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Joint associations of β -amyloidosis and cortical thickness with cognition

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Abstract

In 1164 cognitively unimpaired persons, ages 50-95 years, from the population-based Mayo Clinic Study of Aging, we examined the relationships of baseline cognition and cognitive changes across

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the full range of cortical thickness of an Alzheimer signature region of interest and global β -amyloid levels measured by PIB PET standardized uptake value ratio (SUVR).

In machine learning models accounting for both biomarkers simultaneously, worsening biomarker values were additive and associated with lower baseline global cognition and greater subsequent decline in global cognition. Associations between AD signature cortical thickness or PIB PET β -amyloid SUVR and baseline cognition were mainly linear. Lower AD signature cortical thickness values across the entire range of thickness predicted future decline in global cognitive scores, demonstrating its close relationship to cognitive functioning. PIB PET β -amyloid SUVR also predicted cognitive decline across its full range, even when cortical thickness was accounted for. PIB PET β -amyloid's relationship to cognitive decline was nonlinear, more prominent at lower β -amyloid levels and less prominent at higher β -amyloid levels

Graphical abstract

The figure shows the 3-dimensional relationship between brain β -amyloid levels, cortical thickness and change in global cognitive z-score in a cohort of cognitively unimpaired persons aged 70-79

Keywords

amyloid imaging; neurodegeneration biomarkers; structural MR imaging; Cognitive ageing; Alzheimer's disease

1. Introduction

Understanding the pathophysiology of Alzheimer's Disease (AD) has been greatly facilitated by the development of biomarkers. Studies of the relationship between β -amyloid positron emission tomography (PET) tracer levels and cognition in clinically normal persons generally show a modest inverse relationship (Villemagne et al., 2011; Hedden et al., 2013; Petersen et al., 2015; Insel et al., 2016; Donohue et al., 2017; Farrell et al., 2017). Measures of AD-related neurodegenerative processes such as cortical volume, cortical thickness or glucose metabolic rate are more consistently associated with cognition (Sabuncu et al., 2011;

Wirth et al., 2013a; Fjell et al., 2014; Jack et al., 2015; Weston et al., 2016). Examining associations of cognition with β -amyloid PET imaging markers and neurodegenerative imaging biomarkers individually has allowed for exploration of the full range of each feature, but fails to account for the important inter-relationships of the two. Apparent associations between one of the biomarkers could be largely driven by variance shared with the other biomarker (Becker et al., 2011). Because of the difficulty in manipulating two complex functions in a single model simultaneously, most approaches seeking to examine the role of cognition as a function of β -amyloid PET imaging markers and neurodegenerative imaging biomarkers have been performed by dichotomizing each as normal or abnormal (Chetelat et al., 2012; Wirth et al., 2013b; Mormino et al., 2014; Villeneuve et al., 2014; Mattsson et al., 2015). While categorical approaches are more tractable, large portions of the distribution of each biomarker conditioned on the presence of the other are left unexplored.

Based on recent models of the relationship between β -amyloidosis and neurodegeneration (Hyman 2011; Jack et al., 2013a; Bloom 2014; Musiek et al., 2015; Jagust 2016), we hypothesized that: (1) there would be additivity of elevated β -amyloid and declining cortical thickness for predicting level of cognitive functioning, and (2) cortical thickness would be a better predictor of future cognitive decline than would β -amyloid. There have been many studies that examined both β -amyloid biomarkers and markers of neurodegeneration in cognitively normal persons as well as those with mild cognitive impairment. Those studies have consistently found that those in whom both biomarkers were abnormal had lower cognition and a worse prognosis than those with either only one of those biomarkers abnormal or with neither biomarker abnormal (See (Jack et al., 2016) for a summary of published studies). Second, prior studies have suggested that neurodegenerative biomarker levels were more strongly associated with cognition than was β -amyloidosis (Becker et al., 2011; Chetelat et al., 2012; Wirth et al., 2013b; Mormino et al., 2014; Villeneuve et al., 2014; Mattsson et al., 2015; Vemuri et al., 2017a). Because no prior study, to our knowledge, examined the associations in a multi-dimensional manner, we wished to determine whether the joint relationships between β -amyloid and cortical thickness versus cognition were linear or non-linear. In the present analyses we applied a flexible machine-learning model to explore in a 3-dimensional space, the joint relationship between the continuous distributions of PET-derived β -amyloid deposition, MR-derived cortical thickness (as an imaging proxy for neurodegeneration) and cognition among cognitively unimpaired middle aged and elderly individuals drawn from a population-based study.

