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Cognitive dispersion is not associated with cerebrospinal fluid biomarkers of Alzheimer's disease: results from the European Prevention of Alzheimer's Dementia (EPAD) v500.0 Cohort

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Running title: Cognitive dispersion and AD biomarkers

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ABSTRACT

Background: Cognitive dispersion, variation in performance across cognitive domains, is posited as a non-invasive and cost-effective marker of early neurodegeneration. Little work has explored associations between cognitive dispersion and Alzheimer's disease (AD) biomarkers in healthy older adults. Even less is known about the influence or interaction of biomarkers reflecting brain pathophysiology or other risk factors on cognitive dispersion scores.

Objective: The main aim of this study was to examine whether higher cognitive dispersion was associated with cerebrospinal fluid (CSF) levels of amyloid β ($A\beta_{42}$), total tau (t-tau), phosphorylated tau (p-tau) and amyloid positivity in a cohort of older adults at various severities of AD. A secondary aim was to explore which AD risk factors were associated with cognitive dispersion scores.

Method: Linear and logistic regression analyses explored the associations between dispersion and CSF levels of $A\beta_{42}$, t-tau and p-tau and amyloid positivity ($A\beta_{42}$<1000pg/ml). Relationships between sociodemographics, *APOE*ε4 status, family history of dementia and levels of depression and dispersion were also assessed.

Results: Dispersion did not emerge as associated with any of the analytes nor amyloid positivity. Older ($\beta = -0.007, SE = 0.002$, p=0.001) and less educated ($\beta = -0.009, SE = 0.003$, p =0.009) individuals showed greater dispersion.

Conclusion: Dispersion was not associated with AD pathology, but was associated with age and years of education, highlighting individual differences in cognitive ageing. The use of this metric as a screening tool for existing AD pathology is not supported by our analyses. Follow-up work will determine if dispersion scores can predict changes in biomarker levels and/or positivity status longitudinally.

KEYWORDS: Alzheimer's disease; ageing; cognition; amyloid; tau; risk factors

INTRODUCTION

Alzheimer's disease (AD) is now widely accepted to lie on a continuum, with an asymptomatic neurodegenerative antecedent progressing towards cognitive and functional impairment that ultimately culminates in the Alzheimer's dementia syndrome. Individuals without overt cognitive impairment meeting criteria for preclinical AD (pAD) based on biomarker evidence of AD pathophysiology show subtle cognitive signs detectable on precise neuropsychological tests [1–3]. Recommendations for cognitive testing in pAD exist [4,5] and several new experimental measures have been proposed as sensitive and specific to the emergence of neuropathological change in regions vulnerable to AD [6–8]. Typically, cognitive impairment is determined by deterioration over time in an individual's performance or alternatively by cut-off scores comparing mean performance between groups or an individual's performance against the mean. More recently, research attention has turned to the application of sensitive scoring schemes that rely on existing traditional measures but repurpose their performance metrics to incorporate variations in cognitive performance within an individual participant. The term cognitive dispersion refers to variations in performance for a given individual between cognitive domains, tasks or performance across cognitive tests, while cognitive intra-individual

variability describes variations in performance between trials within a single task at the same testing occasion or over time. Here, we will focus on cognitive dispersion. There are several approaches to quantify cognitive dispersion [9,10], but no consensus on the most appropriate method. The individual standardised deviation (iSD) metric [11], comprising the standard deviation in individual performance across a set of cognitive measures, is one of the most widely used [10]. For this metric, raw scores are z-transformed on the basis of the distribution of scores from a reference sample and the variability between scores is calculated across the number of domains, tasks or tests within the assessment.

Studies of cognitive dispersion reveal significant differences between age groups, with children and older adults showing greater dispersion in cognitive performance cross-sectionally [12–15]. Patterns of dispersion in cognitive function in childhood and later-life may reflect developmental and healthy ageing processes, respectively. However, in older adults, higher baseline dispersion scores have been shown to predict progression to mild cognitive impairment (MCI) and dementia [11,16–19], suggesting such performance dispersion may mark the emergence of a pathological process. In healthy ageing, increased cognitive dispersion may reflect the emergence of impaired attention and executive functions alongside otherwise preserved cognitive domains, in turn reflecting a breakdown in compensatory mechanisms [20] as a result of age-related changes in neurotransmitter efficiency [21], grey and white matter integrity or the disruption of the default node network [22]; mechanisms that become increasingly compromised when a disease process accelerates. It has also been shown, as with most mean or normative indices of cognitive performance, that educational attainment may influence cognitive dispersion in mid-older adults (~65 years old), but not in late-older adults (~80 years old), suggesting that the former age group may uniquely benefit from early life brain stimulation acquired through education [20]. Apart from age and education, there has been little

attempt to understand which other established AD risk factors (e.g. *APOE*ε4, gender, family history or depression) or interactions thereof might influence cognitive dispersion scores.

Importantly, in some studies, cognitive dispersion indices have been shown to be associated with later cognitive impairment where mean performance methods or individual cognitive tasks have not [e.g. 11,15,23], underscoring their usefulness in prediction models of the risk of dementia or a means to identify and then target interventions towards higher risk individuals for secondary prevention of later stages of neurodegeneration. In fact, cognitive dispersion indices have been shown to predict MCI and dementia comparably to *APOE*ε4 carrier status and hippocampal atrophy [17] and independently of cerebrospinal fluid (CSF) analytes [16], further endorsing their use as a cost-effective and less invasive screening tool.

The correlates of cognitive dispersion with structural brain regions have been less well studied, but higher dispersion scores have been associated with smaller corpus callosum volumes [24]; global and regional white matter degeneration [21,22,25], faster entorhinal and hippocampal atrophy rates [26] as well as post-mortem neurofibrillary tangles in AD Dementia, MCI and healthy individuals.

Preclinical AD is characterised by a CSF analyte profile of lower levels of amyloid-beta, reflecting higher amyloid load in the brain, and higher levels of tau pathologies [27]. Only two studies have directly explored relationships between inconsistencies in testing and CSF analyte values of AD biomarkers, both finding significant associations in the expected directions [28,29]. However, their dispersion scores were restricted to intra-individual variability in processing speeds between separate cognitive tasks. Given that in the asymptomatic stages of AD some cognitive domains, such as episodic memory and executive function, may be more sensitive markers of emerging pathology at an earlier stage of disease than others [30],

increased dispersion across domains and/or tasks more sensitive to AD-specific regions at an early stage of disease might constitute a good marker of CSF identified cerebral pathology.

