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Discrepancies between Fluid and Crystallized Ability in Healthy Adults: A Behavioral Marker of Preclinical Alzheimer's Disease

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Abstract

Measures of core cognitive processes (fluid abilities) are highly correlated with measures of knowledge (crystallized abilities) in healthy adults. In early stages of Alzheimer's disease (AD), fluid abilities, however, decline more rapidly than crystallized abilities. We hypothesized that cognitively-normal older adults who evidenced lower fluid ability compared with crystallized ability (an ability discrepancy) would show evidence of early AD neuropathology indexed via *in vivo* measures of beta-amyloid (A β) deposition and cortical thickness in AD-vulnerable regions. A sample of older adults ($n = 112$) aged 65 to 89 underwent a cognitive battery, structural MRI, and a subset ($n = 75$) also completed PET scanning to measure A β deposition using F-18 Florbetapir. Of this sample, 60 older adults (43 with available PET scans) evidenced a discrepancy where fluid ability was lower than crystallized ability. The magnitude of the ability discrepancy was independently associated with a greater A β deposition and thinner cortex in AD-vulnerable regions, as well as age. The data suggest that such a discrepancy may be a marker of preclinical AD.

Keywords

ability discrepancy; aging; beta-amyloid; cortical thickness; dementia; preclinical

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Conflicts of Interest:

The authors declare no competing financial interests.

1.1 Introduction

Detecting Alzheimer's disease (AD) early is of great importance, especially since potential interventions are likely to be most effective at the earliest stages of the disease (Sperling et al., 2011b). AD is characterized by marked declines in episodic memory and aggregation of plaques composed of amyloid-beta ($A\beta$), neuronal tangles (composed of tau protein filaments), and cortical atrophy. Both $A\beta$ imaging and autopsy results have yielded evidence that a significant proportion of cognitively-normal older adults (approximately 25–45%) harbor $A\beta$ deposits (e.g., Bennett et al., 2006; Mintun et al., 2006; Pike et al., 2007; Price & Morris, 1999)—a phase characterized as preclinical AD (e.g., Jack et al., 2012, 2013; Sperling et al., 2011a). Studies have increasingly reported that cognitively-normal older adults with elevated levels of $A\beta$ show subtle behavioral deficits on cognitively challenging tasks, particularly episodic memory (e.g., Hedden et al., 2013; Resnick et al., 2010). A number of researchers also have reported effects in other domains, including processing speed, executive function, and reasoning (e.g., Rodrigue et al., 2012; Snitz et al., 2013; Wirth et al., 2013a, 2013b). Collectively, these deficits are all in cognitive domains that comprise fluid abilities and, like episodic memory, evidence decline in early stages of AD (e.g., Albert et al., 2011; Bastin & Salmon, 2014; Kaszniak, 1986; Rosen, 1983). In the present study, we utilized behavioral theories and measures commonly used in studies of cognitive aging as an important predictor of preclinical AD. Specifically, we used a “discrepancy” score based on the subtraction of fluid from crystallized ability and correlated this score with two AD brain markers: $A\beta$ deposition and cortical thinning (Bakkour et al., 2009; Dickerson et al., 2009; Wong et al., 2010).

Fluid ability represents a set of core processes underlying intelligence that includes processing speed, working memory, and reasoning (e.g., Wechsler, 1944, 1997). These core abilities are drawn upon to engage in complex thought, solve problems, and function in everyday life (e.g., Johnson et al., 2004; Kaszniak, 1986; Lezak, 1995; Wechsler, 1944). Fluid ability tasks are typically unfamiliar and do not rely on past experience to perform the required mental operations. In contrast, people do bring accrued knowledge and experience to many situations and this experiential component of intelligence has been termed “crystallized ability.” Crystallized ability is usually assessed by vocabulary scores (e.g., Ekstrom et al., 1976; Wechsler, 1944; Zachary & Shipley, 1986) or word pronunciation scores (e.g., the National Adult Reading Test; Blair & Spreen, 1989).¹ In cognitively-normal adults, fluid and crystallized abilities are highly correlated with one another ($r = .70$; Cattell, 1965, see also Kaufman et al., 1996), suggesting that individuals with higher fluid ability also have higher crystallized ability. At the same time, it is well-known that individuals afflicted with AD show declines in fluid ability faster than declines in crystallized ability (e.g., O'Carroll & Gilleard, 1986; Wechsler, 1944) and that fluid ability decline is predictive of the rate of symptom progression in AD (e.g., Albert et al., 2011; Bastin & Salmon, 2014; McKhann et al., 2011; Schmid et al., 2013; Tabert et al., 2006). Because crystallized ability is spared initially in AD (e.g., O'Carroll & Gilleard, 1986; Wechsler, 1944), it is considered

¹Because vocabulary and word pronunciation measures are highly correlated with one another ($r = .78$; e.g., Blair & Spreen, 1989; O'Carroll & Gilleard, 1986), we consider them both under the term “crystallized ability.”

to be a good measure of premorbid cognitive ability (e.g., Lehl et al., 1995; Wechsler, 1944; Yates, 1956).

