Journal of the International Neuropsychological Society (2023), **29,** 621–631
doi:10.1017/S1355617722000649

Research Article

Cognitive dispersion is elevated in amyloid-positive older adults and associated with regional hypoperfusion

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Abstract

Objective: Cognitive dispersion across neuropsychological measures within a single testing session is a promising marker predictive of cognitive decline and development of Alzheimer's disease (AD). However, little is known regarding brain changes underlying cognitive dispersion, and the association of cognitive dispersion with in vivo AD biomarkers and regional cerebral blood flow (CBF) has received limited study. We therefore examined associations among cognitive dispersion, amyloid-beta (Aβ) positivity, and regional CBF among older adults free of dementia. **Method:** One hundred and forty-eight Alzheimer's Disease Neuroimaging Initiative (ADNI) participants underwent neuropsychological testing and neuroimaging. Pulsed arterial spin labeling (ASL) magnetic resonance imaging (MRI) was acquired to quantify CBF. Florbetapir positron emission tomography (PET) imaging determined Aβ positivity. **Results:** Adjusting for age, gender, education, and mean cognitive performance, older adults who were Aβ+ showed higher cognitive dispersion relative to those who were Aβ-. Across the entire sample, higher cognitive dispersion was associated with reduced CBF in inferior parietal and temporal regions. Secondary analyses stratified by Aβ status demonstrated that higher cognitive dispersion was associated with reduced CBF among Aβ+ individuals but not among those who were Aβ-. **Conclusions:** Cognitive dispersion may be sensitive to early Aβ accumulation and cerebrovascular changes adjusting for demographics and mean neuropsychological performance. Associations between cognitive dispersion and CBF were observed among Aβ+ individuals, suggesting that cognitive dispersion may be a marker of brain changes among individuals on the AD continuum. Future studies should examine whether cognitive dispersion predicts brain changes in diverse samples and among those with greater vascular risk burden.

Keywords: cognitive dispersion; cognitive intraindividual variability; cerebral blood flow; magnetic resonance imaging; Alzheimer's disease; amyloid; cognition; neuropsychology

(Received 15 July 2021; final revision 9 June 2022; accepted 29 July 2022; First Published online 12 September 2022)

Introduction

There is an important need to identify early cognitive changes in individuals at risk for dementia prior to the development of significant cognitive and functional decline. Cognitive function measured by comprehensive neuropsychological evaluation is typically expressed as mean level of performance within domains such as memory, attention, and executive function. However, there has been growing recognition that intraindividual variability in neuropsychological performance within a single testing session (Bangen et al., 2019; Gleason et al., 2018; Koscik et al., 2016; Malek-Ahmadi et al., 2017), may be sensitive to early cognitive changes and may reflect subtle decline in cognition that can be detected before traditional neuropsychological thresholds for cognitive impairment are met.

Intraindividual variability has two main operationalizations including dispersion and inconsistency. In contrast to dispersion (which examines within-person variability across tasks), inconsistency measures within-person variability on a single task. In the present study, we focus on dispersion. Although some variability across domains is seen in normal cognitive profiles, increased variability has been found to be associated with decreased neurological integrity (Bangen et al., 2019; Malek-Ahmadi et al., 2017). Indeed, greater cognitive dispersion has been associated with an increased likelihood of being classified as having AD (Halliday et al., 2018) and greater dementia incidence at follow-up (Watermeyer et al., 2021). Studies examining brain changes underlying greater cognitive dispersion in aging, dementia risk, and neurodegenerative disease have shown that elevated cognitive dispersion is associated with faster rates of cerebral atrophy in the medial temporal lobes (Bangen et al., 2019), disruptions in functional connectivity networks (Meeker et al., 2021), and reduced integrity of white matter pathways interconnecting cortical regions mediating executive function and attention (Sorg et al., 2021). In addition, an autopsy study showed that greater cognitive dispersion was significantly associated with more severe neurofibrillary tangle pathology and trended toward an association with more severe neuritic plaques (Malek-Ahmadi et al., 2017). However, findings from a study

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Cite this article: Holmqvist S.L., Thomas K.R., Edmonds E.C., Calcetas A., Edwards L., & Bangen K.J. (2023) Cognitive dispersion is elevated in amyloid-positive older adults and associated with regional hypoperfusion. *Journal of the International Neuropsychological Society*, **29:** 621–631, https://doi.org/10.1017/S1355617722000649

examining intraindividual variability and cerebrospinal fluid (CSF) based markers of amyloid-beta (Aβ) found that cognitive dispersion was not significantly associated with CSF Aβ (Watermeyer et al., 2020). We know of no published studies that have examined the association of cognitive dispersion and *in vivo* brain measures of Aβ using positron emission tomography (PET) imaging. In addition, to the best of our knowledge, no published studies have examined the association between cognitive dispersion and subtle cerebrovascular changes including cerebral blood flow (CBF) measured with arterial spin labeling (ASL) magnetic resonance imaging (MRI).

In the present study, we sought to determine whether cognitive dispersion is associated with cerebral amyloidosis *in vivo* by examining whether older adults without clinical dementia who are Aβ-positive (Aβ+) on PET imaging demonstrate higher cognitive dispersion relative to those who are Aβ negative (Aβ-). In the present study, we focused on dispersion given that data from a single task with various intervals suitable to calculate inconsistency (e.g., a reaction time task with several trials) was not available for analysis. In addition, to further elucidate mechanisms underlying increased cognitive dispersion, we examined associations between cognitive dispersion and CBF across our entire sample of older adults as well as the subsample who was Aβ+. We hypothesized that higher cognitive dispersion would be associated with: (1) PET Aβ accumulation; and (2) reduced CBF in AD-vulnerable regions, particularly among those individuals who are Aβ+.

Method

The ADNI dataset

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. This study was approved by the Institutional Review Board at the ADNI study sites. Treatment of human participants during this study was in full accordance with ethical standards set forth by the Helsinki Declaration.

The primary goal of ADNI has been to test whether serial MRI, PET, other biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of mild cognitive impairment (MCI) and early Alzheimer's disease (AD). For up-to-date information, see www.adni-info.org.

Participants

Specific enrollment criteria for ADNI have been previously described in detail elsewhere (Bangen et al., 2019). Briefly, participants from ADNI were 55–90 years old, had ≥6 years of education or work history equivalent, were fluent in English or Spanish, had a Geriatric Depression Scale <6, had a Hachinski Ischemia Scale <5, adequate vision and hearing to perform neuropsychological tests, were in generally good health and without significant head trauma or neurologic disease, were stable on permitted medications, and had a reliable study partner. ADNI includes participants with normal cognition, MCI, and dementia. The current study included 148 participants from ADNI GO/ADNI 2 cohorts when ASL MRI was collected. Participants were included if they had ASL data collected within 12 months of their baseline visit, did not have dementia at their baseline study visit, and had available baseline neuropsychological testing and florbetapir PET imaging data. Although ADNI is a longitudinal study, the present analyses examined cross-sectional associations of baseline data.