In summary, there is growing interest surrounding cognitive dispersion as a non-invasive and less costly marker of early neurodegeneration before clinical symptoms are evident. Consequently, we believe that there is a need for further exploration of the associations between cognitive dispersion and the pathological hallmarks of AD in adults without dementia [16]. In response to this, our main aim was to examine the hypotheses that higher cognitive dispersion will be associated with a) lower amyloid β ($A\beta_{42}$) levels; b) higher total tau (t-tau); c) higher phosphorylated tau (p-tau) levels and d) amyloid positivity status in a cohort of older adults (>64 years) with variable risks for AD Dementia, using a battery of tasks comprising traditional and novel experimental measures recommended for pAD research [4–6]. In addition, we explored which AD risk factors were associated with cognitive dispersion scores in our cohort to better understand the possible influence of such factors upon this index in this age group.

METHOD AND MATERIALS

Participants

Participants were recruited from the European Prevention of Alzheimer's Dementia (EPAD) Longitudinal Cohort Study (LCS) [31]. EPAD is a multi-site pan-European project comprising individuals recruited from parent cohorts across affiliated delivery centres. Eligibility criteria include: aged 50 years or older; possession of at least seven years of formal education and availability of a study partner willing to provide corroborative information (for functional and behavioural measures). Potential participants are excluded at the screening stage if they were unable to consent to the research; had known genetic mutations associated with autosomal-dominant AD, had significant and unstable physical or mental illness; had or had experienced

cancers within last five years (with the exception of localised prostate cancer and basal or squamous carcinoma). The EPAD project will provide a longitudinal observational research cohort in preclinical AD. The current study made use of the EPAD V500.0 data release, which provides baseline visit data from the first 500 participants across all research sites [32]. All participants provided informed consent and local ethical approval was obtained from ethics committees specific to each research site. All procedures were done in accordance with the ethical standards of the Helsinki Declaration.

Cognitive testing and construction of cognitive dispersion index

EPAD makes use of both traditional and exploratory measures that have been recommended for the assessment of cognitive change in pAD. The cognitive measures used for construction of our primary cognitive dispersion score included the Repeatable Battery of Assessment for Neuropsychological Status [33] subscale scores: Verbal Episodic Memory (List Learning & Story Memory); Visual Episodic Memory (Figure Recall); Visuospatial/Constructional (Figure Copy & Line Orientation); Language (Picture Naming); Attention/Executive Functioning (Semantic Fluency, Digit Span, Coding). In addition, we sought to explore if the inclusion of our experimental measures and/or the MMSE [34] in the dispersion composite influenced relationships with biomarkers and AD risk factors. These additional experimental measures included: the Flanker task [35] (set-shifting); the Four Mountains Task [6] (allocentric spatial processing); the Virtual Reality Supermarket Trolley [8] (egocentric spatial processing) and Favourites [35] (paired associate learning).

Biomarker ascertainment. The biomarkers presently available in the EPAD database are cerebrospinal fluid (CSF) measures of $A\beta_{42}$, t-tau and p-tau and *APOE*ε4 status. Participants volunteered for their initial lumbar puncture within three months of their baseline cognitive assessment. All samples are shipped from sites and stored centrally at the EPAD BioBank at

the University of Edinburgh before CSF samples, taken in Sarstedt tubes, are shipped to the Clinical Neurochemistry Lab, University of Gothenburg, Sweden for analysis using the Roche Diagnostics Elecsys Platform [36]. Results are then forwarded to the IQVIA Master Database and then transferred to the Aridhia Analytical Database. Amyloid positivity is defined in EPAD at a cut-off of $A\beta_{42}$ <1000pg/ml following agreement from the EPAD consortium as an approach to best optimise sensitivity and specificity [31]. Blood was taken at screening and Taqman Genotyping was carried out in a single laboratory at the University of Edinburgh on QuantStudio12K Flex to establish *APOE* variants. *APOE*ε4 positivity was defined as possessing at least one *APOE*ε4 allele.

Other information. Demographic information (age, years of education, gender) were self-reported and taken at the baseline visit. Participants reported family history of dementia, which was defined as having at least one first-degree relative (sibling or parent) with dementia and, if they reported they had a first-degree relative with dementia, they were asked to report the age at diagnosis. Depression was measured using the Geriatric Depression Scale (GDS) [37].

Statistical analyses.

Descriptive statistics were produced using standard techniques. Individualised standard deviations were calculated to derive dispersion scores using RBANS index scores and the four experimental tasks. The method [11] first requires the z-transformation of raw scores of each test using parameters from the distribution of the entire sample, and then, the application of the formula:

$$Dispersion = \sqrt{\frac{\sum_{k=1}^{k=K}(T_{ik}-S_i)^2}{K-1}}$$

where T_{ik} is the *k*-th test for participant *i*, *K* is the number of tests, and S_i is participant *i*'s mean of the transformed scores.

Initially, univariate regression analyses were used to evaluate the association of dispersion scores as a function of a core set of sociodemographic data (age, sex and education), family history of Alzheimer's dementia, *APOE*ε4 genotype and depression scores. Then, multivariable linear regression models where all independent variables were included simultaneously were fitted to test for an association between dispersion scores and the set of variables described before. Next, following the same steps, we tested the association of dispersion scores with CSF p-tau, t-tau and $A\beta_{42}$ values fitting univariate and multivariable linear regression analyses to data from the three biomarkers adjusted for dispersion scores, sociodemographic data, family history of AD Dementia, *APOE*ε4 allele status and depression scores. Although the distribution of the biomarkers was right skewed and some deviations from the normality assumptions were present in the data, the large sample size ensured that model assumptions were asymptotically satisfied. Generalised linear models with a Gamma distribution and a log link were also fitted to the data and results remained unchanged. These analyses added confidence to the results presented here showing their robustness to departures from linear regression models' standard distributional assumptions.