These differential rates of AD-related cognitive decline led us to reason that older adults who had a higher crystallized ability compared to their fluid ability (a positive ability discrepancy score) might harbor AD neuropathology. Consistent with this idea, a greater ability discrepancy has been shown not only to differentiate healthy adults from those with probable AD, but these discrepancies also have been shown to increase as disease severity worsens (e.g., Dierckx et al 2008; Lezak, 1995; McCarthy et al., 2005). Hence, we hypothesized that larger discrepancy scores between crystallized versus fluid abilities in healthy adults would be associated with individuals in a preclinical stage of AD as evidenced by elevated levels of A β and more cortical thinning in AD-sensitive brain regions.

Our primary aim was to use ability discrepancy scores to distinguish between normal and pathological aging. It is important to note, however, that ability discrepancies also have been observed in older relative to younger adults in cross-sectional analyses (e.g., Eisdorfer et al., 1959; Rabbitt, 1993). These age discrepancies are small in magnitude and could occur because the samples used included adults at the preclinical AD stage. In a similar way, consider that normal aging is characterized by a relatively modest memory deficit compared with young adults (e.g., Hertzog et al., 2003; Park et al., 1996), but AD is characterized by a very large memory deficit (e.g., McKhann et al., 2011). Perhaps differences in ability discrepancy parallel memory deficits in that a small discrepancy characterizes normal older adults, but a large discrepancy is associated with elevated levels of A β and more cortical thinning—both signs of preclinical AD. Thus, the modest ability discrepancy effect that occurs in normal older adults does not preclude that large differences in this marker might be diagnostic of AD pathology.

We hypothesized that ability discrepancy might covary with the aforementioned brain markers of preclinical AD. To address this issue, 1) the analyses between ability discrepancy and AD brain markers controlled for age, and 2) we focused the analyses on older adults that had positive ability discrepancy scores while also conducting supplemental analyses to test whether individuals with an exaggerated ability discrepancy were more likely to be associated with AD brain markers relative to other older adults in the sample.

2.1 Material and Methods

2.2 Participants

We drew our sample from 112 adults aged 65–89 who underwent MRI scanning, genotyping, and cognitive testing to measure fluid and crystallized ability as a part of the Dallas Lifespan Brain Study (DLBS). From these 112, we selected only subjects who had an ability discrepancy score (z-score crystallized minus z-score fluid ability) greater than zero ($n = 60$). Subjects with negative scores were excluded, as they were unrelated to our research question. In fact, they might be associated with non-dementia-related impairments due to early deficits in vocabulary ability (e.g., Copet et al., 2010; Satz, 1976). All 60 subjects selected had structural MRI data, and those that had behavioral data collected within 12

months also were invited to undergo PET scanning (43 of the 60; for more PET recruitment details, see Rodrigue et al., 2012).

All subjects were community-dwelling volunteers who were free from neurological conditions, major cardiovascular and psychiatric disorders, and no reported head injury with loss of consciousness > 10 min. Subjects also were excluded for reported drug/alcohol abuse, and major heart surgery or chemotherapy within 5 years of testing. All subjects were fluent English speakers, right-handed, and provided written informed consent as approved by the university human investigations committee guidelines. A summary of the sample characteristics is provided in Table 1.

2.3 Overall Protocol

All subjects had completed two neuropsychological assessment visits and one visit for MRI scanning. For those subjects with A β data, a fourth visit for a PET scan was completed.

2.3.1 Neuropsychological Assessment—To assess fluid and crystallized abilities, we selected measures available from the DLBS that were highly reliable, represented multiple domains of cognition, and are commonly used across many studies (e.g., Johnson et al., 2004; Wechsler, 1997). The six fluid measures spanned the cognitive domains of processing speed, working memory, and reasoning. Processing speed was measured using the number of correct items on the Digit Symbol task (Wechsler, 1997) and the Digit Comparison task (Hedden et al., 2002; adapted from Salthouse & Babcock, 1991). Working memory was measured using the number of correct items on the Letter-Number Sequencing task (Wechsler, 1997) and the sum of the number of words in each set on perfectly recalled trials on the Operation Span task (Turner & Engle, 1989). Reasoning was measured using the total score on the ETS Letter Sets task (Ekstrom et al., 1976) and accuracy on the Raven's Progressive Matrices task (Raven, 1938). Crystallized ability was measured using the number of correct items for both the ETS Advanced Vocabulary Test I-V4 (Ekstrom et al., 1976) and the Shipley Vocabulary (Zachary & Shipley, 1986). We submitted all of these measures to a factor analysis, confirming that the six fluid measures and two crystallized measures would generate separate factor loadings (see section 2.4.1).