Cognitive dispersion index

The cognitive dispersion index reflects variability across cognitive measures at a single time point. We calculated the index of dispersion using procedures previously described (Bangen et al., 2019). Briefly, standard summary measures from tests designed to assess multiple different cognitive abilities were included in the cognitive dispersion index. Six neuropsychological measures were selected given their routine use in assessing early cognitive changes in AD, administration across all ADNI waves, and sampling of three different domains of cognition (i.e., language, processing speed/executive function, and episodic memory). These six measures were as follows: (1) Animal Fluency, total score; (2) 30-item Boston Naming Test (BNT) total score; (3) Trail Making Test (TMT), Part A; time to completion; (4) TMT, Part B; time to completion; (5) Rey Auditory Verbal Learning Test (AVLT) 30-min delayed free recall; number of words recalled; and (6) AVLT recognition; number of words correctly recognized.

Prior to calculating the cognitive dispersion index, individual raw scores for each measure were converted into age-, gender-, and education-adjusted Z scores with a mean of 0 and standard deviation of 1 using regression coefficients derived from robust cognitively normal participants ($n = 385$) who had at least 1 year of follow-up and remained cognitively normal throughout their participation in the ADNI study (Bangen et al., 2019; Edmonds et al., 2015). The two TMT Z scores were multiplied by −1 so that higher Z scores represent better performance for all scores. The intraindividual standard deviation across the 6 Z scores was calculated to create the cognitive dispersion index. A high score on the cognitive dispersion index reflects greater variability across neuropsychological measures whereas a low score on the cognitive dispersion index indicates more consistency across measures (regardless of scores on the individual neuropsychological measures included in the cognitive dispersion index). In addition, mean level of cognitive performance was calculated as the average of the 6 Z scores that were included in the cognitive dispersion index.

Cognitive status

Participants diagnosed with dementia by ADNI were excluded from the current study. To determine cognitive status (MCI *vs.* normal cognition), actuarial neuropsychological MCI criteria were applied to all participants in this sample (Edmonds et al., 2015). Participants were considered MCI if they performed >1 *SD* below the age-/education-/sex-adjusted mean on: (1) 2 neuropsychological measures within the same cognitive domain; *or* (2) at least 1 measure across all 3 sampled cognitive domains. The six neuropsychological test scores included in the cognitive dispersion index were considered in the diagnostic criteria for MCI.

T1-weighted anatomical and ASL MRI data acquisition and processing

Detailed information describing the imaging data acquisition and processing is available online at www.loni.usc.edu. MR imaging was performed on a 3.0 Tesla scanner and structural MRI and ASL scans were collected during the same session.

A T1-weighted 3D MPRAGE sequence was collected using the following parameters: field of view = 256 mm, repetition time

https://doi.org/10.1017/S1355617722000649 Published online by Cambridge University Press

= 2300 ms, echo time = 2.98 ms, flip angle = 9°, and resolution = 1.1 x 1.1 x 1.2 mm^3. Structural scans were motion corrected, skull stripped, segmented, and parcellated using FreeSurfer Version 5.1 (surfer.nmr.mgh.harvard.edu; Fischl et al., 2002, 2004).

Pulsed ASL scans were collected using QUIPS II with thin-slice TI1 periodic saturation with echo-planar imaging (Luh et al., 1999). Scan parameters include the following: inversion time of arterial spins (TI1) = 700 ms, total transit time of spins (TI2) = 1900 ms, tag thickness = 100 mm, tag to proximal slice gap = 25.4 mm, repetition time = 3400 ms, echo time = 12 ms, field of view = 256 mm, matrix = 64 x 64, 24 4-mm thick axial slices [52 tag + control image pairs], time lag between slices = 22.5 ms.

As previously described (Bangen et al., 2021; Sanchez et al., 2020; Thomas et al., 2021), ASL data processing was largely automated and involved motion correction, aligning each ASL frame to the first frame using a rigid body transformation, and least squares fitting using SPM 8 (http://www.fil.ion.ucl.ac.uk/spm/). Perfusion-weighted images were computed as the difference of the mean-tagged and mean-untagged ASL images and were intensity scaled to account for signal decay during acquisition and to generate intensities in meaningful physiological units. After geometric distortion correction, ASL images were aligned to structural T1 images using FSL. In order to minimize the effects of lower perfusion in white matter on CBF estimates, a partial volume correction was performed that assumed that CBF in gray matter is 2.5 times greater than in white matter. The partial volume corrected perfusion-weighted images were normalized by the reference image (i.e., an estimate of blood water magnetization) to convert the signal into physical units (ml/100 g tissue/min). ADNI quality control procedures to determine a global pass/fail rating were based on visual inspection of signal uniformity, geometrical distortions, gray matter contrast, and presence of large artifacts. A rating of "unusable" in any of these categories resulted in a global "fail" and that participant was excluded from the present study.

FreeSurfer-derived anatomical regions of interest (ROIs) were applied to CBF maps to extract regional CBF estimates for each participant. Our primary analyses examined the following five *a priori* ROIs: (1) hippocampus; (2) inferior parietal lobe (IPL); (3) inferior temporal gyrus (ITG); (4) medial orbitofrontal cortex (mOFC); and (5) rostral middle frontal gyrus (rMFG). These regions were selected given prior work showing these regions are vulnerable to early AD-related change (Dickerson et al., 2011) as well as to be consistent with our previous studies examining CBF in ADNI (e.g., Sanchez et al., 2020; Thomas et al., 2021). CBF ROI values were residualized by precentral CBF, which was selected to serve as a reference region as it is not thought to be impacted in early AD (allowing for adjustment of individual variation in CBF that is likely not due to AD pathologies) as well as to be consistent with previous ADNI ASL studies that used this approach (Mattson et al., 2014; Yew & Nation., 2017). Mean CBF corrected for partial volume effects was extracted for each of the ROIs and reference region for each hemisphere separately. To reduce the number of statistical comparisons, averaged bilateral CBF estimates for each ROI were used as the dependent variable in analyses. Bilateral CBF estimates were calculated by averaging the mean CBF of each hemisphere. If participants were missing baseline ASL but had ASL within the first year of their baseline visit, the first occasion of ASL data was used in analyses. In addition, for use in secondary analyses examining brain morphometry, the mean bilateral cortical thickness of IPL, ITF, mOFC, and rMFG was computed by averaging thickness estimates for the left and right hemispheres for each ROI. Total hippocampal volume was computed by summing the volume of left and right hippocampi and was normalized by estimated total intracranial volume.

Florbetapir PET data acquisition and processing

PET scanning with an 18F-florbetapir tracer was used to measure amyloid burden. A detailed description of ADNI florbetapir PET imaging data acquisition and processing can be found online (www.loni.usc.edu). Briefly, florbetapir scans were co-registered, averaged, reoriented into a standard $160 \times 160 \times 96$ voxel image grid with 1.5 mm^3 voxels and smoothed to a uniform isotropic resolution of 8 mm full width at half maximum. Each participant's first florbetapir image was co-registered with the T1-weighted image.