Logistic regression was also used to test whether dispersion scores predicted amyloid positivity after adjustment for sociodemographic variables, family history of AD Dementia and *APOE*ε4 allele status and depression scores.

All analyses were repeated in the subsample of individuals who reported that a first-degree relative had dementia. In this subgroup, we further adjusted the models for a variable that measured the time elapsed between the participant's age and the age of diagnosis of the first-degree relative who had dementia, as a proxy for preclinical AD [4]. If the participant's mother

had dementia, we used the mother's age at diagnosis in the calculations and the father's age at diagnosis if not.

Sensitivity analyses were conducted after two alternative derivations of dispersion scores. First, we derived dispersion scores using results from the RBANS subscales, the MMSE and the 4 experimental tasks, maximising the use of all data on cognitive function in the study. Second, we derived a third version of dispersion scores only including the EPAD experimental tasks. All analyses were repeated using these newly derived versions of dispersion scores in the full sample and the subsample of individuals with family history of dementia.

RESULTS

See Table 1 for descriptive statistics of the sample. The total number of individuals who contributed data to the derivation of the dispersion scores was 439, after exclusion of data from 61 individuals with missing values for either biomarker tests or cognitive tasks. These individuals did not differ from the individuals with complete data on the cognitive tests in terms of age (t-test, p =0.09), sex (t-test, p=0.62), education (t-test, p=0.76), family history (t test, p=0.65), *APOE*ε4 (t test, p=0.68) status or depression scores (t-test, p=0.32). Graphical display of the characteristics of the sample are depicted in Figure 1. Participants were split into separate categories according to sociodemographic and AD risk factors: age (51-64 years; 65-74 years; >75 years); gender (male/female); above or below the median years of education (+/- 14 years); *APOE*ε4 status (*APOE*ε4, not *APOE*ε4); Family history of AD Dementia (family risk, no family risk). We opted to categorise the age and education variables along similar cut-offs used by other groups [e.g. 15,38–40] for the purpose of comparability. As depicted, dispersion is higher for older individuals (Anova, p-value<0.001), those who have had fewer years in formal

education (t-test, p-value<0.001) but no differences were found between carriers and noncarriers of at least one *APOE*ε4 allele (t-test, p-value=0.27).

Genetic, depression and sociodemographic risk factors associated with dispersion scores: of all variables examined, age and education were the only variables that emerged as associated with dispersion scores. Older adults had higher dispersion scores ($\beta = 0.007, SE = 0.002$, p=0.001) and individuals with more education had less dispersion ($\beta = -0.009, SE = 0.003$, p =0.009). Results are shown in Table 2.

Dispersion scores and AD biomarkers: dispersion scores did not emerge as associated with p-tau, t-tau or $A\beta_{42}$ in the univariate or multivariable linear regression analyses that tested for an association between dispersions scores and the three biomarkers (Table 3). Older adults were found to have higher values of p-tau ($\beta = 0.52, SE = 0.07$, p<0.001) and t-tau ($\beta = 5.02, SE = 0.67$, p<0.001). Similarly, *APOE*ε4 carriers were found to have higher values of p-tau ($\beta = 2.83, SE = 0.92$, p =0.002) and t-tau ($\beta = 24.86, SE = 8.77$, p =0.005), as well as lower values of $A\beta_{42}$ ($\beta = -361.31, SE = 58.59$, p<0.001). In these analyses, depression scores were found to be associated with $A\beta_{42}$. Specifically, individuals who scored higher in the GDS scale had lower values of $A\beta_{42}$ ($\beta = -13.73, SE = 6.09$, p=0.025).

When dispersion scores were used in univariate and multivariable logistic regression to test their association with amyloid positivity (multivariable logistic regression results shown in Table 3), the association did not reach traditional significance levels (OR = 0.96, CI=[0.46,2.00], p=0.914 and OR = 0.63, CI=[0.28,1.44], p=0.280 for univariate and multivariable results respectively). Older age (OR= $1.06, CI = [1.03, 1.10]$, p<0.001), *APOE*ε4 (OR= $2.29, CI = [1.50,3.51]$, p<0.001) and depression (OR= $1.06, CI = [1.01,1.11]$, p=0.011) increased the odds of amyloid positivity in fully adjusted logistic regression models.

The analyses of the subsample of participants who reported family history of dementia (n=195) did not alter our findings in relation to the null association of dispersion scores with p-tau, t-tau and $A\beta_{42}$ or amyloid positivity (results not shown).

Sensitivity analyses: Analyses of the extended formulation of dispersion scores that included RBANS index and the MMSE did not change results in a meaningful manner. Similarly, results remained robust when associations were tested using dispersion scores that only included experimental tasks (Flanker and Four Mountains Tasks, Virtual Reality Supermarket Trolley and Favourites). Results from these sensitivity analyses are presented in the Supplementary material, Tables S1-S3.

DISCUSSION

The current study investigated the association between dispersion in cognitive scores with sociodemographic factors, depression, *APOE*ε4 status and familial risk and the core AD CSF biomarkers p-tau, t-tau, $A\beta_{42}$ and (derived) amyloid positivity in the EPAD V500.0 database, from the EPAD LCS study. The main aims of the current work were to assess cognitive dispersion as a sensitive indicator of AD pathology and also explore sociodemographic and other AD risk factors impact upon cognitive dispersion scores. In our analyses, we failed to find an association of dispersion scores with amyloid ($A\beta_{42}$ or amyloid positivity), t-tau or p-tau. Yet, dispersion scores emerged as associated with increasing age and fewer years of formal education, in keeping with previous studies [14,20,41].

Very few studies have examined predictors of dispersion scores or assessed dispersion as a marker for AD pathology. Our work takes some steps to address this. From a selection of established risk factors for AD, we found that cognitive dispersion increased with age - findings that resonate with comparisons between age-groups [14,15,39,41,42] - and decreased in

individuals with higher educational attainment, possibly reflecting more efficient compensatory strategies in response to neuronal senescence [20]. This latter suggestion could be explored further through exploring structural and functional neuroimaging changes and their association with cognitive dispersion to better understand the influence of cognitive or brain reserve on variability in older age.