2.3.2 Structural MRI Acquisition & Processing—Subjects underwent MRI scanning on a 3T Philips Achieva scanner equipped with an 8-channel head coil. High-resolution anatomical images were collected using a T1-weighted MP-RAGE sequence with 160 sagittal slices, $1 \times 1 \times 1 \text{ mm}^3$; $256 \times 256 \times 160$ matrix, TR = 8.18 ms, TE = 3.76 ms, flip-angle = 12° , FOV = 220 mm. To estimate cortical thickness, T1-weighted images were processed using a surface-based processing stream provided by FreeSurfer v5.1 (<http://surfer.nmr.mgh.harvard.edu>), including bias-field correction, intensity normalization, skull-stripping (Dale et al., 1999; Segonne et al., 2004). Following these steps, FreeSurfer segments of gray/white matter and pial surfaces were used to estimate distance between boundaries, which were checked for accuracy and edited, if necessary, by extending white matter boundaries or removing non-brain tissue. The resulting surface maps were then transformed to a common space and smoothed using 10 mm FWHM Gaussian filter. From these maps, nine bilateral regions of interest (ROIs) were hand traced on the cortical surface

and averaged across hemispheres and included anterior medial temporal lobe, inferior temporal gyrus, temporal pole, angular gyrus, superior frontal gyrus, superior parietal lobule, supramarginal gyrus, precuneus, and inferior frontal sulcus (see Figure 1). These ROIs were selected based on prior research identifying them as regions vulnerable to AD, also known as AD signature regions (Bakkour et al., 2009; Dickerson et al., 2009). An additional bilateral region in the occipital cortex served as a control ROI.

2.3.3 PET Imaging Acquisition and Processing—To measure A β deposition, subjects underwent PET scanning with ^{18}F -Florbetapir (Avid Radiopharmaceuticals). Subjects were injected with a 370 MBq (10 mCi) bolus of ^{18}F -Florbetapir for a 10 min emission and a 10 min transmission scan. A 2-frame by 5-min each dynamic emission acquisition protocol was started 50 min post-injection. An internal rod source transmission scan was acquired for 7 min. The transmission image was reconstructed using back projection and a 6 mm FWHM Gaussian filter. The emission images were processed by iterative reconstruction, 4 iterations and 16 subsets with a 3 mm FWHM ramp filter. Each subject's PET scan was spatially normalized to a Florbetapir uptake template ($2 \times 2 \times 2$ mm³ voxels) using SPM8 and in-house MATLAB scripts and visually inspected for registration quality. A β counts were assessed from eight bilateral ROIs in MNI space in regions where amyloid typically aggregates in AD patients (Wong et al., 2010). These ROIs included subregions in orbital frontal, dorsolateral prefrontal, anterior cingulate, posterior cingulate, lateral temporal, lateral parietal, and occipital cortex, as well as precuneus. To minimize inclusion of nonspecific white matter binding in these ROIs, we identified the gray/white matter boundary threshold in the PET images in a separate group of young adults (age < 35, $n = 9$), and eroded each ROI by the resulting binarized white matter mask. Within these final ROIs, counts were extracted, averaged across voxels within each ROI, and then normalized by counts in the gray matter of the cerebellum to produce standardized uptake value ratios (SUVRs).

2.4 Statistical Analysis

All statistical analyses were performed using SPSS version 20 (IBM Corp., Armonk, NY). Bias-corrected and accelerated confidence intervals were determined using 1,000 bootstrap samples and significance was set at $p < .05$.

2.4.1 Deriving Measures of Fluid and Crystallized Ability—Fluid and crystallized measures were first calculated using factor analysis. Factor analysis was chosen because it is a widely used technique that captures similar variance across measures to help reduce data to a smaller set of measures. Specifically, the eight neuropsychological measures (two each for processing speed, working memory, reasoning, and vocabulary) were z-transformed and then entered into a factor analysis using direct oblimin rotation (Kline, 1994). This rotation was chosen because it allows the resulting factors to be correlated with one another, thus better representing the true underlying nature of the data. We intentionally constrained the model to two factors because of our *a priori* interest in fluid and crystallized abilities, but we also inspected the resulting eigenvalues to ensure that two factors were the best fit for the dataset.

2.4.2 Calculating the Ability Discrepancy Score—Using the results from the factor analysis, we subtracted the fluid score from the crystallized score to create an ability discrepancy score for each subject. Increasingly positive values represented an increasingly greater discrepancy in ability (e.g. Kaufman, 1990; Matarazzo & Herman, 1985; Schretlen et al, 1994). Our primary analyses focused on individuals that had an ability discrepancy score greater than zero.