2. Methods

2.1. Participants

Cognitively unimpaired participants from the Mayo Clinic Study of Aging (MCSA) were included in this longitudinal study if they were 50 years of age or older, had cognitive testing, MRI and PIB-PET scans and had returned for one or more follow-up cognitive evaluations. Baseline was defined as a MCSA participant's first visit with cognitive testing and imaging.

The participants were adjudicated by a consensus panel as being cognitively unimpaired using previously described procedures (Petersen 2004; Roberts et al., 2008; Petersen et al., 2010; Roberts et al., 2012; Roberts et al., 2014). The consensus panel consisted of a physician who examined the participant and performed a brief mental status examination, a study coordinator who interviewed both the participant and a study partner, and a neuropsychologist.

The neuropsychological test battery consisted of 9 instruments (Roberts et al., 2008) that were grouped into four domains: *memory* (Logical Memory-II (delayed recall), Visual Reproduction-II (delayed recall) from the Wechsler Memory Scale-Revised (Wechsler 1987), and Auditory Verbal Learning Test (Ivnik et al., 1992)); *attention/executive* functioning (Trail Making Test B (Reitan 1958), Digit Symbol Substitution test from the Wechsler Adult Intelligence Scale-Revised (WAIS-R) (Wechsler 1981)); *language* (Boston Naming Test (Kaplan et al., 1978), Category Fluency (Lucas et al., 1998)); and *visuospatial* (Picture Completion and Block Design from the WAIS-R). Cognitive test scores were converted to z scores based on a reference cohort of clinically normal MCSA participants ages 50-89 enrolled between 2004-2012, and weighted to the Olmsted County population. Individual test z-scores were averaged to create a z-score for each of the 4 cognitive domains, and a global z-score was derived from the average of the 4 domain z-scores. We chose to use the global z-score to present our findings for data reduction purposes and because it generally reflected the key domains relevant to AD, namely memory and attention/executive.

2.2. Imaging

We took advantage of our prior work in selecting a set of regions that optimally distinguished persons in the AD pathway from those not in the pathway. Because of the computational intensity of our approach, we chose to limit our investigations to a single set of ROIs—albeit ones with demonstrated validity for the AD pathway—for each biomarker. That meant that we did not select the identical ROIs for the two biomarkers. This is an implicit acknowledgement that while cortical thickness has anatomic specificity for cognitive functions relevant to AD, β -amyloidosis may reflect more of a marker of network dysfunction.

PIB-PET imaging used methods previously described (Jack et al., 2017). A PIB PET scan consisted of four 5-minute dynamic frames acquired from 40–60 minutes after injection of ^{11}C -PIB. The PIB PET regions of interest (ROIs) were derived from an MR template generated from each participant based on an in-house modification of the AAL atlas (Tzourio-Mazoyer et al., 2002). Regional PIB uptake was defined as the median uptake across all voxels in an ROI. A global PIB standardized uptake value ratio (SUVR) was calculated from a group of target regions in both hemispheres including parietal, cingulate precuneus, prefrontal, orbito-frontal, temporal, anterior cingulate and posterior cingulate regions, with cerebellar crus serving as the reference region. This meta-ROI was based on our prior work (Jack et al., 2008), and has been validated neuropathologically (Murray et al., 2015). Target and reference regions were gray matter and white matter sharpened, and

partial volume correction was not used. The global PIB meta-ROI SUVR is denoted as PIB_{AD} .