Most previous work has compared the predictive value of cognitive dispersion in relation to CSF analytes and other AD biomarkers for the conversion to later cognitive impairment [16,17]. Our aim departs from these studies, in that we were interested to explore whether cross-sectional dispersion scores, ascertained at a baseline assessment, could predict current levels of CSF biomarkers and/or amyloid positivity in people without dementia since this would be informative for enrichment strategies within clinical trials of preclinical AD. We did not find any support for cognitive dispersion as an indicator of current AD pathology, beyond established risk factors, such as age and *APOE*ε4 carrier status. This remained the case even when additional (experimental) cognitive measures were included in the calculation of the dispersion composite (see Supplementary material, Table S1). In previous smaller samples of healthy older adults (n=291 [29]; n=29 [28]), cognitive dispersion scores, computed from reaction times within a task-switching test [29] and a cued-Stroop task [28] did show significant associations with $A\beta_{42}$ levels [28,29] and with ratios of tau/$A\beta_{42}$ [29] and p-tau/$A\beta_{42}$ [28,29] in the expected directions. The lack of replication for these relationships in our larger study questions the robustness of these previously observed effects but might be explained by differences in sample characteristics, CSF sampling methods, dispersion measures and the cognitive tests used between studies. The dispersion metric adopted in these studies, coefficient of variation (CoV), constitutes a ratio of the intra-individual standard deviation and intra-individual mean performance and is typically used for reaction time data. It differs from the iSD metric, in that it takes into account overall performance to mitigate the confounds of the

mean. However, the metric has been criticised for clouding underlying contributions towards any observed effects, as these might be explained by either increased variability or, in the cases of reaction time data, mean slowing [10]. We did not deem the CoV to be suitable for the purposes of our study because we were interested in variations in performance between cognitive domains and tasks from a neuropsychological battery purposefully selected in order to be sensitive to early AD changes; not trial-to-trial variability within a task loading on one cognitive domain. Importantly, we wanted to construct a dispersion composite that reflected standardised assessment practices in research and clinic settings which typically emphasise accuracy metrics over reaction time measures.

Given the cross-sectional nature of our work, we cannot rule out that our baseline dispersion scores could be a valuable indicator for the development of or deterioration in future AD pathology at follow-up. Ante-mortem cognitive dispersion scores were positively associated with neurofibrillary tangles, but not diffuse or neuritic plaques, the defining AD lesions, at post-mortem [43]. Moreover, in previous research, baseline dispersion indices were not associated with cross-sectional entorhinal cortex or hippocampal volumes but did predict reduction in entorhinal cortex volumes at a two-year follow-up of healthy older adults [26]. Together with our results, these findings suggest that the value of cognitive dispersion as an indicator of AD pathology may not be realised until longitudinal changes in disease hallmarks are evident.

A major limitation of the current work is its cross-sectional design; although, we were specifically interested in assessing relationships between dispersion and current pathology in the context of baseline data in order to explore its potential usefulness as a screening or enrichment tool in ageing cohorts. Future longitudinal work with this cohort will explore dynamic relationships between dispersion measures and CSF analytes, as well as structural (and functional) neuroimaging changes in individuals with and without genetic and other AD risks, to better elucidate evolving associations between these variables over time and towards AD

Dementia. It is possible that change scores over time in both biomarkers and dispersion may be more sensitive than either change score alone in predicting dementia onset. Additionally, the quantification method and composition of our dispersion indices, as well as the number and nature of tests used, might also have influenced the results obtained. While no consensus has been reached on which measures or approach is preferable, future work could compare which combination of measures and quantification approaches are most sensitive to CSF and other biomarkers changes in AD.

In conclusion, cognitive dispersion scores were positively and negatively associated with age and education years, respectively. Our investigation of sensitivity of results to the tasks and tests included in the derivation of the dispersion scores was a first step towards future research to gain a better understanding of the optimal selection of tests to maximise the use of dispersion scores as an early marker of poor brain health. Furthermore, additional research is also needed to identify which variables moderate cognitive dispersion, as this would further highlight the contribution of individual differences to successful cognitive aging. Our study failed to provide support for cognitive dispersion as an indicator of AD pathology obtained through CSF. This latter observation contrasts with previous findings from smaller cohorts and questions the usefulness of cognitive dispersion for the purposes of screening for existing CSF abnormalities in older adults. Nonetheless, follow-up work will determine if dispersion scores can predict changes in CSF levels and/or positivity status over time. If so, this could inform secondary prevention trial designs by providing an inexpensive adjunct screening tool to enrich ageing or readiness cohorts with individuals possessing emerging abnormal CSF profiles.

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CONFLICTS OF INTEREST/DISCLOSURE STATMENT

KB has served as a consultant, at advisory boards, or at data monitoring committees for Abcam, Axon, Biogen, Julius Clinical, Lilly, MagQu, Novartis, Roche Diagnostics, and Siemens Healthineers, and is a co-founder of Brain Biomarker Solutions in Gothenburg AB (BBS), which is a part of the GU Ventures Incubator Program. CWR has served as a consultant in the last 5 years for: Actinogen, Biogen, Roche Pharmaceuticals and Roche Diagnostics, Eisai, Abbott Pharmaceuticals, Eli Lilly, Kyowa Kirin, Signant Health, Merck and Nutricia. He is also the Chief Investigator and Co-coordinator of IMI-EPAD which is a public-private partnership of 39 partners www.ep-ad.org. The other authors have no conflicts of interest to report.

REFERENCES

[1] Sperling RA, Aisen PS, Beckett LA, Bennett DA, Craft S, Fagan AM, Iwatsubo T, Jack CRJ, Kaye J, Montine TJ, Park DC, Reiman EM, Rowe CC, Siemers E, Stern Y, Yaffe K, Carrillo MC, Thies B, Morrison-Bogorad M, Wagster M V, Phelps CH (2011) Toward defining the preclinical stages of Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement* **7**, 280–292.