A cortical summary standardized uptake value ratio (SUVR) was calculated by dividing the mean florbetapir uptake across four main cortical regions (i.e., frontal, anterior/posterior cingulate, lateral parietal, and lateral temporal cortices) by whole cerebellar (white and gray matter) florbetapir uptake. Greater cortical Aβ load is thought to increase retention of florbetapir. Aβ positivity was established using the recommended threshold for cross-sectional florbetapir analyses of 1.11 using the whole cerebellum as the reference region (Landau et al., 2014).

Statistical analyses

Demographic and clinical characteristics were examined with descriptive statistics. *T* tests for continuous variables and chi-square (X^2) tests for categorical variables were used to compare Aβ+ *versus* Aβ- groups on demographics and clinical variables. Analysis of covariance (ANCOVA) was used to compare Aβ+ and Aβ- groups in terms of cognitive dispersion after adjusting for age, gender, education, and mean cognitive performance. In addition, hierarchical linear regression, adjusting for age, gender, education, and mean cognitive performance was used to examine the associations between the cognitive dispersion index and CBF in the five *a priori* ROIs: hippocampus, IPL, ITG, mOFC, and rMFG. In addition, we performed linear regressions substituting regional volume or cortical thickness of the ROI as the dependent variable in place of CBF to determine whether dispersion was significantly associated with morphometry. For all models, covariates were entered on Step 1 and cognitive dispersion was entered on Step 2. In a series of sensitivity analyses, in an attempt to further clarify the potential role of cognitive dispersion, we re-ran our primary models reversing the position of mean cognitive performance and cognitive dispersion. That is, we entered age, gender, education, and cognitive dispersion on Step 1 and mean cognitive performance on Step 2. Finally, to explore whether the pattern of findings was driven by those participants who were Aβ+ (on the AD continuum as evidenced by significant cerebral amyloidosis), secondary analyses stratified by Aβ status (Aβ+ and Aβ-) were performed. To address potential inflation of type I error resulting from multiple comparisons, we applied the Benjamini–Hochberg procedure (Benjamini & Hochberg, 1995) to our results. We assessed results when the false discovery rate (FDR) was controlled at 0.05 and 0.10.

All analyses were performed using Statistical Package for the Social Sciences (SPSS) version 26 (SPSS IBM, New York, USA). Figures were made with R version 4.5.0 (https://cran.r-project.org/) and SPSS. An alpha = 0.05 was set for statistical significance; all tests were two-tailed.

https://doi.org/10.1017/S1355617722000649 Published online by Cambridge University Press

Table 1. Demographics for overall sample and by Aβ PET imaging status

	Entire sample ($n = 148$)	Aβ+ ($n = 63$)	Aβ- ($n = 85$)	t or χ^2	95% CI	Cohen's d or phi	p
Age, years	70.98 (6.83)	73.45 (6.55)	69.15 (6.49)	−3.97	[−6.44, −2.15]	0.66	**<0.001**
Education, years	16.68 (2.51)	16.48 (2.85)	16.82 (2.24)	0.80	[−0.48, 1.17]	0.14	0.42
Gender (% Female)	48.6%	42.9%	52.9%	1.47	–	0.10	0.23
Race (%)				3.96	–	0.16	0.27
White	93.9%	92.1%	95.3%	–			–
Asian	1.4%	0%	2.4%	–			–
Black	2.7%	4.8%	1.2%	–			–
More than one	2.0%	3.2%	1.2%	–	–		–
Aβ+ (%)[a]	42.6%	–	–	–	–		–
MCI (%)	28.4%	41.3%	18.8%	8.97	–	0.25	**0.003**
Mean cognitive performance[b]	−0.17 (0.54)	−0.28 (0.59)	−0.09 (0.49)	2.16	[0.02, 0.37]	0.36	**0.03**
Cognitive dispersion	1.02 (0.67)	1.27 (0.62)	0.83 (0.43)	−3.82	[−0.67, −0.21]	0.69	**<0.001**
Animal fluency	−0.18 (1.04)	−0.32 (0.10)	−0.07 (1.07)	1.44	[−0.09, 0.58]	0.24	0.15
Boston Naming Test	−0.39 (1.41)	−0.72 (1.75)	−0.14 (1.05)	2.36	[0.09, 1.08]	0.42	**0.02**
Trails A	−0.11 (1.12)	−0.40 (1.41)	0.10 (0.79)	2.52	[0.11, 0.89]	0.45	**0.01**
Trails B	−0.32 (1.22)	−0.61 (1.52)	−0.10 (0.10)	2.33	[0.08, 0.94]	0.42	**0.02**
AVLT delayed recall	−0.39 (1.18)	−0.78 (1.15)	−0.10 (1.12)	3.59	[0.30, 1.05]	0.60	**<0.001**
AVLT recognition	−0.50 (1.20)	−0.86 (1.42)	−0.23 (0.94)	3.04	[0.22, 1.03]	0.54	**0.003**

Note. Results from t tests for continuous variables and chi-square tests for dichotomous variables. Data are summarized as mean (standard deviation), unless otherwise indicated. Effects sizes (Cohen's d for t tests and phi for chi-square tests) are reported as absolute values. Significant group differences ($p < .05$) appear in bold font. CI = confidence interval; Aβ = amyloid beta; MCI = mild cognitive impairment; AVLT = Rey Auditory Verbal Learning Test.

[a]Amyloid negativity *versus* positivity was based on the recommended threshold for cross-sectional florbetapir analyses of 1.11 using the whole cerebellum as the reference region (Landau et al., 2014).

[b]Mean cognitive performance is the mean of the six age-, sex-, and education-adjusted neuropsychological Z scores included in the cognitive dispersion index. The six scores were Animal Fluency, total score; 30-item Boston Naming Test (BNT) total score; Trail Making Test (TMT), Part A; time to completion; TMT, Part B; time to completion; Rey Auditory Verbal Learning Test (AVLT) 30-min delayed free recall; number of words recalled; and AVLT recognition; number of words correctly recognized.

Results

Participant characteristics

Participants' demographic and clinical data are presented in Table 1. One hundred and forty-eight older adults ranging in age from 55 to 85 (mean ± $SD = 70.98 \pm 6.3$) comprised the present sample. There were 72 women (48.6%), the sample was 93.9% white, and the average number of years of formal education was approximately 17 ($SD = 2.51$). Compared to Aβ- participants, the Aβ+ group were significantly older, more likely to be characterized as MCI, and exhibited poorer cognitive scores (i.e., lower mean level of cognitive performance and poorer performance on each of the individual cognitive measures included in the cognitive dispersion index with the exception of animal fluency on which the groups did not differ). There were no significant group differences in terms of education, gender, or race (p-*values* > 0.05).

Cognitive dispersion by Aβ status

After adjusting for age, gender, education, and mean cognitive performance, there was a significant main effect of Aβ status on cognitive dispersion such that participants who were Aβ+ showed higher cognitive dispersion relative to those who were Aβ- ($F(1,142) = 9.132$, $p = .003$) (See Figure 1).