2.4.3 The Effects of Ability Discrepancy across Regions on Cortical Thickness

—Here, we tested the hypothesis that older adults with higher positive discrepancy scores would have lower cortical thickness across the nine AD signature regions. We conducted a mixed analysis of covariance (ANCOVA) with ability discrepancy score treated as a continuous independent variable, ROIs as a within-subjects independent variable, and their interaction. The dependent measure was cortical thickness. This analysis allowed us to test whether ability discrepancy exerted a consistent effect across all nine ROIs or whether there was an interaction, suggesting that ability discrepancy exerted a different relationship across the ROIs. Testing this interaction enabled a closer inspection of the robustness of this relationship, and could potentially reveal particularly sensitive regions to preclinical AD. In addition, we controlled for age and sex in the analysis to generalize the results to all older age groups (65–90 year olds) and both sexes. These analyses provided input for which ROIs to include as summary scores to simplify the data when testing for independent associations of ability discrepancy and preclinical AD brain markers (see section 2.4.4).

2.4.4 The Effects of Ability Discrepancy across Regions on Cortical A β Deposition

—In this analysis, we tested the hypothesis that ability discrepancy scores would exert a main effect on A β deposition. We also assessed whether the effects exerted a consistent effect across the eight regions utilized from which A β SUVRs were extracted. We conducted an ANCOVA with ability discrepancy as a continuous variable, ROI as a within-subjects variable, and their interaction. The dependent measure was a continuous measure of A β deposition. We also controlled for age and sex. In addition to treating A β deposition as a continuous variable, we also used a threshold approach, whereby A β was treated as a categorical value and subjects were classified as A β ⁺ or A β ⁻. Using the threshold value of 1.22 (see Rodrigue et al., 2012), 17 (40%) were classified as A β ⁺ and 26 (60%) as A β ⁻ (out of 43 subjects) for older adults in the positive ability discrepancy group. In the negative discrepancy group, 14 (44%) were classified as A β ⁺ and 18 (56%) as A β ⁻ (out of 32 subjects). These proportions are consistent with previous research suggesting that approximately 25–45% of cognitively-normal older adults harbor A β deposits (e.g., Bennett et al., 2006; Mintun et al., 2006; Pike et al., 2007; Price & Morris, 1999). This categorical approach is commonly used (e.g., Dickerson et al., 2009; Landau et al., 2012; Okello et al., 2009; Resnick et al., 2010; Snitz et al., 2013; Wirth et al., 2013a, 2013b) and provided additional reliability of the results.

2.4.5 Independent Contributions of Cortical Thickness and A β Deposition on Ability Discrepancy—Because cortical thickness and A β deposition are both markers of preclinical AD, they might not provide independent information regarding the status of preclinical AD. On the other hand, models of preclinical AD (e.g., Jack et al., 2012, 2013)

propose that A β deposition precedes neurodegeneration (e.g., cortical thinning), potentially leading to independent contributions of each measure. To assess whether the two types of AD brain markers independently affected ability discrepancy, we also conducted a multiple regression analysis. We treated cortical thickness and A β deposition as predictor variables and ability discrepancy as the outcome variable. ROIs that were significant in the ANCOVAs described above were averaged separately to derive a summary measure of cortical thickness and A β deposition. As in the previous analyses, age and sex were included as covariates. To maximize degrees of freedom, backward regression was used to eliminate insignificant higher-order factors.

In addition to the primary regression analysis, a supplemental regression analysis was conducted on the full sample with Group (Positive and Negative Discrepancy) as a between subjects factor. An interaction with Group and either of the AD brain markers would provide evidence that any of the relationships with the AD brain markers depended on which end of the ability discrepancy scale older adults fell.

3.1 Results

3.2 Factor Analysis of Neuropsychological Assessment

The factor analysis yielded two factors that, as expected, clearly differentiated crystallized from fluid abilities. For the first factor, the zero-order factor loadings (i.e., structure coefficients) were largest for Shipley Vocabulary (.91) and ETS Advanced Vocabulary (.84), thus representing crystallized ability. This factor explained 32.20% of the variance in the data. For the second factor, the factor loadings, in order of magnitude, were Digit Symbol (.74), Digit Comparison (.69), ETS Letter Sets (.65), Letter Number Sequencing (.46), Raven's (.45), and Operation Span (.45). The second factor was designated as the fluid ability factor and explained an additional 16.57% of the variance. The other eigenvalues were less than 1.0 (the third eigenvalue had a value of .88), and explained little variance beyond the first two factors. Consistent with prior work (e.g., Cattell, 1965; Kaufman et al., 1996), the crystallized and fluid ability factors were positively correlated with one another, $r(112) = .47$, $p < .001$, $CI(.32, .61)$.