[2] Dubois B, Hampel H, Feldman HH, Scheltens P, Aisen P, Andrieu S, Bakardjian H, Benali H, Bertram L, Blennow K, Broich K, Cavedo E, Crutch S, Dartigues J-F, Duyckaerts C, Epelbaum S, Frisoni GB, Gauthier S, Genthon R, Gouw AA, Habert M-O, Holtzman DM, Kivipelto M, Lista S, Molinuevo J-L, O'Bryant SE, Rabinovici GD, Rowe C, Salloway S, Schneider LS, Sperling R, Teichmann M, Carrillo MC, Cummings J, Jack Jr CR, Proceedings of the Meeting of the International Working Group (IWG) and the American Alzheimer's Association on "The Preclinical State of

AD"; July 23 USA 2015; Washington D C (2016) Preclinical Alzheimer's disease: Definition, natural history, and diagnostic criteria. *Alzheimers Dement* **12**, 292–323.

[3] Jack Jr. CR, Knopman DS, Jagust WJ, Petersen RC, Weiner MW, Aisen PS, Shaw LM, Vemuri P, Wiste HJ, Weigand SD, Lesnick TG, Pankratz VS, Donohue MC, Trojanowski JQ (2013) Update on hypothetical model of Alzheimer's disease biomarkers. *Lancet Neurol* **12**, 207–216.

[4] Ritchie K, Ropacki M, Albala B, Harrison J, Kaye J, Kramer J, Randolph C, Ritchie CW (2017) Recommended cognitive outcomes in preclinical Alzheimer's disease: Consensus statement from the European Prevention of Alzheimer's Dementia project. *Alzheimers Dement* **13**, 186–195.

[5] Rentz DM, Parra Rodriguez MA, Amariglio R, Stern Y, Sperling R, Ferris S (2013) Promising developments in neuropsychological approaches for the detection of preclinical Alzheimer's disease: a selective review. *Alzheimers Res Ther* **5**, 58.

[6] Hartley T, Bird CM, Chan D, Cipolotti L, Husain M, Varga-Khadem F, Burgess N (2007) The hippocampus is required for short-term topographical memory in humans. *Hippocampus* **17**, 34–38.

[7] Parra MA, Mikulan E, Trujillo N, Sala S Della, Lopera F, Manes F, Starr J, Ibanez A (2017) Brain Information Sharing During Visual Short-Term Memory Binding Yields a Memory Biomarker for Familial Alzheimer's Disease. *Curr Alzheimer Res* **14**, 1335.

[8] Tu S, Spiers HJ, Hodges JR, Piguet O, Hornberger M (2017) Egocentric versus Allocentric Spatial Memory in Behavioral Variant Frontotemporal Dementia and Alzheimer's Disease. *J Alzheimer's Dis* **59**, 883–892.

[9] Bunce D, Bauermeister S (2019) Intraindividual reaction time variability, attention, and age-related outcomes. In *Oxford Research Encyclopedia of Psychology* Oxford University Press, Oxford, UK.

[10] Stawski RS, MacDonald SWS, Brewster PWH, Munoz E, Cerino ES, Halliday DWR (2019) A Comprehensive Comparison of Quantifications of Intraindividual Variability in Response Times: A Measurement Burst Approach. *J Gerontol B Psychol Sci Soc Sci* **74**, 397–408.

[11] Holtzer R, Verghese J, Wang C, Hall CB, Lipton RB (2008) Within-person across-neuropsychological test variability and incident dementia. *JAMA* **300**, 823–830.

[12] Mella N, Fagot D, de Ribaupierre A (2016) Dispersion in cognitive functioning: Age differences over the lifespan. *J Clin Exp Neuropsychol* **38**, 111–126.

[13] Mella N, Fagot D, Lecerf T, de Ribaupierre A (2015) Working memory and intraindividual variability in processing speed: A lifespan developmental and individual-differences study. *Mem Cognit* **43**, 340–356.

[14] Bielak AAM, Cherbuin N, Bunce D, Anstey KJ (2014) Intraindividual variability is a fundamental phenomenon of aging: Evidence from an 8-year longitudinal study across young, middle, and older adulthood. *Dev Psychol* **50**, 143–151.

[15] Hultsch DF, MacDonald SWS, Dixon RA (2002) Variability in reaction time performance of younger and older adults. *Journals Gerontol - Ser B Psychol Sci Soc Sci* **57**, 101–115.

[16] Gleason CE, Norton D, Anderson ED, Wahoske M, Washington DT, Umucu E, Koscik RL, Dowling NM, Johnson SC, Carlsson CM, Asthana S (2018) Cognitive Variability Predicts Incident Alzheimer's Disease and Mild Cognitive Impairment Comparable to a Cerebrospinal Fluid Biomarker. *J Alzheimers Dis* **61**, 79–89.

[17] Anderson ED, Wahoske M, Huber M, Norton D, Li Z, Koscik RL, Umucu E, Johnson SC, Jones J, Asthana S, Gleason CE (2016) Cognitive variability-A marker for incident MCI and AD: An analysis for the Alzheimer's Disease Neuroimaging Initiative. *Alzheimer's Dement Diagnosis, Assess Dis Monit* **4**, 47–55.

[18] Tales A, Leonards U, Bompas A, Snowden RJ, Philips M, Porter G, Haworth J, Wilcock G, Bayer A (2012) Intra-Individual Reaction Time Variability in Amnestic Mild Cognitive Impairment: A Precursor to Dementia? *J Alzheimer's Dis* **32**, 457–466.

[19] Roalf DR, Quarmley M, Mechanic-Hamilton D, Wolk DA, Arnold SE, Moberg PJ (2016) Within-Individual Variability: An Index for Subtle Change in Neurocognition in Mild Cognitive Impairment. *J Alzheimers Dis* **54**, 325–335.

[20] De Felice S, Holland CA (2018) Intra-individual variability across fluid cognition can reveal qualitatively different cognitive styles of the aging brain. *Front Psychol* **9**,.

[21] MacDonald SWS, Li SC, Bäckman L (2009) Neural Underpinnings of Within-Person Variability in Cognitive Functioning. *Psychol Aging* **24**, 792–808.

[22] Jackson JD, Balota DA, Duchek JM, Head D (2012) White matter integrity and reaction time intraindividual variability in healthy aging and early-stage Alzheimer disease. *Neuropsychologia* **50**, 357–366.