Cortical thickness measurements have several attractive methodological features that have led us to prefer it over grey matter regional density (eg (Vemuri et al., 2009)). Thickness can be measured reliably with widely available software (Schwarz et al., 2016b), and it is not sensitive to head size (Jack et al., 2015). Cortical thickness was measured as previously described (Jack et al., 2017). Cortical thickness in an AD signature meta-ROI represented an area-weighted average of mean cortical thickness across both hemispheres generated from the following FreeSurfer (v5.3) ROIs: entorhinal, inferior temporal, middle temporal, and fusiform. These regions were previously selected on the basis of discriminating between AD dementia and clinically normal individuals (Whitwell et al., 2013; Schwarz et al., 2016b). The AD signature meta-ROI cortical thickness is referred to as TK_{AD} .

2.3. Statistical Analyses

Cognition was modeled as a function of current age, PIB_{AD} and TK_{AD} using a gradient boosting machines (GBM) model, also adjusting for sex, education, and the number of exposures to the cognitive test battery prior to baseline. The number of cognitive test exposures prior to the study baseline is relevant because of learning effects in unimpaired individuals (Machulda et al., 2013). GBM is a machine learning technique which allows for arbitrary non-linear and interaction effects which was particularly important in the 3-dimensional space we were modeling. GBM fits a very large number of binary classification trees and then averages the results. The approach makes no assumptions about the functional form of the relationships. A strength of this particular method is avoidance of overfitting (Friedman 2001). For these models we specified a monotonic relationship on age (increasing), PIB_{AD} (increasing), and TK_{AD} (decreasing), based on the expectation that their relationship with cognition should plateau or worsen, but not improve. Because some participants had undergone cognitive testing prior to the first PIB PET, we also accounted for the number of prior exposures to cognitive testing and specified the monotonicity as improving to reflect the expectation of a learning effect. The GBM models allowed for an interaction depth of 2. The model complexity (number of subtrees) was chosen using 8-fold cross-validation. GBM package version 2.2 was employed with the R statistical software version 3.3.1 (R Core Team (2016), R Foundation for Statistical Computing, Vienna).

We created two GBM models. From the first GBM model on baseline global z-score (COG_b), we obtained model-based predictions in relation to TK_{AD} and PIB_{AD} . The second GBM model used annual change in global z-score (ΔCOG) predictions made in relation to TK_{AD} and PIB_{AD} . To develop a metric for ΔCOG , we derived slopes for each participant based on their serial cognitive testing using a linear mixed model adjusting for age, education, prior cognitive testing, and sex with random subject-specific intercepts and slopes. A natural cubic spline on age and education allowed us to capture potential nonlinearities. By fitting the model on the time-scale we can consider the slopes as an estimate of annualized cognitive change. In order to decrease the noise in the slope measurements, we included up to 2 cognitive testing values that preceded the PIB PET scan to be used in the calculation of slope.

We predicted the marginal effects of the selected variables (PIB_{AD} , TK_{AD} , and age) over the other covariates of sex, education, and prior exposure to cognitive testing. The output of the GBM model was visualized as a 3-dimensional surface in which PIB_{AD} and TK_{AD} are represented in the x- and y- axes while predicted COG_b or COG is represented on the z-axis. MATLAB 2013a was used to generate the 3-D surface plots from the models (The MathWorks, Inc., Natick, Massachusetts). Because there were age effects, we found it useful to present different age strata as individual plots. In order to make it easier to recognize contour lines and to apply tests of reliable differences, we also generated 2-dimensional plots from the GBM model in which one imaging feature is represented on the x-axis and select values of the other imaging feature are depicted as a series of cubic smoothing spline curves representing fixed values of the other imaging feature.

Confidence limits for the contour plots and for the average difference between sets of lines were calculated using a bootstrap estimate. For each of 1000 bootstrap samples a random set of subjects was chosen, with replacement, and a new GBM model fit to the resulting data set, the subsequent curves derived, and results tabulated over the 1000 resamples.

Statistical tests were presented for descriptive purposes; none of the sets of statistical tests were therefore corrected for multiple testing.

3. Results

Table 1 shows the demographic and imaging features of the 1164 participants, all of whom were cognitively unimpaired by a consensus diagnostic process. By virtue of the stratified sampling design of the MCSA, the group represented the 4 decades from ages 50-90 years approximately equally, with balance between men and women. In the analyses of the relationships between cognition and biomarkers to follow, differences between women and men were limited to a simple shift in baseline global z-scores (higher in women), so that all analyses are presented with men and women combined.