3.3 Calculating Ability Discrepancy Scores and Partitioning Groups

Subtracting fluid from crystallized ability resulted in an ability discrepancy score for each subject that ranged from -2.97 to 2.32 ($M = -0.01$). Sixty of the 112 subjects had an ability discrepancy score greater than zero as well as MRI scans and hence were retained for the primary analyses pertaining to cortical thickness. Of these 60 subjects, 43 subjects were retained for the A β analysis as they had completed both MRI and PET scans. A comparison of the positive and negative discrepancy groups indicated that the two groups did not differ in chronological age, MMSE, cortical thickness averaged across the nine ROIs, or A β averaged across the eight ROIs (all p 's $> .26$). However, the positive group had higher levels of education ($M = 16.82$ vs. 15.57 ; $t(110) = 2.75$, $p = .007$) and relatively more men than women (48% male/52% females vs. 23% male/77% female; $\chi^2(112) = 7.66$, $p = .006$) compared with the negative group. In the negative group, mean cortical thickness was not related to mean cortical A β ($r(28) = .02$, $p = .94$). We next assessed the same associations

within the positive group. No relationship was observed between mean cortical thickness and mean cortical A β ($r(39) = -.23, p = .15$). Among age, sex, education, and MMSE, only age significantly correlated with ability discrepancy ($r(60) = .26, p = .05$; for the other variables all p 's $> .49$).

3.4 Effects of Ability Discrepancy on Cortical Thickness

We conducted an Ability discrepancy $\times$ ROI ANCOVA on cortical thickness. This ANCOVA yielded a main effect of ability discrepancy and of ROI, but no interaction. The ability discrepancy effect was significant ($F(1, 56) = 7.54, p = .008, \eta_p^2 = .12$); subjects with a greater ability discrepancy had lower cortical thickness. The accompanying parameter estimates for the main effect of ROI ($F(8, 448) = 5.49, p < .001, \eta_p^2 = .09$) indicated that temporal regions were thicker than frontal and parietal regions ($t(59) = 16.42, p < .001, d = 2.36$ and $t(59) = 26.64, p < .001, d = 3.77$, respectively), and frontal regions were thicker than parietal regions ($t(59) = 15.67, p < .001, d = 1.63$). However, the absence of a significant interaction ($F(8, 448) = 1.15, p = .33, \eta_p^2 = .02$) suggested that the ability discrepancy effect generalized across regions.² Thus, the cortical thickness values in each of the nine AD signature regions were averaged together to form a composite cortical thickness score for subsequent analyses. Cortical thickness as a function of ability discrepancy is displayed in Figure 2 (top left).³ Notably, thickness in the control region (primary visual cortex) was not associated with ability discrepancy ($p = .38$).

3.4 Effects of Ability Discrepancy on Cortical A β Deposition

We conducted an Ability discrepancy $\times$ ROI ANCOVA on A β Deposition. This ANCOVA yielded a main effect of ability discrepancy ($F(1, 39) = 6.40, p = .016, \eta_p^2 = .14$), which was significant because, as predicted, subjects with a higher ability discrepancy score had more A β deposition. The main effect of ROI was not significant ($p > .38$). However, an ability discrepancy $\times$ ROI interaction was significant ($F(7, 273) = 4.38, p < .001, \eta_p^2 = .10$), suggesting that the relationship between ability discrepancy and A β deposition differed across the ROIs. The parameter estimates from the ANCOVA indicated that the ability discrepancy effect was observed across only four of the eight ROIs: precuneus, temporal cortex, posterior cingulate, and anterior cingulate (Table 2). Marginal significance was observed for dorsolateral prefrontal cortex ($p = .053$), parietal ($p = .077$) and orbitofrontal cortex ($p = .10$) and non-significance was observed for occipital cortex ($p > .16$).⁴ Because of these observed regional differences, A β values were averaged across only the four significant regions to form a composite cortical A β score for subsequent analysis. Figure 2

²Controlling for APOE status and education did not change the significance of the results, nor was APOE status or education a significant factor (all p 's $> .05$). Because we had a modest age range (65–89), we also tested whether age interacted with ability discrepancy, but no interaction with age was significant (all p 's $> .46$).

³One subject did have a mean cortical thickness value about 4 standard deviations below the group mean thickness level (subject mean thickness = 2.00 mm, group mean thickness = 2.70 mm). Visual inspection of the FreeSurfer segmentation did not reveal clear errors in the segmentation, but rather verified substantial atrophy throughout the cortex. Nevertheless, the above analyses were re-run excluding this subject with nearly identical results, suggesting that this person did not inflate the relationships between ability discrepancy and cortical thickness. This subject also did not undergo PET scanning, and so was not included in the subsequent PET analyses.

⁴Controlling for APOE status did not change the significance of the results, nor was APOE status a significant factor ($p = .64$). Controlling for education changed the significance between ability discrepancy and A β in the anterior cingulate from $p = .044$ to $p = .058$, although education itself was not significant ($p > .05$). Ability discrepancy did not interact with age (all p 's $> .50$).