[23] MacDonald SWS, Hultsch DF, Dixon RA (2003) Performance variability is related to change in cognition: Evidence from the Victoria longitudinal study. *Psychol Aging* **18**, 510–523.

[24] Anstey KJ, Mack HA, Christensen H, Li S-C, Reglade-Meslin C, Maller J, Kumar R, Dear K, Easteal S, Sachdev P (2007) Corpus callosum size, reaction time speed and variability in mild cognitive disorders and in a normative sample. *Neuropsychologia* **45**, 1911–1920.

[25] Fjell AM, Westlye LT, Amlien IK, Walhovd KB (2011) Reduced white matter integrity is related to cognitive instability. *J Neurosci* **31**, 18060–18072.

[26] Bangen KJ, Weigand AJ, Thomas KR, Delano-Wood L, Clark LR, Eppig J, Werhane ML, Edmonds EC, Bondi MW (2019) Cognitive dispersion is a sensitive marker for early neurodegenerative changes and functional decline in nondemented older adults.

Neuropsychology **33**, 599–608.

[27] Jack CRJ, Holtzman DM (2013) Biomarker modeling of Alzheimer's disease. *Neuron* **80**, 1347–1358.

[28] Patten R Van, Fagan AM, Kaufman DAS (2018) Differential Cued-Stroop Performance in Cognitively Asymptomatic Older Adults with Biomarker-Identified Risk for Alzheimer's Disease: A Pilot Study. *Curr Alzheimer Res* **15**, 820–827.

[29] Duchek JM, Balota DA, Tse C-S, Holtzman DM, Fagan AM, Goate AM (2009) The utility of intraindividual variability in selective attention tasks as an early marker for Alzheimer's disease. *Neuropsychology* **23**, 746–758.

[30] Mortamais M, Ash JA, Harrison J, Kaye J, Kramer J, Randolph C, Pose C, Albala B, Ropacki M, Ritchie CW, Ritchie K (2017) Detecting cognitive changes in preclinical Alzheimer's disease: A review of its feasibility. *Alzheimers Dement* **13**, 468–492.

[31] Solomon A, Kivipelto M, Molinuevo JL, Tom B, Ritchie CW (2018) European Prevention of Alzheimer's Dementia Longitudinal Cohort Study (EPAD LCS): study protocol. *BMJ Open* **8**, e021017.

[32] Ritchie CW, Muniz-Terrera G, Kivipelto M, Solomon A, Tom B, Molinuevo JL, EPAD Consortium (2020) The European Prevention of Alzheimer's Dementia (EPAD) Longitudinal Cohort Study: Baseline Data Release V500.0. *J Prev Alzheimer's Dis* **7**, 8–13.

[33] Randolph C, Tierney MC, Mohr E, Chase TN (1998) The Repeatable Battery for the Assessment of Neuropsychological Status (RBANS): preliminary clinical validity. *J Clin Exp Neuropsychol* **20**, 310–319.

[34] Folstein MF, Folstein SE, McHugh PR (1975) "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res* **12**, 189–198.

[35] Kramer JH, Mungas D, Possin KL, Rankin KP, Boxer AL, Rosen HJ, Bostrom A, Sinha L, Berhel A, Widmeyer M (2014) NIH EXAMINER: conceptualization and development of an executive function battery. *J Int Neuropsychol Soc* **20**, 11–19.

[36] Bittner T, Zetterberg H, Teunissen CE, Ostlund REJ, Militello M, Andreasson U, Hubeek I, Gibson D, Chu DC, Eichenlaub U, Heiss P, Kobold U, Leinenbach A, Madin K, Manuilova E, Rabe C, Blennow K (2016) Technical performance of a novel, fully automated electrochemiluminescence immunoassay for the quantitation of beta-amyloid (1-42) in human cerebrospinal fluid. *Alzheimers Dement* **12**, 517–526.

[37] Debruyne H, Van Buggenhout M, Le Bastard N, Aries M, Audenaert K, De Deyn PP, Engelborghs S (2009) Is the geriatric depression scale a reliable screening tool for depressive symptoms in elderly patients with cognitive impairment? *Int J Geriatr Psychiatry* **24**, 556–562.

[38] Bielak AAM, Hultsch DF, Strauss E, Macdonald SWS, Hunter MA (2010) Intraindividual Variability in Reaction Time Predicts Cognitive Outcomes 5 Years Later. *Neuropsychology* **24**, 731–741.

[39] Hilborn J V, Strauss E, Hultsch DF, Hunter MA (2009) Intraindividual variability across cognitive domains: investigation of dispersion levels and performance profiles in older adults. *J Clin Exp Neuropsychol* **31**, 412–424.

[40] Christensen H, Mackinnon AJ, Korten AE, Jorm AF, Henderson AS, Jacomb P (1999) Dispersion in Cognitive Ability as a Function of Age: A Longitudinal Study of an Elderly Community Sample. *Aging, Neuropsychol Cogn* **6**, 214–228.

[41] Ardila A (2007) Normal aging increases cognitive heterogeneity: Analysis of dispersion in WAIS-III scores across age. *Arch Clin Neuropsychol* **22**, 1003–1011.

[42] Gorus E, De Raedt R, Mets T (2006) Diversity, dispersion and inconsistency of reaction time measures: Effects of age and task complexity. *Aging Clin Exp Res* **18**,

407–417.

[43] Malek-Ahmadi M, Lu S, Chan Y, Perez SE, Chen K, Mufson EJ (2017) Cognitive Domain Dispersion Association with Alzheimer's Disease Pathology. *J Alzheimer's Dis* **58**, 575–583.