The distribution of baseline global z-scores (COG_b) and the annualized change in global z-scores (COG) is shown in Figure 1, by age groups. Within the substantial variability of the relationship COG_b and COG , lower baseline scores were more likely to be associated with more annual decline. With advancing age, COG_b was generally lower and COG larger.

Figure 2 shows the distributions of baseline TK_{AD} and PIB_{AD} . The PIB_{AD} distribution was highly skewed, which is evident even in the logarithmic scale in Figure 2; the median value was 1.3 SUVR. TK_{AD} was more symmetrically distributed with a median of 2.7 mm. There was a strong age dependence of more abnormal values of TK_{AD} and PIB_{AD} . In the youngest decade of this population-based cohort, there were very few participants with $TK_{AD} < 2.67$ mm or $PIB_{AD} > 1.4$ (cut-points previously derived in our laboratory (Jack et al., 2017)), and no one with both. However, in the older 3 groups, the number of participants with abnormal values (ie, above the PIB_{AD} cutpoint and below the TK_{AD} cut-point) increased substantially. Those with higher PIB_{AD} were likely to have lower TK_{AD} . Correlations between PIB_{AD} and TK_{AD} were age-dependent: ages 50-59, $\rho=0.05$ (ns), 60-69, $\rho=-0.17$ ($p=0.002$), 70-79, $\rho=-0.13$ ($p=0.008$) and 80-89, $\rho=-0.10$, ($p=0.14$).

The relationship of PIB_{AD} and TK_{AD} to COG_b (Figure 3) was represented as a surface that tilted downwards in both x- and y-axes, reflecting the joint effect of both PIB_{AD} and TK_{AD} on cognition. There was a steepening of slope for COG_b at a TK_{AD} of approximately 2.5 to 2.6 mm. The bootstrap estimates of reliability showed that COG_b values were reliably worse at TK_{AD} of 2.3 or 2.5 mm than at thicker TK_{AD} values (Table 2). COG_b appeared linearly and inversely related to rising levels of PIB_{AD}. COG_b values at PIB_{AD} SUVR of 1.2 or 1.8 differed reliably only from those at the highest PIB_{AD} value; there was no difference in COG_b at the highest levels (2.1 vs 2.5) of PIB_{AD}. The two dimensional relationships are summarized in Figure 4 across all ages, and broken down by age decades in Supplemental Figure 1.

The relationship of PIB_{AD} and TK_{AD} to COG also showed that both biomarkers contributed to predicting decline in cognition (Figure 5). At more abnormal biomarker values, COG became larger (ie there was greater decline in cognition). The bootstrap estimates of reliability (Table 3) showed that COG declined monotonically from the highest TK_{AD} value to the lowest. PIB_{AD} also predicted COG across the full range of PIB_{AD}, but the reliability statistics showed that at PIB_{AD} 1.8 SUVR, more abnormal values of PIB_{AD} were associated with a deceleration of COG. The 2-dimensional relationships are summarized in Figure 6 across all ages, and broken down by age decades in Supplemental Figure 2.

The GBM model for COG_b generated a table of the relative contributions of variables. In the model used for prediction of baseline cognition and including age, education, cognitive test cycle (overall number of cognitive test exposures), sex, APOE e4 genotype, TK_{AD} and PIB_{AD}, age accounted for 40% of effects on cognition, education 23%, TK_{AD} 17% and PIB_{AD} 14%. Sex contributed only 3%, APOE e4 carriage 0.5% and cognitive test cycle 1%.

4. Discussion

Using a 3-dimensional model in a population-based sample of cognitively unimpaired individuals aged 50-90 years, we found that cortical thickness (of a group of regions most affected in AD) and global measure of brain β -amyloid (as measured by PIB PET) were both related to baseline cognition and changes in cognition. We confirmed our first hypothesis, that TK_{AD} and PIB_{AD} were additive with respect to cognitive function. While the relationship of TK_{AD} to COG was mainly linear, PIB_{AD} SUVR > 1.8 values predicted smaller values for COG compared to lower PIB_{AD} values. The differing shapes of the TK_{AD} $\times$ COG and PIB_{AD} $\times$ COG functions suggests, in accordance with our second hypothesis, that TK_{AD} may represent a more mechanistically proximate marker of the pathophysiology of cognitive decline than abnormal PIB_{AD}. Nonetheless, β -amyloid levels in the range observed in most of our cognitively unimpaired individuals demonstrated a relationship with declining cognition, even when cortical thickness was accounted for. Our findings are consistent with a model of sporadic late-onset AD in which lower levels of β -amyloid accelerate the deleterious effect of other neurodegenerative processes, which eventually become autonomous of β -amyloid, and then go on to cause cognitive decline (Hyman 2011; Jack et al., 2013a; Bloom 2014; Musiek et al., 2015; Jagust 2016).