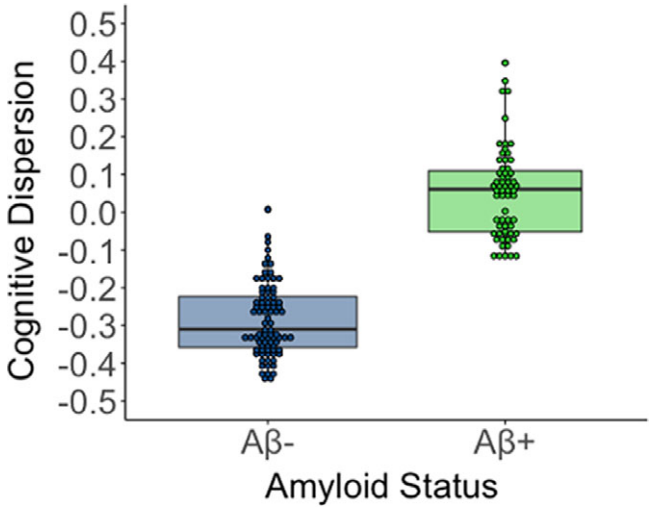

Figure 1. Cognitive dispersion by amyloid-beta (Aβ) positivity *versus* negativity. The lines represent group medians and the boxes represent the interquartile range; the y axis represents the model predicted cognitive dispersion values after controlling for age, gender, education, and mean cognitive performance.

Associations of cognitive dispersion and regional CBF

Hierarchical linear regression models showed that, across the entire sample, after adjusting for age, gender, education, and mean cognitive performance, higher cognitive dispersion was significantly associated with reduced CBF in IPL ($\beta = -.183$, $p = .027$; Overall model: $R^2 = .117$, $F(5,142) = 3.748$, $p = .003$) and ITG ($\beta = -.214$, $p = .011$; Overall model: $R^2 = .091$, $F(5,142) = 2.858$, $p = .017$). There were no significant associations between cognitive dispersion and CBF in mOFC, rMFG, or hippocampal regions (all p's > .05) (See Table 2 and Figure 2). When we performed sensitivity analyses in which we re-ran our primary models reversing the position of mean cognitive performance and cognitive dispersion, results remained similar to the primary models. That is, mean level of cognitive performance related to hippocampal CBF whereas cognitive dispersion was associated with CBF in IPL and ITG. There were no other significant associations between mean level of cognitive performance or cognitive dispersion and CBF. See *Supplemental Material* file for results of these sensitivity analyses.

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Table 2. Hierarchical linear regression models for association of cognitive dispersion and regional CBF adjusting for demographics and mean level of cognitive performance

	Hippocampal CBF $R^2 = .082$ $F(4,143) = 3.20$, $p = .015$				IPL CBF $R^2 = .086$ $F(4, 143) = 3.345$, $p = .012$				ITG CBF $R^2 = .049$ $F(4,143) = 1.851$, $p = .122$				mOFC CBF $R^2 = .020$ $F(4,143) = .722$, $p = .578$				rMFG CBF $R^2 = .091$ $F(4,143) = 3.575$, $p = .008$			
Block 1	*B*	*SE*	*p*	sr	*B*	*SE*	*p*	sr	*B*	*SE*	*p*	sr	*B*	*SE*	*p*	sr	*B*	*SE*	*p*	sr
Age	.024	.066	.709	.030	.135	.069	.052	.157	−.156	.075	**.039**	−.170	−.003	.063	.968	−.003	−.052	.053	.327	−.078
Gender	.366	.883	.680	.033	2.525	.927	**.007**	.218	.425	1.011	.675	.034	−1.314	.851	.125	−.128	2.486	.712	**.001**	.279
Education	.411	.177	**.022**	.186	.320	.186	.088	.138	.185	.203	.363	.074	.089	.171	.601	.043	.150	.143	.295	.084
Mean cognitive performance	−22.960	8.046	**.005**	−.229	−.913	8.445	.914	−.009	8.481	9.214	.359	.075	−.003	.063	.726	−.029	−.397	6.485	.951	−.005
	$R^2 = .086$, R^2 change = .004 $F(5,142) = 2.671$, $p = .024$				$R^2 = 0.117$, R^2 change = 0.03 $F(5,142) = 3.748$, $p = .003$				$R^2 = .091$, R^2 change = .042 $F(5,142) = 2.858$, $p = .017$				$R^2 = .022$, R^2 change = .002 $F(5,142) = .647$, $p = .664$				$R^2 = .094$, R^2 change = .003 $F(5,142) = 2.934$, $p = .015$			
Block 2																				
Age	.031	.066	.641	.037	.154	.068	**.026**	.178	−.132	.074	.078	−.142	−.007	.064	.908	−.010	−.056	.053	.293	−.084
Gender	.326	.886	.713	.030	2.406	.916	**.010**	.207	.276	.994	.782	.022	−1.284	.854	.135	−.125	2.514	.714	**.001**	.281
Education	.398	.178	**.027**	.179	.280	.184	.131	.120	.135	.200	.501	.054	.099	.172	.564	.048	.159	.144	.270	.088
Mean cognitive performance	−24.103	8.194	**.004**	−.236	−4.352	8.471	.608	−.041	4.189	9.192	.649	.036	−1.854	7.900	.815	−.019	.389	6.608	.953	.005
Cognitive dispersion	−.642	.836	.444	−.062	−1.929	.864	**.027**	−.176	−2.409	.938	**.011**	−.205	.484	.806	.549	.050	.441	.674	.514	.052

SE = standard error; CBF = cerebral blood flow; IPL = inferior parietal lobe; ITG=inferior temporal gyrus; mOFC = medial orbitofrontal cortex; rMFG = rostral middle frontal gyrus; sr = semi partial correlation coefficient. For gender, women are the reference group. Bold values are statistically significant ($p < .05$). Cognitive dispersion was calculated by using the intraindividual standard deviation across 6 *Z* scores.

Associations of cognitive dispersion and brain morphometry

After adjusting for age, gender, education, and mean cognitive performance, cognitive dispersion was not significantly associated with hippocampal volume or cortical thickness of IPL, ITG, mOFC, or rMFG regions (all *p*-values > 0.05; See Table 3).

Secondary analyses stratified by Aβ status

Analyses were conducted to examine whether the associations among cognitive dispersion and regional CBF and volume/cortical thickness were driven by those participants who were considered Aβ+. Among Aβ+ individuals ($n = 62$), adjusting for age, gender, education, and mean cognitive performance, higher cognitive dispersion was significantly associated with reduced IPL CBF ($\beta = -.341$, $p = .011$; Overall model: $R^2 = .113$, $F(5,57) = 1.457$, $p = .218$) and reduced ITG CBF ($\beta = -.295$, $p = .028$; Overall model: $R^2 = .100$, $F(5,57)=1.265$, $p = .292$). See Figure 2. Cognitive dispersion was not significantly associated with CBF in hippocampal, mOFC, or rMFG regions. When examining volume/cortical thickness, cognitive dispersion was not significantly associated with hippocampal volume or thickness of IPL, OTG, mOFC, or rMFG, ITG. Among Aβ- individuals ($n = 84$), there were no significant associations between cognitive dispersion and CBF across ROIs or between cognitive dispersion and volume/cortical thickness (all *p*-values > 0.05) (See Tables 4 and 5 and Figure 2).