Table 1. Descriptive characteristics of analytical sample (N=439)

	Mean (SD)		N (%)
Age (years)	66.13 (6.65)	Sex (Female / Male)	231 (52.62) / 208 (47.38)
Education (years)	14.03 (3.67)	*APOE*ε4 (Y/N)	177 (40.32) / 262 (59.68)
		Family History (Y/ N)	251 (57.18) / 188 (42.82)
RBANS subtasks	Mean (SD)		Mean (SD)
Coding	44.34 (10.63)	List recall	5.96 (2.29)
Digit Span	9.56 (2.27)	List recognition	19.25 (1.09)
Figure Copy	18.62 (1.86)	Picture naming	9.79 (0.90)
Figure Recall	14.27 (3.75)	Semantic fluency	19.61 (5.33)

List learning	28.36 (4.67)	Story memory	18.25 (3.17)
Line orientation	18.08 (2.22)	Story recall	8.92 (1.92)
MMSE	28.68 (1.51)		
Experimental tasks	Mean (SD)	CSF biomarkers	Mean (SD)
Flanker	8.41 (0.69)	p-tau	19.23 (9.80)
Mountain	6.16 (4.73)	t-tau	221.77 (93.64)
Supermarket Trolley	9.05 (3.86)	abeta	1333.3 (617.2)
Favourite	6.24 (5.07)	Amypos Yes: N (%)	154 (35.08 %)

Table 2. Results from multivariable linear regression analyses of RBANS subscale dispersion scores and 4 experimental tasks adjusted for sociodemographic variables.

	Dispersion scores derived using RBANS subscale scores, MMSE and experimental tasks		Dispersion scores derived only using experimental tasks	
Variable	Beta (SE)	p-value	Beta (SE)	p-value
Age	0.007 (0.002)	0.001	-0.002 (0.002)	0.291
Sex	0.037 (0.024)	0.134	0.08 (0.03)	0.020
Education	-0.009 (0.003)	0.009	0.007 (0.005)	0.115
*APOE*ε4	0.037 (0.025)	0.140	-0.02 (0.04)	0.614
Family history	-0.021 (0.026)	0.410	-0.02 (0.04)	0.476
Depression scores	0.0006 (0.002)	0.815	-0.001 (0.003)	0.708

Dispersion = variability across RBANS indices and 4 experimental tasks

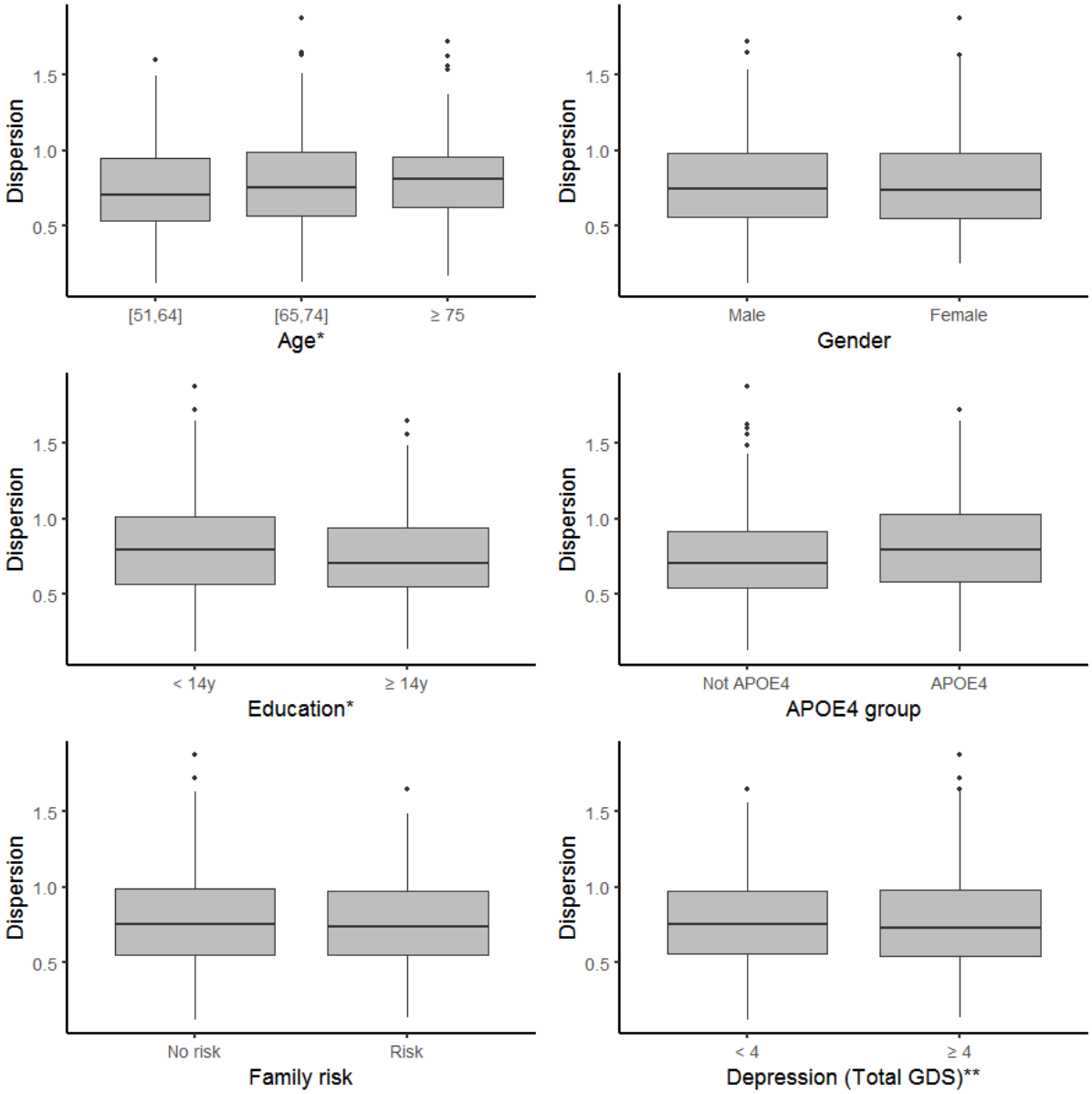
Table 3. Results from linear regression models fitted to p-tau, t-tau, $A\beta_{42}$ and logistic regression analysis of amyloid positivity to study their association with cognitive dispersion scores derived using RBANS Subscale and 4 experimental task dispersion

	p-tau		t-tau		$A\beta_{42}$		Amyloid Positivity	
	Beta (SE)	p-value	Beta (SE)	p-value	Beta (SE)	p-value	OR (95% CI)	p-value
Dispersion	1.14 (1.69)	0.500	9.15 (16.14)	0.571	9.90 (110.5)	0.950	0.63 (0.28, 1.44)	0.280
Age	0.52 (0.07)	<0.001	5.02 (0.67)	<0.001	-6.17 (4.51)	0.183	1.06 (1.03, 1.10)	<0.001
Female gender	0.90 (0.89)	0.313	14.36 (8.53)	0.093	87.89 (57.41)	0.124	0.75 (0.50, 1.14)	0.178