Cortical thickness in an AD-meta-ROI (TK_{AD}) is a prototypical biomarker of neurodegeneration, based on evidence from antemortem clinical observations (Sabuncu et al., 2011; Wirth et al., 2013a; Jack et al., 2015; Weston et al., 2016); neuropathological observations (Gomez-Isla et al., 1997; Giannakopoulos et al., 2003; Sawa et al., 2009) and prediction of future dementia (Bakkour et al., 2009; Dickerson et al., 2012; Bakkour et al., 2013). Our current findings extend these prior studies by showing the quantitative relationships of cortical thickness to change in cognition in cognitively unimpaired people across the spectrum of β -amyloid levels. Visually (though not statistically), our modeling showed an increase in downward slope in COG at a TK_{AD} value around 2.6 mm, which corresponds to the cut-point that we had derived using different methodology (Jack et al., 2017). Both below and above that point, cognition was sensitive to TK_{AD} .

Despite its face validity, TK_{AD} is an incomplete biomarker for AD-related neurodegeneration. As shown elsewhere (Wirth et al., 2013a; Alexopoulos et al., 2014; Toledo et al., 2014; Caroli et al., 2015; Jack et al., 2015), cortical thickness has only moderate correlations with other measures of neurodegeneration, such as cerebrospinal fluid tau levels, hippocampal atrophy or glucose metabolic rate by PET. Our findings are specific to cortical thickness in one meta-ROI, and should not be mistaken as interchangeable with other biomarkers of neurodegeneration. Furthermore, loss of cortical thickness is not specific for AD, as other non-AD neurodegenerative (e.g., primary age related tauopathy (Josephs et al., 2017) or vascular processes (eg, overt cerebrovascular disease (Knopman et al., 2015b), metrics of cerebrovascular health (Leritz et al., 2011) or reduced cardiac output (Sabayan et al., 2015)) are associated with cortical thinning. Nonetheless, our findings demonstrate the linkage between declining cortical thickness in regions relevant to AD and cognition in cognitively unimpaired individuals.

The additive association of PIB_{AD} with TK_{AD} for cognition suggests that PIB_{AD} may be a proxy for neurodegenerative processes independent of cortical thickness. Elevated β -amyloidosis and neurodegeneration, broadly defined, are correlated (Dore et al., 2013; Jack et al., 2013a; Fortea et al., 2014; Villeneuve et al., 2014). It was this confound we sought to shed light on by evaluating PIB PET β -amyloid in the presence of cortical thickness. Indeed, PIB_{AD} in our GBM modeling was associated with cognition consistent with the observations in univariate analyses (Mormino et al., 2012; Hedden et al., 2013; Petersen et al., 2015; Villeneuve et al., 2015; Donohue et al., 2017). Others have also asserted that the relationship of cortical β -amyloidosis to cognition is through neurodegeneration (Becker et al., 2011; Chetelat et al., 2012; Wirth et al., 2013b; Mormino et al., 2014; Villeneuve et al., 2014; Mattsson et al., 2015). Elevated β -amyloid levels, even in cognitively unimpaired persons, are associated with higher tau PET signal (Vemuri et al., 2017b).