(top right) displays the aggregated values for A β as a function of ability discrepancy. Using a threshold approach, the A β + group had larger ability discrepancy scores than the A β - group ($M_{A\beta+} = .91$ & $M_{A\beta-} = 0.54$; $t(41) = 2.16$, $SEM = .18$, $p = .037$). When including subjects in the full sample of 112 individuals, ability discrepancy was numerically larger in the A β + than A β - group ($M_{A\beta+} = 0.30$ & $M_{A\beta-} = -0.089$), but did not reach significance $t(73) = 1.78$, $SEM = .22$, $p = .078$).

3.5 Independent Contributions of Cortical Thickness and A β on Ability Discrepancy

Using backward regression, we entered chronological age, sex, mean cortical thickness, mean cortical A β , and mean cortical thickness $\times$ mean cortical A β interaction to predict ability discrepancy. As shown in Table 3, the final regression model was significant ($F(4, 38) = 5.74$, $MSE = .24$, $p = .001$) and explained 37.7% of the variance in ability discrepancy. Mean cortical thickness ($p = .05$) and mean cortical A β ($p = .03$) were each significantly related to ability discrepancy and accounted for 6.5% and 8.1% unique variance in the model, respectively. The interaction term (Thickness $\times$ A β) was not significant ($p = .57$), and was removed from the model. Age ($p = .02$) also accounted for unique variance (9.7%), but sex did not ($p = .83$).⁵

These findings are based on individuals that had a small to large positive ability discrepancy (Range = 0.01 – 2.32). To test the extent that the relationship between ability discrepancy and AD brain markers was greater in older adults with a positive ability discrepancy compared with those with a negative ability discrepancy, we conducted the final multiple regression on the full sample ($n = 112$) with group (Positive and Negative Discrepancy) as a factor and interactions with each of the AD brain markers to predict ability discrepancy (Figure 2, bottom panel). We found a significant group $\times$ mean cortical thickness interaction ($\beta = 1.71$, $p = .045$), but not a significant group $\times$ mean cortical A β interaction ($\beta = 0.44$, $p = .42$). Follow-up partial correlations (controlling for age $\times$ sex) indicated that the relationship between ability discrepancy and cortical thickness was specific to the positive ability discrepancy group ($r(39) = -.37$, $p = .018$ and $r(28) = .08$, $p = .67$, for the positive and negative ability discrepancy group, respectively). This finding suggests that all ranges of ability discrepancy scores are associated with increased A β deposition, but only exaggerated ability scores (in the positive direction) are associated with declines in cortical thickness.

4.1 Discussion

The present study sought to assess whether a positive difference between crystallized and fluid ability in cognitively normal adults was associated with two brain markers of preclinical AD—cortical thinning and A β deposition. Results indicated that (a) decreased thickness and greater A β deposition in AD-related regions were associated with a larger discrepancy score; (b) both cortical thickness and A β deposition were significant and independent factors associated with a greater positive ability discrepancy score; (c) these

⁵Adding APOE status in the model did not change the significance of the results, nor was APOE status a significant factor ($p > .05$). Controlling for education changed the significance between ability discrepancy and A β in the anterior cingulate from $p = .050$ to $p = .055$, although education itself was not significant ($p > .05$). Conducting separate regression analyses adding interactions with age yielded no significant interactions with age (all p 's $> .16$).

relationships were significant in both positive and negative discrepancy groups for A β deposition, but only in the positive discrepancy group for cortical thickness; and (d) age was independently associated with ability discrepancy after accounting for cortical thickness and A β deposition.

The cortical thickness regions selected as ROIs have previously been found to be specific to mild AD in four independent samples by Dickerson and colleagues (2009). In Dickerson et al. (2009), cortical thickness was reduced in AD patients compared with cognitively-normal controls and was associated with the severity of cognitive symptoms in the AD patients. Moreover, cortical thickness in these regions also was negatively associated with an *in vivo* measure of A β deposition in cognitively-normal older adults (e.g., Bakkour et al., 2009; Dickerson et al., 2009). Our finding that cortical thinning in these same regions was associated with higher ability discrepancy scores suggests that ability discrepancy may be an early behavioral indicator of early stages of preclinical AD in currently normal adults. This relationship was only found in older adults with more exaggerated discrepancies in ability (i.e., the positive ability discrepancy group), suggesting that this marker is sensitive in later stages of preclinical AD, when neurodegeneration has already begun. We also report that, consistent with Dickerson et al. (2009), the relationship between ability discrepancy and thickness did not occur in primary visual cortex, providing specificity of the thickness effects to AD-sensitive regions. Although recent models of AD focus on hippocampal volume as the primary structural measure that declines in the cascade of events towards AD (e.g., Jack et al., 2012, 2013), the present findings support the notion that cortical thinning in these AD-related regions might be included as a marker of preclinical AD as well (e.g., Bakkour et al., 2009; Dickerson et al., 2009).