Education	-0.04 (0.12)	0.726	-0.42 (1.16)	0.716	3.76 (7.82)	0.646	0.99 (0.94, 1.05)	0.745
*APOE*ε4	2.83 (0.92)	0.002	24.86 (8.77)	0.005	-361.31 (58.59)	<0.001	2.29 (1.50, 3.51)	<0.001
Family History	0.67 (0.94)	0.476	1.90 (9.00)	0.833	-51.12 (60.56)	0.395	1.16 (0.75, 1.81)	0.490
Depression scores	-0.11 (0.09)	0.217	-1.04 (0.90)	0.252	-13.73 (6.09)	0.025	1.06 (1.01, 1.11)	0.011

Dispersion = variability across RBANS subscale indices and 4 experimental tasks

Figure 1. Dispersion by sociodemographic and AD risk factors



*Age: We split the sample in three groups according to age: from 51 to 64 years old (N= 186), from 65 to 74 years old (N=206) and 75 and olders (N=47). Education: We split the sample in two groups according to the median years of education: less educated are below the median (less than 14 years; N=200) and the others (14 years or more; N=239).

Supplementary material

Table S1. Results from linear regression analyses of alternative formulations of dispersion scores adjusted for sociodemographic variables.

	Dispersion scores derived using RBANS subscale scores, MMSE and experimental tasks		Dispersion scores derived only using experimental tasks	
Variable	Beta (SE)	p-value	Beta (SE)	p-value
Age	0.006 (0.002)	0.001	-0.002 (0.002)	0.291
Sex	0.037 (0.024)	0.134	0.08 (0.03)	0.020
Education	-0.009 (0.003)	0.009	0.007 (0.005)	0.115
APOEε4	0.037 (0.025)	0.140	-0.02 (0.04)	0.614
Family history	-0.021 (0.026)	0.410	-0.02 (0.04)	0.476
Depression scores	0.0006 (0.002)	0.815	-0.001 (0.003)	0.708

Dispersion = variability across RBANS indices, MMSE and 4 experimental tasks (Flanker and Four Mountains Tasks, Virtual Reality Supermarket Trolley and Favourites)

Table S2. Results from linear regression models fitted to p-tau, t-tau, $A\beta_{42}$ and logistic regression analysis of amyloid positivity to study their association with dispersion scores derived using RBANS subscale scores, MMSE and experimental tasks.

	p-tau		t-tau		$A\beta_{42}$		Amyloid Positivity	
	Beta (SE)	p-value	Beta (SE)	p-value	Beta (SE)	p-value	OR (CI)	p-value
Dispersion	1.05 (1.72)	0.541	7.98 (16.43)	0.627	-9.90 (110.5)	0.929	0.56 (0.24, 1.29)	0.173
Age	0.52 (0.07)	<0.001	5.03 (0.67)	<0.001	-6.17 (4.54)	0.175	1.06 (1.03, 1.10)	<0.001
Female gender	0.90 (0.89)	0.314	14.38 (8.53)	0.093	87.89 (57.41)	0.127	0.76 (0.50, 1.15)	0.188
Education	-0.04 (0.12)	0.724	-0.43 (1.17)	0.712	3.76 (7.87)	0.633	0.99 (0.93, 1.05)	0.708
APOEε4	2.84 (0.92)	0.002	24.99 (8.77)	0.004	-361.31 (58.59)	<0.001	2.30 (1.50, 3.52)	<0.001
Family History	0.66 (0.94)	0.481	1.83 (9.00)	0.839	-51.12 (60.54)	0.399	1.16 (0.75, 1.81)	0.493
Depression scores	-0.11 (0.09)	0.214	-1.04 (0.90)	0.249	-13.73 (6.10)	0.025	1.06 (1.01, 1.11)	0.010

Dispersion = The Repeatable Battery of Assessment for Neuropsychological Status subscale scores, Working memory, Choice reaction time and set shifting, Visuospatial Navigation: Four Mountains Task and Virtual Reality Supermarket Trolley and MMSE

Table S3. Results from linear regression models fitted to p-tau, t-tau, $A\beta_{42}$ and logistic regression analysis of amyloid positivity to study their association with dispersion scores

derived only including the 4 experimental tasks (Flanker and Four Mountains Tasks, Virtual Reality Supermarket Trolley and Favourites)

	p-tau		t-tau		$A\beta_{42}$		Amyloid Positivity	
	Beta (SE)	p-value	Beta (SE)	p-value	Beta (SE)	p-value	OR (CI)	p-value
Dispersion	-0.25 (1.92)	0.828	-5.07 (11.36)	0.656	-33.35 (76.40)	0.663	0.84 (0.48, 1.46)	0.538
Age	0.52 (0.07)	<0.001	5.07 (0.67)	<0.001	-6.21 (4.49)	0.167	1.06 (1.02, 1.09)	0.001
Female gender	0.96 (0.89)	0.284	15.10 (8.57)	0.079	91.06 (57.62)	0.115	0.75 (0.5, 1.14)	0.182
Education	-0.05 (0.12)	0.678	-0.46 (1.16)	0.690	3.93 (7.83)	0.615	0.99 (0.94, 1.05)	0.892
APOEε4	2.88 (0.91)	0.002	25.20 (8.69)	0.004	-361.55 (58.45)	<0.001	2.22 (1.46, 3.39)	<0.001
Family History	0.64 (0.94)	0.501	1.52 (9.00)	0.866	-52.24 (60.51)	0.388	1.18 (0.76, 1.83)	0.458
Depression scores	-0.11 (0.09)	0.215	-1.04 (0.90)	0.248	-13.77 (6.09)	0.024	1.06 (1.01, 1.10)	0.011

Dispersion = 4 experimental tasks (Flanker and Four Mountains Tasks, Virtual Reality Supermarket Trolley and Favourites)