Our results showed a diminution of the association of cognitive decline with PIB_{AD} SUVR > 1.8, suggesting that higher PIB_{AD} levels are less strongly linked to neurodegeneration. We cannot exclude the possibility that associations between β -amyloidosis at high PIB_{AD} levels and cognition could be mediated by some other β -amyloid species not detected by PIB PET (e.g., oligomers (Esparza et al., 2013)). However, the dramatically long time period and slow rate over which β -amyloid accumulation occurs preclinically (Rowe et al., 2010; Jack et al., 2013b; Villemagne et al., 2013) could contribute to the de-linking of high levels of β -

amyloid and subsequent cognitive decline. It is likely that β -amyloid levels are an indicator of the maturity of neuronal dysfunction induced by non β -amyloid mechanisms.

Age had large effects on baseline cognition and on biomarker levels. As shown in Figure 1, very few study participants under age 60 years experienced cognitive decline. Figure 2 shows the increasing proportion of participants over age 70 years with $TK_{AD} < 2.5$ mm, in keeping with well recognized declines in cortical thickness that occur with aging (Salat et al., 2004; Raz et al., 2005; Fjell et al., 2014; Knopman et al., 2016). Age has a similarly substantial role in driving associations with cortical thickness in persons with AD dementia (Knopman et al., 2016). The same was true for the strong age dependence of elevated brain β -amyloid (Jack et al., 2014). The other confounding effect of age is that cerebrovascular disease and non-AD neurodegenerative diseases increase in prevalence with advancing age (Nelson et al., 2011); their presence could attenuate associations between cognition and β -amyloidosis or cortical thickness. Despite all of these age-dependent differences, the GBM model showed that the joint relationships between cortical thickness and brain β -amyloid to cognition were very similar across ages 50 and 90 years.

Our results show both the limitations of using dichotomous models to characterize cortical thickness and brain β -amyloid: within the “normal” and “abnormal” ranges of each biomarker, cognition varies over a substantial range. On the other hand, the modest amount of nonlinearity plus the clear demonstration of the additive effects of PIB_{AD} and TK_{AD} support the use of dichotomous models.

Strengths of our analysis included the large, well characterized cohort and the ability to implement the GBM model. In contrast to linear mixed models, GBM has a number of advantages, the two major ones being that GBM makes no assumptions about the functional form of relationship and that GBM does not result in over-fitting of the data. Its disadvantage is that as currently operationalized, the method requires a boot-strap method to generate measures of statistical reliability.

There were limitations to our analyses that were necessitated by our strategic focus on cognitively unimpaired individuals, as well as limitations imposed by the complexity of the processes we studied. Thus, there was a truncated range of cortical thickness, β -amyloid and cognitive function because our analyses included only unimpaired individuals. Second, we included individuals who were given consensus diagnoses of cognitively unimpaired. We strongly favor the use of consensus clinical diagnoses based on discussion among the clinicians who interacted with the participant because expert consensus diagnoses are an efficient way to include information from different sources into a single diagnosis. That meant that a small fraction of persons (4.5%) in our study group had global z-scores that were worse than -1.5, the commonly used but arbitrary cut score for cognitive impairment (Knopman et al., 2015a). We reran our analyses with excluding these individuals, and there were no differences in outcomes. We therefore retained these individuals in our analyses in order to maintain consistency with our prior and future publications. Third, we focused on global cognition rather than individual domains to demonstrate relationships. We have conducted analyses with memory or attention/executive cognitive domains, and found very similar relationships to those with global cognition. Furthermore, the current cortical

thickness meta-ROI is the one our laboratory is using in categorical analyses. Fourth, our period of follow-up was relatively short. While that attenuated effects of drop-out, short observation periods make determinations of cognitive changes in high-functioning persons noisy. We attempted to mitigate that problem by including cognitive test data from visits that preceded the initial imaging visit. Fifth, we chose to examine only one cortical thickness meta-ROI, rather than perform the analyses on either all ROI's or on all cortical voxels. Prior analyses demonstrated that the AD signature ROI that we used faithfully reflected volumetric changes in persons in the AD pathway (Whitwell et al., 2013; Schwarz et al., 2016b).

Finally, we did not include tau PET in our analyses. Although regional tau PET and cortical thickness are strongly correlated in persons with AD dementia (Xia et al., 2017), the low tau PET signal outside of the medial temporal lobe in cognitively unimpaired individuals (Johnson et al., 2015; Brier et al., 2016; Cho et al., 2016; Ossenkoppele et al., 2016; Scholl et al., 2016; Schwarz et al., 2016a) will present unique challenges to modeling that are beyond the scope of the current analyses.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

Predicted “baseline” cognition

global z-score (COG_b), Annual Change in global z-score (COG), cortical thickness measured in an AD signature meta-ROI (TK_{AD}).