False discovery rate

Statistical significance of all reported findings was retained under a 0.10 FDR but not maintained under a 0.05 FDR.

Discussion

In a sample of well-characterized older adults free of clinical dementia, we found that those individuals who were Aβ+ on PET imaging showed greater cognitive dispersion than their counterparts who were Aβ-. In addition, greater cognitive dispersion was significantly associated with reduced CBF in IPL and ITG regions after adjusting for age, gender, education, and mean cognitive performance. Secondary analyses stratified by Aβ status revealed that these associations were driven primarily by Aβ+ individuals rather than Aβ- individuals. Across the entire sample and within the Aβ+ and Aβ- subgroups, there were no significant associations between cognitive dispersion and brain morphometry (i.e., cortical thickness and volume).

The study of cognitive dispersion has a long history in the field of psychology (Vance et al., 2021). It has been long believed that a large degree of test scatter or variation characterizes some types of psychological disorders (Plake et al., 1981) and many commonly administered neuropsychological measures include indices of scatter or discrepancy as standardized variables (e.g., Wechsler Adult Intelligence Scale beginning with the Revised (WAIS-R) version, Delis-Kaplan Executive Function Scale, California Verbal Learning Test), although base rate information is not always available (Jacobson et al., 2009). Nonetheless, there is recent growing interest in using cognitive dispersion indices to predict future decline and cognitive outcomes in various neurological disorders including AD, human immunodeficiency virus, and traumatic brain injury. Increased cognitive dispersion may manifest in a reduced ability to integrate cognitive processes, which could then lead to reduced cognitive control and functional inefficiency (Fellows & Schmitter-Edgecombe, 2015). It has been theorized that increasing cognitive dispersion may reflect a disruption of neural

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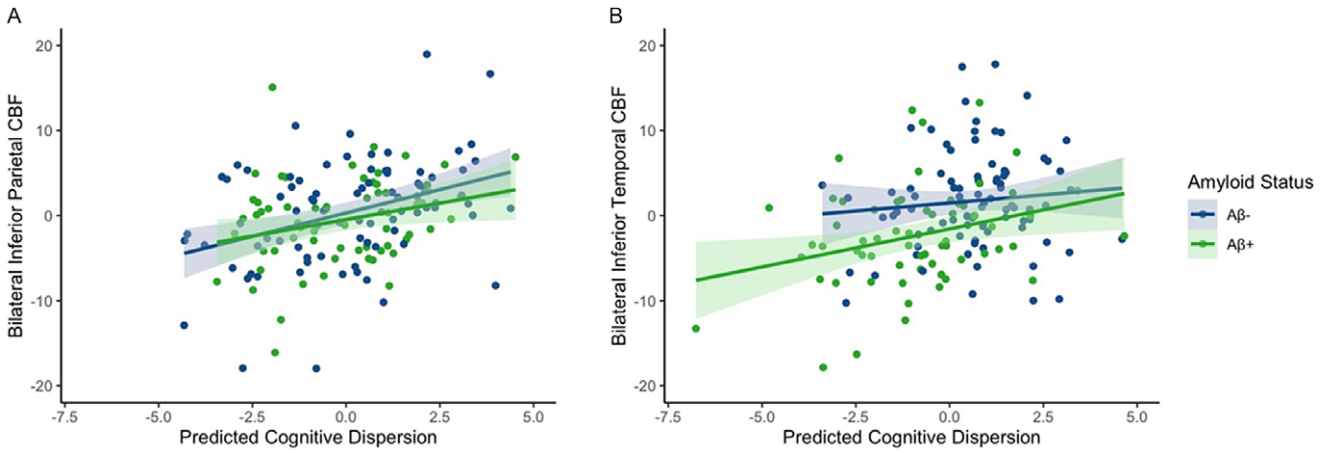

Figure 2. Scatterplot depicting the association between cognitive dispersion and CBF across the entire sample for inferior parietal (A) and inferior temporal (B) cortices by amyloid status. The x axes depict model predicted cognitive dispersion values adjusting for age, gender, education, and mean level of cognitive performance. The y axes depict regional CBF residualized by precentral CBF. Shaded area represents 95% confidence intervals.

networks (Jacobson et al., 2009; Parasuraman & Martin, 1994), and several neuroimaging studies have shown that increasing intraindividual variability is associated with reduced functional connectivity (Lin & McDonough, 2022). AD has long been conceptualized as involving a disconnection syndrome (Delbeuck et al., 2003) given that early AD is characterized by the loss of cortico-cortical projections that promote interactions of multiple brain regions. Recent neuroimaging studies have shown disruption of multiple networks including the frontoparietal and default mode networks in AD (Contreras et al., 2020; Meeker et al., 2021). The current findings suggest that cognitive dispersion is elevated in individuals who are Aβ+ and that reduced CBF may play a role in increasing dispersion, although future longitudinal studies are needed to confirm this.

Previous studies have shown that greater cognitive dispersion at baseline predicts progression to MCI (Gleason et al., 2018), faster rates of medial temporal atrophy (Bangen et al., 2019), and increased risk of incident MCI (Holtzer et al., 2020). Our current findings suggest that higher cognitive dispersion is also associated with cerebral amyloidosis, which dovetails with previously published studies including an autopsy study showing that greater cognitive dispersion was significantly associated with more severe neurofibrillary tangle pathology and trended toward an association with more severe neuritic plaques (Malek-Ahmadi et al., 2017) and a second study what showed that CSF measured Aβ moderated the relationship between cognitive dispersion and resting-state functional connectivity (Meeker et al., 2021). However, our findings differ from another recent study which reported that cognitive dispersion was not associated with CSF markers of AD pathology (Watermeyer et al., 2020). Differences between the current study and that by Watermeyer and colleagues (2020) may account for the discrepant findings including the method of measuring amyloid status (CSF *vs.* PET) and the type and number of cognitive tests used to calculate the cognitive dispersion index (Watermeyer and colleagues used more measures than the 6 included in the present study and they also included experimental measures).

In the present study we found greater cognitive dispersion was associated with hypoperfusion in posterior but not anterior regions, which is in line with previous MRI studies showing brain changes in posterior regions in AD risk (Brickman et al., 2015; Yew & Nation, 2017). Previous research examining small vessel cerebral vascular disease as measured by white matter hyperintensities (WMH) has shown normal aging-related increases in WMH volume in anterior regions but AD-specific increases in WMH in posterior regions (Brickman et al., 2015). Our current finding is also in line with a previous ADNI ASL study that examined the same 5 *a priori* regions we studied in the present study and found that the only region that showed CBF differences between Aβ+ older adults free of dementia *versus* participants with AD dementia was the inferior parietal region. In addition, individuals with AD showed reduced CBF in hippocampus, inferior parietal, and inferior temporal regions relative to Aβ- older adults but there were no CBF differences among the cognitive groups in frontal regions (Yew & Nation., 2017). Our finding of significant associations between higher cognitive dispersion and reduced CBF in posterior but not frontal regions is in line with previous research within the ADNI sample that focused on group differences in CBF based on cognitive status (i.e., unimpaired cognition, objectively defined subtle cognitive decline [Obj-SCD], and MCI). This previous study (which had some overlap with the current study's sample) showed that those with Obj-SCD had altered CBF in the IPL and hippocampus relative to a cognitively normal group, suggesting early neurovascular dysfunction in these key regions may precede later cognitive impairment (Thomas et al., 2021). Similar to the present study, Thomas and colleagues did not find significant differences between cognitive groups in CBF in frontal regions.

