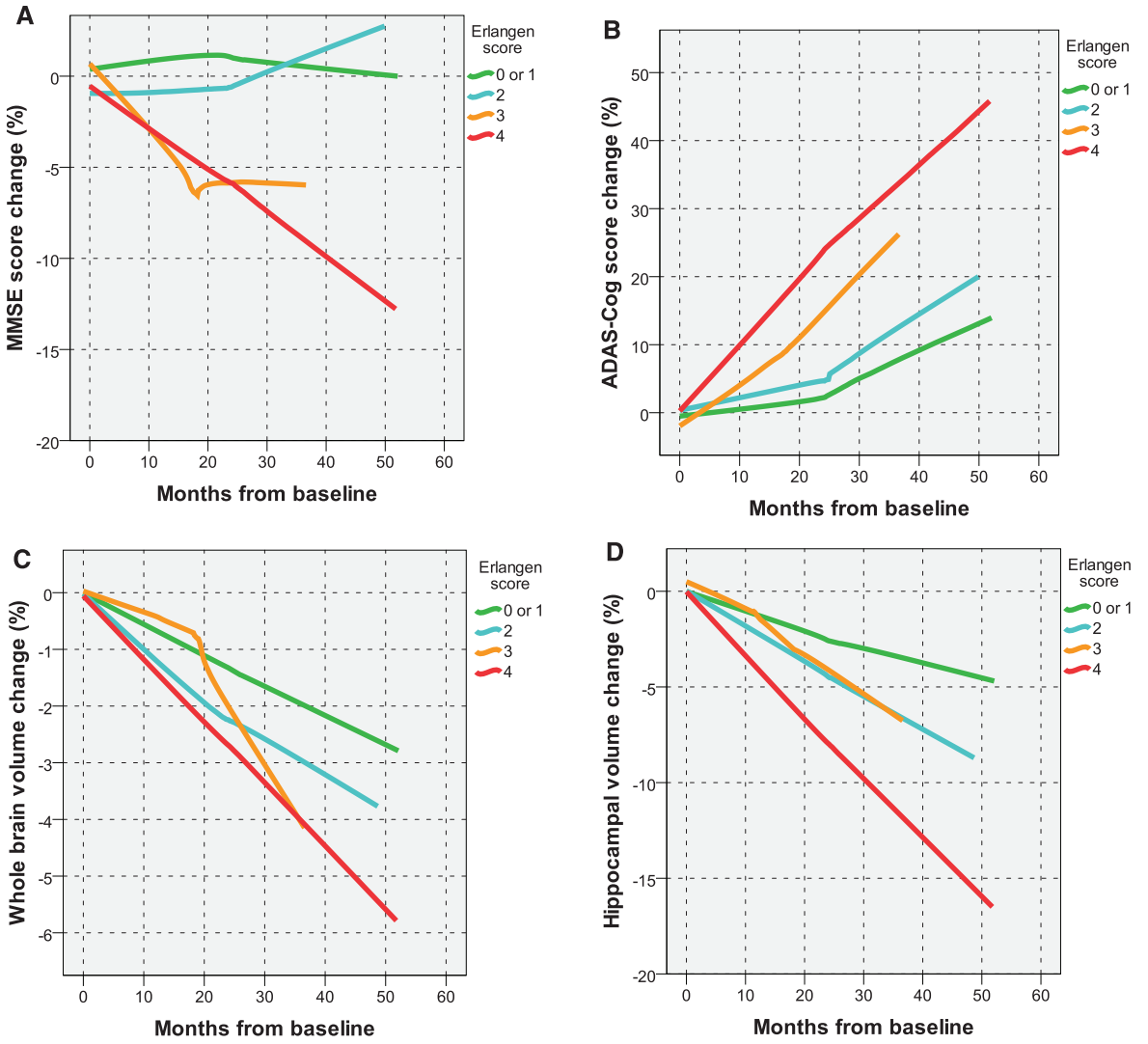

Fig. 1. Correlations between follow up time and the neuropsychologic and neuroimaging population-averaged (marginal) metrics in the three ES categories: A) MMSE score change from the baseline; B) ADAS-Cog score change from the baseline; C) whole brain volume change from the baseline; D) hippocampal volume change from the baseline.

neurochemically possible AD divert from each other in structural but not in cognitive measures. A possible explanation for this is that, in AD, structural alterations are observable before cognitive decline can be detected by MMSE or ADAS-Cog [18]. This means, that some of the subjects with no or only moderate CSF alterations (i.e., those with ES = 0–3) at baseline are most probably already at the stage of the disease when the first structural changes can already be seen. On the other hand, it takes much longer for the cognitive decline to reach pathological levels, particularly in patients at the earlier stages of the ongoing AD pathology (i.e., those with less pronounced CSF alterations as reflected by ES). Studies suggest that hippocampal volume is altered early in AD and a good measure of disease progression in the MCI stage, while whole brain volumes change later and is not a good measure of progression until in later stages of the disease [19]. This provides grounds for the ES as a good proxy for neuroradiological AD staging as hippocampal volumes are significantly altered already at baseline in the ES 0-1 group versus the ES 2-3 group, while whole brain volumes were only altered between the ES 0-1 and the ES 4 groups at baseline. Taken together, the time-dependent differences in sequences of the patterns of the CSF, structural,

and cognitive alterations observed in this study are fully in line with the postulated models.

Interestingly, in a recent study we found that MCI patients with neurochemically possible AD had, compared to the patients with neurochemically improbable AD, 6–8 times higher hazards to progress to the dementia stage of AD in the first three follow up years, and then their hazards decreased and became comparable to those with improbable AD; on the other hand, MCI patients with neurochemically probable AD had hazards to develop AD dementia 8–12 times higher compared to the patients with neurochemically improbable AD [13].

The most serious limitation of this study is the unavailability of results of CSF $A\beta_{1-40}$ in this cohort, which precluded integration of the $A\beta_{42/40}$, a biomarker known to better reflect the Aβ pathology than $A\beta_{1-42}$ concentration [20, 21], into the calculation of the ES. This can perhaps explain, why some subjects categorized as neurochemically improbable AD based on the three available CSF biomarkers (ES = 0 or 1), show progression in neuroimaging modalities (see Fig. 1C, D). Certainly, some of these subjects would be categorized as neurochemically possible AD category (ES = 2 or 3), if their $A\beta_{42/40}$ ratio had been available and turned out pathologic. Nevertheless, it must be stressed that even in the absence of $A\beta_{42/40}$ ratio, the interpretation based on the ES performed very well in this validation study. Another limitation of this study is the missing data in the follow-up biomarker measurements, especially after month 36, as detailed in Table 2.

It should be noted that Fig. 1 is intended as an illustration, while the GEE model provide statistical proof of differences. Some seeming anomalies between the GEE results and the graphical representations of data in the local regression illustrations occur, likely due to the linear nature of the GEE model contrasting with the adaptive nature of the local regression, and also the low number of participants, particularly at follow up, in the neurochemically probable AD group.

The findings of this study outline a new property of the ES that has not been demonstrated before, namely its predictive features of disease progression rates in MCI. This adds to the value of the algorithm that has previously been shown, including: 1) precise estimation of risk to develop dementia in pre-dementia AD; 2) allowing inter-laboratory comparisons of laboratory test results, despite use of different assays and biomarker cut-offs between centers; 3) interpretation and presentation of all possible biomarker patterns, including those that are inconsistent with hallmark AD-like biomarker patterns, 4) proxying of the neuroimaging AD staging.

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