Pittsburgh Compound B Positron emission tomography (PIB PET)

Standardized uptake value ratio (SUVR), PIB PET SUVR in regions associated with β -amyloid (PIB_{AD})

Key points

PIB PET and cortical thickness were analyzed in cognitively unimpaired individuals

Cortical thickness was associated with cognition and cognitive decline

PIB PET was associated with cognition, even with cortical thickness in model

Continuous modeling supports the use of dichotomous categorization of biomarker status.

Figure 1.

The distribution of baseline global cognitive z-scores (x-axis) and the annualized change in global cognitive z-scores (y-axis) is shown by age groups: 50-59, 60-69, 70-79 and 80-89 years. For purposes of visual display, the change values were calculated from a linear mixed effects model. We modeled $\log(\text{global z-score})$ to estimate change expressed as percentage per year. The overall mean (dashed lines) and medial (dotted lines) values are indicated.

Figure 2.

The joint distribution of PiB_{AD} and TK_{AD} by decade of age. The scatterplot shows global β -amyloid in PiB SUVR units (PiB_{AD}) on the x-axis and AD signature cortical thickness (TK_{AD}) in millimeters at baseline on the y-axis, at baseline by decades of age: 50-59, 60-69, 70-79 and 80-89 years. PiB_{AD} is displayed on a logarithmic scale because of its highly skewed distribution. The overall mean (dashed lines) and medial (dotted lines) values are indicated.

Figure 3.

Predicted average “baseline” cognitive global z-score (COG_b) from the GBM model by decade of age. (A) Three dimensional plot of PIB_{AD} (x-axis), TK_{AD} (y-axis) and COG_b (z-axis) for participants in the age ranges of 50-59, 60-69, 70-79 and 80-89 years. The color code to the right of each figure depicts the level of COG_b. The surfaces are truncated according to the range of PIB_{AD} and TK_{AD} values that were found in each decade as shown in Figure 2.

Figure 4.

Two dimensional renderings show (A) TK_{AD} (y-axis) by COG_b (z-axis) with 4 levels of PIB_{AD} : PIB SUVR values of 1.2, 1.8, 2.1 and 2.5; and (B) PIB_{AD} (x-axis) by COG_b (z-axis) with 4 levels of TK_{AD} : cortical thickness in mm: 3, 2.7, 2.5 and 2.3. The curves are combined across ages and on the right hand side of each figure, a bar coding scheme summarizes the reliability statistics (see Table 2 for means and confidence intervals of pairwise differences). The 2-dimensional renderings for each age group are shown in Supplementary Figure 1.

Figure 5.

Predicted average annual change in cognitive global z-score (COG) from the GBM model by decade of age. COG is a slope estimate calculated for each participant based on their serial cognitive testing using linear mixed models to represent annualized cognitive change. (A) Three dimensional plot of PIB_{AD} (x-axis), TK_{AD} (y-axis) and COG (z-axis) for participants in the age ranges of 50-59, 60-69, 70-79 and 80-89. The color code to the right of each figure quantitates COG. The surfaces are truncated according to the range of PIB_{AD} and TK_{AD} values that were found in each decade as shown in Figure 2.

Figure 6.

Two dimensional renderings show (A) TK_{AD} (y-axis) by COG (z-axis) with 4 levels of PIB_{AD} : PIB SUVR values of 1.2, 1.8, 2.1 and 2.5; and (B) PIB_{AD} (x-axis) by COG (z-axis) with 4 levels of TK_{AD} : cortical thickness in mm: 3, 2.7, 2.5 and 2.3. The curves are combined across ages and on the right hand side of each figure, a bar coding scheme shows the reliability statistics (see Table 3 for means and confidence intervals of pair-wise differences). The 2-dimensional renderings for each age group are shown in Supplementary Figure 1

Table 1
Demographic and Imaging Characteristics of MCSA Participants who were Cognitively Unimpaired at Baseline