Cognitive dispersion was not associated with morphometry including regional gray matter volume (hippocampus) or cortical thickness (IPL, ITG, mOFC, rMFG), consistent with our previous findings showing no cross-sectional associations between baseline cognitive dispersion and morphometry (Bangen et al., 2019). However, in our previous study we found that higher cognitive dispersion predicted faster rates of medial temporal lobe atrophy at 24-month follow-up in the ADNI cohort (Bangen et al., 2019). This pattern of findings suggests that cognitive dispersion is a sensitive marker of future neurodegeneration. This previously published paper (Bangen et al., 2019) included 736 participants some of which overlapped with the present study, although did not examine the majority of the regions included in the current paper. The present findings that cognitive dispersion is associated with reduced CBF but not morphometry at baseline suggests that

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Table 3. Hierarchical linear regression models for association of cognitive dispersion and regional volume/cortical thickness adjusting for demographics and mean level of cognitive performance

	Hippocampal volume $R^2 = .182$ $F(4,143) = 7.979$, $p =<.001$				IPL thickness $R^2 = .114$ $F(4,143) = 4.621$, $p = .002$				ITG thickness $R^2 = .199$ $F(4,143) = 8.867$, $p =<.001$				mOFC CBF $R^2 = .044$ $F(4,143) = 1.628$, $p = .170$				rMFG CBF $R^2 = .043$ $F(4,143) = 1.595$, $p = .179$			
Block 1	*B*	*SE*	*p*	sr	*B*	*SE*	*p*	sr	*B*	*SE*	*p*	sr	*B*	*SE*	*p*	sr	*B*	*SE*	*p*	sr
Age	−.343	.084	**<.001**	−.310	−.005	.002	**.001**	−.259	−.009	.002	**<.001**	−.357	.002	.002	.158	.116	−.001	.001	.239	−.097
Gender	1.352	1.128	.233	.091	.034	.022	.128	.120	−.036	.024	.140	−.111	−.004	.021	.856	−.015	.034	.016	**.037**	.173
Education	.115	.226	.612	.038	.003	.004	.516	.051	.001	.005	.794	.020	.001	.004	.903	.010	−.001	.003	.666	−.035
Mean cognitive performance	28.582	10.283	**.006**	.210	.290	.204	.156	.112	.539	.219	**.015**	.184	−.356	.194	.068	−.150	.018	.148	.903	.010
Block 2	$R^2 = .204$, R^2 change = .022 $F(5, 142) = 7.266$, $p =< .001$				$R^2 = .121$, R^2 change = .007 $F(5,142) = 3.919$, $p = .002$				$R^2 = .201$, R^2 change = .003 $F(5,142) = 7.164$, $p =< .001$				$R^2 = .049$, R^2 change = .005 $F(5,142) = 1.454$, $p = .209$				$R^2 = .050$, R^2 change = .007 $F(5,142) = 1.482$, $p = .199$			
Age	−.322	.082	**<.001**	−.289	−.005	.002	**.002**	−.247	−.008	.002	**<.001**	−.348	.002	.002	.197	.106	−.001	.001	.299	−.085
Gender	1.225	.024	.276	.082	.033	.022	.145	.115	−.037	.024	.131	−.114	−.003	.021	.897	−.011	.033	.016	**.043**	.167
Education	.072	.180	.749	.024	.002	.005	.586	.043	.001	.005	.848	.014	.001	.004	.837	.017	−.002	.003	.597	−.043
Mean cognitive performance	24.915	−.146	**.017**	.180	.251	.207	.227	.095	.511	.223	**.024**	.172	−.325	.197	.102	−.135	−.010	.150	.949	−.005
Cognitive dispersion	−2.057	−.289	.054	−.146	−.022	.021	.296	−.082	−.016	.023	.489	−.052	.018	.020	.382	.072	−.016	.015	.312	−.083

SE = standard error; CBF = cerebral blood flow; IPL = inferior parietal lobe; ITG=inferior temporal gyrus; mOFC = medial orbitofrontal cortex; rMFG = rostral middle frontal gyrus; sr = semi partial correlation coefficient. For gender, women are the reference group. Bold values are statistically significant ($p < .05$). Cognitive dispersion was calculated by using the intraindividual standard deviation across 6 baseline *Z* scores.

Table 4. Hierarchical linear regression models for association of cognitive dispersion and regional cerebral blood flow adjusting for demographics and mean level of cognitive performance in Aβ+ individuals

	Hippocampal CBF $R^2 = .178$ $F(4,58) = 3.139$, $p = .021$				IPL CBF $R^2 = .006$ $F(4,58) = .930$, $p = .984$				ITG CBF $R^2 = .020$ $F(4,58) = .293$, $p = .881$				mOFC CBF $R^2 = .054$ $F(4,58) = .834$, $p = .509$				rMFG CBF $R^2 = .135$ $F(4,58) = 2.254$, $p = .074$			
Block 1	*B*	*SE*	*p*	sr	*B*	*SE*	*p*	sr	*B*	*SE*	*p*	sr	*B*	*SE*	*p*	sr	*B*	*SE*	*p*	sr
Age	.063	.107	.560	.070	.051	.107	.636	.062	−.107	.122	.381	−.115	.083	.103	.425	.103	−.142	−.196	.125	−.190
Gender	1.115	1.408	.432	.094	.524	1.399	.709	.049	.384	1.595	.811	.031	−1.773	1.351	.194	−.168	2.492	1.196	**.042**	.255
Education	.658	.248	**.010**	.317	.075	.246	.763	.040	.045	.280	.873	.021	.103	.237	.667	.055	.109	.210	.606	.063
Mean Cognitive Performance	−31.418	11.319	**.007**	−.330	−2.039	11.250	.857	−.024	4.763	12.823	.712	.048	−5.880	10.858	.590	−.069	−2.138	9.614	.825	−.027
Block 2	$R^2 = 0.207$, R^2 change = .029 $F(5,57) = 2.972$, $p = .019$				$R^2 = .113$, R^2 change = .107 $F(5,57) = 1.457$, $p = .218$				$R^2 = .100$, R^2 change = .080 $F(5,57) = 1.265$, $p = .292$				$R^2 = .057$, R^2 change = .003 $F(5,57) = .689$, $p = .634$				$R^2 = .136$, R^2 change = .002 $F(5,57) = 1.801$, $p = .127$			
Age	.091	.108	.404	.099	.099	.103	.341	.120	−.059	.119	.622	−.062	.090	.105	.396	.110	−.148	.093	.119	−.195
Gender	1.275	1.400	.366	.107	.803	1.338	.551	.075	.660	1.547	.671	.054	−1.730	1.365	.210	−.163	2.459	1.209	**.047**	.250
Education	.664	.245	**.009**	.319	.084	.235	.722	.045	.054	.271	.842	.025	.104	.239	.665	.056	.108	.212	.613	.063
Mean Cognitive Performance	−35.108	11.506	**.003**	−.360	−8.466	10.997	.445	−.096	−1.617	12.716	.899	−.016	−6.867	11.220	.543	−.079	−1.366	9.937	.891	−.017
Cognitive Dispersion	−1.635	1.136	.156	−.170	−2.848	1.086	**.011**	−.327	−2.828	1.256	**.028**	−.283	−.437	1.108	.694	−.051	.342	.982	.728	.043