Next we turn to the findings regarding A β deposition. The presence of A β at autopsy is one requirement for a diagnosis of AD (McKhann et al., 2011). There is growing evidence that A β deposition in cognitively normal adults is associated with subtle fluid processing decline (e.g., Hedden et al., 2013; Rodrigue et al., 2012; Snitz et al., 2013; Wirth et al., 2013a, 2013b) and later is related to the progression to mild cognitive impairment (e.g., Blasko et al., 2008; Okello et al., 2009), resulting in the categorization of such individuals as having preclinical AD. In the present study, we report that a greater magnitude of ability discrepancy was consistently associated with more A β deposition. We found this relationship both in the positive and negative ability discrepancy groups, suggesting this marker is sensitive to both early and later stages of preclinical AD.

This A β effect on ability discrepancy was specific to regions associated with AD such as the precuneus (e.g., Braak & Braak, 1991), but was absent in the occipital cortex, a region that shows little accumulation of A β in the earliest stages of AD (Rodrigue, 2012; Vlassenko et al., 2012). This specificity nicely dovetails with the cortical thickness findings that also showed the same dissociation with the occipital cortex. The convergence of the cortical thickness and A β deposition findings strengthen evidence for the two markers together serving as a behavioral index of preclinical AD.

4.3 Ability Discrepancy Scores: Normal Aging or Neuropathology?

The results suggest that an ability discrepancy score might provide unique information, in the absence of expensive imaging data, regarding the increased likelihood that an individual is harboring A β and is already exhibiting signs of neurodegeneration. In the context of this conclusion, it is important to consider whether ability discrepancy is a specific indicator of neuropathology or merely a general characteristic of normal aging. There is some evidence that ability discrepancy increases with age (e.g., Eisdorfer et al., 1959; Rabbitt, 1993). It is well-recognized that cross-sectional studies of aging typically yield a decrease in fluid abilities from young adulthood into old age, while crystallized ability remains stable or even increases with age (e.g., Baltes, 1987; Park et al., 1996). Recently, an impressive study sampling over 48,000 adults found that performance on fluid measures such as processing speed peaked as early as late teens/early 20's, whereas crystallized abilities peaked later in the 50's (Hartshorne & Germine, 2015). These different peaks in performance, on the surface, suggest that ability discrepancies are characteristic of normal aging and may not confer important information regarding early stages of pathology.

However, there are two important reasons that the present findings support the use of a greater discrepancy score as a potential indicator of preclinical AD. First, many subjects in presumably "normal" samples will have latent neuropathology, including A β deposition, and are on an initial trajectory of pathological decline (cf. Sliwinski et al., 1996). In such cases, those individuals might actually drive the discrepancies between fluid and crystallized abilities found in other studies, rather than the cognitively-normal adults without latent neuropathology. Second, even if such discrepancies do exist in normal aging, the present results show that the *magnitude* of ability discrepancy might separate normal from pathological aging. Just as a moderate memory decline occurs almost universally with advanced age (e.g., Hertzog et al., 2003; Park et al., 1996) and a precipitous memory decline is diagnostic of AD, the same appears to be true for an ability discrepancy; a moderate ability discrepancy occurs with advanced age, but a precipitous increase in discrepancy is diagnostic of latent pathology and early neurodegeneration. The fact that we found the effects of A β deposition and cortical thickness on ability discrepancy after chronological age was statistically controlled further bolsters this idea.

We are unaware of any studies that have related AD risk factors to ability discrepancy, but the extant literature does show that patients with AD evidence greater ability discrepancies than cognitively-normal adults and these discrepancies increase as disease severity worsens (e.g., Dierckx et al 2008; Lezak, 1995; McCarthy et al., 2005). In addition, longitudinal evidence has shown that the combination of increases in A β and greater cortical thinning is associated with steeper declines in cognition (e.g., Dickerson & Wolk, 2012; Landau et al., 2012; Resnick et al., 2010) and greater likelihood to convert to AD (e.g., Dickerson et al., 2011; Julkunen et al., 2010; Landau et al., 2012; Okello et al., 2009; Querbes et al., 2009). Together, these sources of information converge on the conclusion that a large ability discrepancy is, at the least, an additional signal to researchers and clinicians that an individual harbors AD brain markers and therefore might be in the preclinical stages of AD. In the presence of cognitive complaints or other symptoms, further investigation into an individual's condition is warranted.

Using an ability discrepancy score has an important advantage over other measures of cognition such as memory. Because crystallized ability often is used as a premorbid measure of ability, the difference between fluid and crystallized ability could serve as a proxy for longitudinal decline in a cross-sectional sample. Thus, unlike cross-sectional measures of memory, intra-individual variability is not confounded with longitudinal decline. As more longitudinal data become available, we would predict that older adults with an exaggerated ability discrepancy would exhibit faster rates of cognitive decline and eventual clinical symptomatology of AD. However, until these predictions can be confirmed, it is premature to diagnose a cognitively-normal individual with a high ability discrepancy score as having preclinical AD, but it is more reasonable to consider a high discrepancy score as evidence for increased risk that an individual harbors A β deposition and cortical thinning in AD signature regions.