Feature	Result
No. of participants	1164 *
Age, years mean (SD)	70 (10)
median (IQR), (range)	71 (63, 77), (51 to 95)
Sex, male, no. (%)	611 (52%)
APOE ε4 carrier, no. (%)	316 (28%)
Education, years, mean (SD)	15 (3)
Number (%) of participants by number of exposures to cognitive testing prior to baseline imaging visit	
0	605 (52%)
1	255 (22%)
2+	304 (26%)
Global PIB SUVR mean (SD)	1.5 (0.3)
median (IQR), range	1.3 (1.3, 1.5), 1.0 to 3.2
AD Signature thickness mean (SD)	2.7 (0.1)
median (IQR), (range)	2.7 (2.6, 2.8), (2.2 to 3.1)
Time in study, years mean (SD)	3.1 (1.7)
median (IQR), (range)	2.6 (1.4, 4.3), (1.0 to 7.1)
Baseline MRI scan date range	Feb-2005 to Nov-2014
Baseline PIB PET scan date range	Jan-2006 to Nov-2014
Last follow-up date range	Oct-2007 to Feb-2016

* 1200 participants imaged of whom 36 lacked a usable baseline global z-score

SD=standard deviation; IQR=interquartile range; SUVR= Standardized uptake value ratio; PIB= Pittsburgh Compound B

Table 2
Differences in predicted Cognition according to different levels of TK_{AD} and PIB_{AD}, from 1000 replications with replacement. Values across age groups are averaged

Thickness	PiB	Mean (SD)	95% Confidence Interval	P-value
2.3 v 2.5	fixed	-0.579 (0.144)	(-0.86, -0.30)	<0.001
2.3 v 2.7	fixed	-0.870 (0.173)	(-1.21, -0.53)	<0.001
2.3 v 3	fixed	-1.156 (0.201)	(-1.55, -0.76)	<0.001
2.5 v 2.7	fixed	-0.291 (0.102)	(-0.49, -0.09)	0.004
2.5 v 3	fixed	-0.576 (0.151)	(-0.87, -0.28)	<0.001
2.7 v 3	fixed	-0.285 (0.113)	(-0.51, -0.06)	0.01
fixed	1.2 v 1.8	0.228 (0.084)	(0.06, 0.39)	0.007
fixed	1.2 v 2.1	0.423 (0.135)	(0.16, 0.69)	0.002
fixed	1.2 v 2.5	0.629 (0.159)	(0.32, 0.94)	<0.001
fixed	1.8 v 2.1	0.195 (0.099)	(0.00, 0.39)	0.05
fixed	1.8 v 2.5	0.401 (0.129)	(0.15, 0.65)	0.002
fixed	2.1 v 2.5	0.206 (0.104)	(0.00, 0.41)	0.05

Table 3
Differences in Estimates of Change in Cognition according to different levels of TK_{AD} and
PIB_{AD}, from 1000 replications with replacement

Thickness	PiB	Mean (SD)	95% Confidence Interval	P-value
2.3 v 2.5	fixed	-0.037 (0.019)	(-0.07, 0.00)	0.06
2.3 v 2.7	fixed	-0.056 (0.026)	(-0.11, -0.01)	0.03
2.3 v 3	fixed	-0.074 (0.027)	(-0.13, -0.02)	0.005
2.5 v 2.7	fixed	-0.020 (0.013)	(-0.05, 0.01)	0.14
2.5 v 3	fixed	-0.038 (0.015)	(-0.07, -0.01)	0.01
2.7 v 3	fixed	-0.018 (0.007)	(-0.03, -0.00)	0.009
fixed	1.2 v 1.8	0.036 (0.013)	(0.01, 0.06)	0.006
fixed	1.2 v 2.1	0.050 (0.016)	(0.02, 0.08)	0.002
fixed	1.2 v 2.5	0.066 (0.018)	(0.03, 0.10)	<0.001
fixed	1.8 v 2.1	0.014 (0.009)	(-0.00, 0.03)	0.13
fixed	1.8 v 2.5	0.030 (0.013)	(0.00, 0.06)	0.03
fixed	2.1 v 2.5	0.017 (0.012)	(-0.01, 0.04)	0.15