Aβ = amyloid beta; *SE* = standard error; CBF = cerebral blood flow; IPL = inferior parietal lobe; ITG = inferior temporal gyrus; mOFC = medial orbitofrontal cortex; rMFG = rostral middle frontal gyrus; sr = semi partial correlation coefficient. For gender, women are the reference group. Bold values are statistically significant ($p < .05$). Cognitive dispersion was calculated by using the intraindividual standard deviation across 6 baseline *Z* scores.

Table 5. Hierarchical linear regression models for association of cognitive dispersion and regional cerebral blood flow adjusting for demographics and mean level of cognitive performance in Aβ- individuals

	Hippocampal CBF $R^2 = .063$ $F(4,80) = 1.349$, $p = .259$				IPL CBF $R^2 = .178$ $F(4,80) = 4.324$, $p = .003$				ITG CBF $R^2 = .020$ $F(4,80) = .407$, $p = .803$				mOFC CBF $R^2 = .014$ $F(4,80) = .0289$, $p = .884$				rMFG CBF $R^2 = .076$ $F(4,80) = 1.634$, $p = .174$			
Block 1	*B*	*SE*	*p*	sr	*B*	*SE*	*p*	sr	*B*	*SE*	*p*	sr	*B*	*SE*	*p*	sr	*B*	*SE*	*p*	sr
Age	.106	.094	.261	.122	.210	.102	**.044**	.208	−.053	.105	.616	−.056	−.040	.093	.667	−.048	.045	.074	.547	.065
Gender	−.577	1.177	.626	−.053	3.375	1.285	**.010**	.266	−.236	1.318	.858	−.020	−.872	1.168	.457	−.083	1.972	.931	**.037**	.228
Education	.127	.258	.622	.053	.528	.281	.064	.190	.272	.288	.349	.104	.081	.256	.751	.035	.169	.204	.409	.089
Mean cognitive performance	−18.082	12.063	.138	−.162	.307	13.174	.981	.002	7.240	13.506	.593	.059	−4.766	11.971	.692	−.044	5.196	9.542	.588	.059
	$R^2 = .072$, R^2 change = .009 $F(5,79) = 1.229$, $p = .304$				$R^2 = .179$, R^2 change = .001 $F(5,79) = 3.435$, $p = .070$				$R^2 = .020$, R^2 change = .001 $F(5,79) = .326$, $p = .896$				$R^2 = .053$, R^2 change = .039 $F(5,79) = .887$, $p = .494$				$R^2 = .088$, R^2 change = .012 $F(5,79) = 1.517$, $p = .194$			
Block 2																				
Age	.107	.094	.257	.124	.210	.103	**.045**	.208	−.053	.106	.617	−.056	−.038	.092	.680	−.045	.046	.074	.538	.066
Gender	−.457	1.187	.701	−.042	3.417	1.301	**.010**	.268	−.259	1.335	.846	−.022	−.631	1.160	.588	−.060	2.083	.937	**.029**	.239
Education	.167	.262	.525	.069	.542	.287	.063	.192	.264	.295	.373	.100	.161	.256	.530	.069	.206	.207	.323	.107
Mean cognitive performance	−16.949	12.151	.167	−.151	.701	13.327	.958	.005	7.021	13.668	.609	.057	−2.480	11.874	.835	−.023	6.245	9.594	.517	.070
Cognitive dispersion	1.171	1.342	.385	.095	.408	1.472	.782	.028	−.227	1.509	.881	−.017	2.363	1.311	.075	.197	1.084	1.059	.310	.110

Aβ = amyloid beta; *SE* = standard error; CBF = cerebral blood flow; IPL = inferior parietal lobe; ITG = inferior temporal gyrus; mOFC = medial orbitofrontal cortex; rMFG = rostral middle frontal gyrus; sr = semi partial correlation coefficient. For gender, women are the reference group. Bold values are statistically significant ($p < .05$). Cognitive dispersion was calculated by using the intraindividual standard deviation across 6 baseline *Z* scores.

ASL CBF is a useful marker of early and subtle brain changes that may be observed prior to significant atrophy, and dovetails with our previous research showing hypoperfusion predicts later neurodegeneration (Bangen et al., 2021).

Cognitive dispersion indices may be influenced by relative differences in the difficulty, sensitivity, and score distributions of the component tasks as well as floor or ceiling effects (Cherry et al., 2002; Jacobson et al., 2009). However, intraindividual variability indices have been used as a means of identifying subtle decline in cognitive skills relative to those cognitive abilities that may be more resilient to neurodegenerative processes (Jacobson et al., 2009). In the early phases of neurodegeneration, an individual may show mild declines in one or two cognitive abilities while other abilities may be less affected. Given that some individuals in a preclinical stage of AD may not show a significant memory impairment and may perform within the intact or normal range on individual cognitive tests, it may be that intraindividual variability metrics are more sensitive than individual tests scores, particularly in identifying individuals who are experiencing very subtle decline and/or who are high functioning (Jacobson et al., 2009; Storandt et al., 2006).

Although comparing different dispersion metrics was not a primary purpose for the current study, in an effort to determine whether our findings may relate to differences in sensitivity to AD across tasks (mean level of performance) rather than pure measures of dispersion, we calculated dispersion two additional ways and re-ran our primary models with these alternative dispersion metrics. Given that episodic memory is typically affected early in AD together with our results suggesting that the two AVLT measures may be more sensitive to Aβ status relative to other measures included in the dispersion index (see Table 1), we re-ran our models with alternative dispersion indices that varied based on whether or how the AVLT measures were included. First, we calculated a dispersion variable not including the two AVLT measures. That is, we calculated a dispersion variable with the following four variables: BNT, Animals Fluency, Trails A, and Trails B. Results from the model with inferior parietal CBF as the dependent variable remained significant ($p = .006$) although the results from the model with inferior temporal CBF as the dependent variable was somewhat attenuated and was a trend ($p = .080$). As with our primary models, the models with hippocampal CBF and frontal CBF as the dependent variables were not significant. Next, we created a dispersion variable using the same 6 measures including in our original variable but partialed out mean AVLT performance. The pattern of results remained similar to our primary analyses although results were attenuated with cognitive dispersion relating to CBF at a trend level ($p = .052$ for inferior parietal CBF and $p = .072$ for inferior temporal lobe). Given that differences in sensitivity to AD across different measures may contribute to dispersion effects, future research should more directly compare the predictive utility of different dispersion metrics as well of intraindividual variability indices relative to individual test scores.