5.1 Conclusion

One of the most pressing questions in aging research is determining whether some older adults are on a pathological aging trajectory toward dementia or on a normal aging trajectory. The current study utilizes theoretical models of cognitive aging to direct attention toward discrepancies between fluid and crystallized abilities as a significant risk factor that has not been considered in the recent past. These discrepancies might be important in predicting who is more likely to be in the preclinical stages of AD in a cross-sectional sample.

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Highlights

- A much lower fluid than crystallized ability may signify preclinical dementia.
- A greater ability discrepancy was related to a thinner cortex and more amyloid.
- Cortical thickness and amyloid independently correlated with ability discrepancy.

Alzheimer Signature Regions in Cortical Thickness Analyses

Figure 1.

The nine AD signature regions were hand-traced in FreeSurfer and included a) anterior medial temporal lobe, b) inferior temporal gyrus, c) temporal pole, d) angular gyrus, e) superior frontal gyrus, f) superior parietal lobule, g) supramarginal gyrus, h) precuneus, and i) inferior frontal sulcus. The occipital cortex (j) was used as a control region.

Figure 2.

Scatterplot shows the relationship between AD brain markers and ability discrepancy in all participants as a function of ability discrepancy group (positive and negative). In the positive discrepancy group, discrepancies in ability (crystallized minus fluid) were associated with lower mean cortical thickness across brain regions previously shown to be vulnerable to AD (red), and elevated A β deposition (yellow). In the negative discrepancy group, discrepancies in ability were associated with greater A β deposition (purple), but no relationship was found for cortical thickness (green). Age and sex were controlled in all variables. Removing the subject with the lowest mean cortical thickness score did not change the strength of the correlation.

Table 1

Demographic Characteristics as a Function of Sample

	Full Sample	Ability Discrepancy > 0	Ability Discrepancy > 0 with PET	Ability Discrepancy = 0
N	112 (75 with PET)	60	43	52 (32 with PET)
Age (years)	75.58 (7.1)	76.28 (7.2)	76.14 (7.0)	74.77 (7.0)
Age Range	65–89	65–89	65–89	65–88
Sex (M/F)	41/71	29/31 ^a	23/20	12/40
Education (years)	16.13 (2.5)	16.75 (2.5) ^a	16.93 (2.5)	15.41 (2.4)
Education Range	12–21	12–21	12–21	12–21
MMSE Score	27.75 (1.3)	27.78 (1.2)	27.84 (1.2)	27.71 (1.3)
MMSE Range	26–30	26–30	26–30	26–30
Mean Cortical Thickness	2.69 (0.16)	2.70 (0.16)	2.71 (0.13)	2.68 (0.17)
Mean Cortical Thickness Range	2.00–3.03	2.00–3.03	2.39–3.03	2.15–2.95
Mean Cortical A β	1.23 (0.18)	–	1.25 (0.19)	1.22 (0.17)
Mean Cortical A β Range	0.97–1.77	–	1.07–1.77	0.97–1.58
N A β + (%)	31 (41%)	–	17 (40%)	14 (44%)
Discrepancy Score	–0.01 (1.0)	0.69 (0.6)	0.69 (0.6)	–0.82 (0.7)
Discrepancy Score Range	–2.97–2.32	0.01–2.32	0.01–2.32	–2.97–0.03

Notes. Standard deviation is in parentheses; Mean cortical thickness and A β deposition is calculated across all regions of interest;

^aSubjects with an ability discrepancy score greater than zero were more educated and were more likely to be male than those with a score zero or less (p 's < .01).

Table 2
Relationship Ability Discrepancy and Cortical A β across the Significant Regions of Interest

Factor	β	SE	Lower CI	Upper CI	p-value	η^2
Precuneus	.27	.089	.09	.45	.004	.19
Temporal Cortex	.12	.046	.03	.22	.011	.15
Posterior Cingulate	.18	.070	.03	.32	.016	.14
Anterior Cingulate	.19	.090	.006	.37	.044	.10

Notes. β = Standardized beta values; SE = Standard error; CI = Confidence intervals. Age and Sex were controlled.

Table 3

Effects of Chronological Age, Mean Cortical Aβ, and Mean Cortical Thickness in Multiple Regression Models Associated with Ability Discrepancy

Factor	β	<i>b</i>	<i>SE</i>	<i>Lower CI</i>	<i>Upper CI</i>	<i>p-value</i>
Sex	-.031	-.036	.17	-.37	.30	.83
Chronological Age	.35	.030	.012	.005	.055	.02
Mean Cortical Thickness	-.28	-1.27	.64	-2.56	.018	.05
Mean Cortical Aβ	.30	.67	.30	.059	1.29	.03

Notes. β = Standardized beta values; *b* = Unstandardized beta values; *SE* = Standard error; *CI* = Confidence intervals; the model explained a total of 37.2% of the variance in ability discrepancy.