Cognitive dispersion has been measured using different approaches across studies. Consistent with several previous studies, we assessed cognitive dispersion as within-person variability across different neuropsychological measures (Bangen et al., 2019; Gleason et al., 2018; Watermeyer et al., 2020) rather than the inconsistency of trial performance across one task. Although few studies have directly compared dispersion and inconsistency, one previous study have found that these two methods of measuring intraindividual variability are moderately correlated ($r = .38$ on a choice reaction time task; $r = .31$ on a 1-back task) and are both

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associated with increasing age and cognitive decline (Hilborn et al., 2009). Future studies comparing dispersion and inconsistency will help determine how these two metrics may complement each other. To improve generalizability and to consider multiple cognitive domains, we selected neuropsychological tests that are commonly used in research and clinical settings to be included in our dispersion metric. In addition, the approach we used to calculate cognitive dispersion has been found to be particularly advantageous as it can be calculated from one testing session, showing cognitive dispersion has potential for clinical utility due to its ease of implementation without change to standardized testing procedures (Holtzer et al., 2008). Notably, however, there is not yet consensus on how to best operationalize cognitive dispersion. Additional studies providing empirical support for which measures and how many measures form the optimal dispersion index, establishment of a universally accepted method for calculating dispersion, and development of normative databases will increase the utility of dispersion in both research and clinical settings.

Strengths of the study include the well-characterized sample of older adults; integration of multimodal imaging data including PET Aβ, ASL perfusion, and structural MRI; and use of a sensitive measure of cognitive dispersion (i.e., an intraindividual standard deviation across multiple domains of cognitive functioning). Cognitive dispersion has several advantages relative to other proposed markers to detect early brain changes (e.g., PET imaging or lumbar puncture to measure CSF) including being low-cost and noninvasive. ASL MRI has advantages over other imaging techniques designed to measure CBF due to its noninvasive nature (i.e., does not require injection of contrast agent). Reduced CBF is also a well-established marker of subtle vascular change and has been associated with poorer everyday functioning (Sanchez et al., 2020), faster rater rates of memory decline, neurodegeneration, and progression of small vessel disease (Bangen et al., 2021). This study expands on previous research on cognitive functioning and CBF by linking hypoperfusion to increased cognitive dispersion.

It should be noted that the effects of cognitive dispersion in our models are modest and accounted for 3–4% and 8–11% of the variance in regional CBF across the entire sample and within the Aβ+ subgroup, respectively (entire sample: sr = −.176 for IPL and sr = −.205 for ITG; Aβ+ subgroup: sr = −.327 for IPL and sr = −.283 for ITG). Although these are modest effects, these models adjust for important demographic variables that influence CBF (i.e., age, gender) and mean-level cognitive performance and findings remained similar in sensitivity analyses in which the position of cognitive dispersion and mean cognitive performance were reversed (i.e., cognitive dispersion served as a covariate and mean cognitive performance served as the independent variable). Taken together, these findings provide support for the notion that cognitive dispersion may have incremental utility in assessing dementia risk although future studies comparing multiple cognitive metrics (e.g., dispersion, inconsistency, episodic memory indices) and additional risk factors are needed to clarify this. Limitations of the study include a homogeneous racial/ethnic distribution and a highly educated sample so results may not be generalizable to groups with differing demographic characteristics. Future research in more diverse samples is needed. Additional limitations include the cross-sectional design. Future studies using larger samples should examine data longitudinally to determine whether cognitive dispersion predicts future changes in CBF levels, interacts with biomarkers including Aβ levels to predict clinical outcomes, and adds incremental value in predicting outcomes relative to other cognitive indices and risk factors. Future research is also needed to further evaluate the specificity and sensitivity of dispersion metrics in preclinical and prodromal dementia. In particular, it will be important to examine the associations between dispersion and biomarkers beyond Aβ including those related to cerebrovascular disease burden.

In summary, in conjunction with previous evidence linking cognitive dispersion to faster rates of cerebral atrophy in AD-vulnerable brain regions (Bangen et al., 2019) and increased AD neuropathology (Malek-Ahmadi et al., 2017), our findings suggest that cognitive dispersion may be a useful noninvasive marker of early cognitive and brain changes especially in the context of those who are Aβ+. Since greater cognitive dispersion was not associated with brain morphometry, but was associated with reduced CBF, this indicates that cognitive dispersion may be a marker of early vascular changes in the brain and may be useful in identifying participants for clinical trials that target vascular risk or amyloid although future longitudinal studies are needed to confirm this.

Supplementary material. The supplementary material for this article can be found at https://doi.org/10.1017/S1355617722000649

Acknowledgments. Data used in this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). ADNI investigators contributed to the design and implementation of ADNI and/or provided data but did not participate in analysis or writing of this manuscript. A complete listing of ADNI investigators can be found at: http://adni.loni.usc.edu/wpcontent/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf

Funding statement. The analyses in this manuscript were funded by the US Department of Veterans Affairs Clinical Sciences Research and Development Service (Career Development Award-2 1IK2CX001865 to K.R.T. and 1IK2CX001415 to E.C.E.; and Merit Award 1I01CX001842 to K.J.B), NIH grants (R01 AG063782 to K.J.B.), and the Alzheimer's Association (AARF-17-528918 to K.R.T., AARG-18-566254 to K.J.B., AARG-17-500358 to E.C.E.). The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health. Data collection and sharing for this project was funded by the Alzheimer's Disease Neuroimaging Initiative (ADNI) (National Institutes of Health Grant U01 AG024904) and DOD ADNI (Department of Defense award number W81XWH-12-2-0012). ADNI is funded by the National Institute on Aging, the National Institute of Biomedical Imaging and Bioengineering, and through generous contributions from the following: AbbVie, Alzheimer's Association; Alzheimer's Drug Discovery Foundation; Araclon Biotech; BioClinica, Inc.; Biogen; Bristol-Myers Squibb Company; CereSpir, Inc.; Cogstate; Eisai Inc.; Elan Pharmaceuticals, Inc.; Eli Lilly and Company; EuroImmun; F. Hoffmann-La Roche Ltd and its affiliated company Genentech, Inc.; Fujirebio; GE Healthcare; IXICO Ltd.; Janssen Alzheimer Immunotherapy Research & Development, LLC.; Johnson & Johnson Pharmaceutical Research & Development LLC.; Lumosity; Lundbeck; Merck & Co., Inc.; Meso Scale Diagnostics, LLC.; NeuroRx Research; Neurotrack Technologies; Novartis Pharmaceuticals Corporation; Pfizer Inc.; Piramal Imaging; Servier; Takeda Pharmaceutical Company; and Transition Therapeutics. The Canadian Institutes of Health Research is providing funds to support ADNI clinical sites in Canada. Private sector contributions are facilitated by the Foundation for the National Institutes of Health (www.fnih.org). The grantee organization is the Northern California Institute for Research and Education, and the study is coordinated by the Alzheimer's Therapeutic Research Institute at the University of Southern California. ADNI data are disseminated by the Laboratory for Neuro Imaging at the University of Southern California.

Conflicts of interest. None.

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