Supplementary Online Content


eMethods 1. Determination of ND Status

eMethods 2. Hierarchical Linear Mixed Models

eFigure 1. Adjustment of Hippocampus Volume by Estimated Intracranial Volume

eFigure 2. Distribution of ND Markers in CNs

eFigure 3. Distribution of ND Markers in AD

eFigure 4. Association Between ND and Aβ Status

eFigure 5. ND vs Continuous Levels of Aβ

eFigure 6. Change in Cognition vs Continuous Levels of Aβ

eTable. Longitudinal Mixed Models Predicting Global Cognition

This supplementary material has been provided by the authors to give readers additional information about their work.
eMethods 1: Determination of ND status

Neurodegeneration (ND) status was determined based on aHV and MetaROI FDG, using an independent sample of 98 ADNI AD patients with both aHV and MetaROI FDG values available (median age=76, interquartile range=71 to 81). ADNI aHV and MetaROI FDG values were directly downloaded from the ADNI website. To ensure comparability between aHV and MetaROI FDG values across HABS and ADNI, we first compared each measure’s distribution between our 166 HABS CNs and 196 ADNI CNs that had both aHV and MetaROI FDG values available (median age=76, interquartile range=71 to 81). We found no difference between these distributions (eFigures 4-5), suggesting that a cut off derived using ADNI AD patients could be applied to HABS CNs.

Cut offs were derived for each ND marker separately by identifying the value corresponding to 90% sensitivity within the AD patients, yielding cut off values of 1.249 for the MetaROI FDG and 6723mm³ for aHV (eFigure 6). CNs were considered ND+ if they fell below the cut off value for either ND marker. Of the 166 CNs from HABS, 100 were negative on both markers, 16 were positive on both markers, 35 were positive on FDG only, and 15 were positive on aHV only.
eMethods 2: Hierarchical Linear Mixed Models

Two linear mixed regression models were implemented to investigate contributions of ND and Aβ status to longitudinal cognitive change in each neuropsychological composite score:

(1) Interactions of ND with time and Aβ with time in the same model

\[ \text{Score}_{ij} = \beta_1 \beta_2 \text{Age}_i + \beta_3 \text{Education}_i + \beta_4 \text{Sex}_i + \beta_5 \text{Time}_{ij} + [\beta_6 \text{Age}_i \times \text{Time}_{ij}] + [\beta_7 \text{Education}_i \times \text{Time}_{ij}] + [\beta_8 \text{Sex}_i \times \text{Time}_{ij}] + \beta_9 \text{Status}_i + [\beta_{10} \text{ND Status}_i \times \text{Time}_{ij}] + \beta_{11} \text{Aβ Status}_i + [\beta_{12} \text{Aβ Status}_i \times \text{Time}_{ij}] + b_{1i} \]

(2) Joint interactions of ND and Aβ with time added to model 1

\[ \text{Score}_{ij} = \beta_1 + \beta_2 \text{Age}_i + \beta_3 \text{Education}_i + \beta_4 \text{Sex}_i + \beta_5 \text{Time}_{ij} + [\beta_6 \text{Age}_i \times \text{Time}_{ij}] + [\beta_7 \text{Education}_i \times \text{Time}_{ij}] + [\beta_8 \text{Gender}_i \times \text{Time}_{ij}] + \beta_9 \text{Status}_i + [\beta_{10} \text{ND Status}_i \times \text{Time}_{ij}] + \beta_{11} \text{Aβ Status}_i + [\beta_{12} \text{Aβ Status}_i \times \text{ND Status}_i \times \text{Time}_{ij}] + b_{1i} \]

\[ \text{Score}_{ij} = \text{CN's score at each testing session} \]
\[ \text{Education}_i = \text{Years of education} \]
\[ \text{Age}_i = \text{CN's age at neuropsychological testing session 1} \]
\[ \text{Time}_{ij} = \text{Time at testing session, relative to neuropsychological testing session 1} \]
\[ \text{Aβ Status}_i = \text{High or Low Aβ} \]
\[ \text{ND Status}_i = \text{ND+ or ND-} \]
\[ b_{1i} = \text{random intercept for each subject} \]
**eFigure 1: Adjustment of hippocampus volume by estimated intracranial volume.** Total hippocampus volume (HV) plotted by estimated total estimated intracranial volume (eTIV) for HABS (yellow) and ADNI (red). The relationship between HV and eTIV was similar for both groups [HABS (yellow line): HV=4562+0.001946*(eTIV); ADNI (red line): HV=3974+0.002332*(eTIV)]. Therefore, HABS and ADNI CN data were combined to derive a single linear equation to be used to adjust all HV (combined=black line): HV=4281+0.00213*(eTIV)). Hippocampus adjustment was performed for each subject using the following formula: aHV = HV—0.00213 (eTIV —mean eTIV), with mean eTIV reflecting the mean of the combined sample of ADNI CN and HAB CNs (1483839mm³).
eFigure 2: Distribution of ND Markers in CNs. Distributions of A) MetaROI FDG and B) aHV for ADNI and HABS CNs. There was no significant difference between cohorts in either marker of ND (p-values>0.71), suggesting that cut off derived using the ADNI AD sample can be applied to the HABS CN sample. AD-derived cut offs for each marker are overlaid in red.
**eFigure 3: Distribution of ND Markers in AD.** Distributions of A) Landau FDG and B) aHV for ADNI AD patients. Cut offs corresponding to 90% sensitivity for each marker are shown in red. By definition, 10% of AD subjects from this distribution will fall above the cut off value for each marker.
eFigure 4: Association between ND and A\(\beta\) status. Predicted probabilities for being classified as ND+ is plotted by age and A\(\beta\) status for females with 16 years of education. 95% confidence intervals are plotted as dashed lines.
**eFigure 5: ND vs continuous levels of Aβ.** The association between ND and continuous levels of Aβ within A) Aβ- and B) Aβ+ groups. A trend level relationship was observed within the Aβ- group, whereas no relationship was present within Aβ+ CNs. Note that spacing differs on each x-axis (a larger range of Aβ values is present within the Aβ+ group). 95% confidence intervals are plotted as dashed lines.
**eFigure 6: Change in cognition vs continuous levels of Aβ.** Each CN’s trajectory of raw cognitive composite scores is plotted (y-axis), anchored by their global PIB value (x-axis). CNs with negative slopes are colored red (indicating decline over time), whereas CNs with positive slopes are colored green (indicating improvement over time). The PIB cut off of 1.196 used to separate CNs into Aβ- and Aβ+ groups is indicated by the dashed line. This plot highlights the association between continuous levels of Aβ and cognitive change in Aβ- CNs but not Aβ+ CNs.
<table>
<thead>
<tr>
<th>Contrast</th>
<th>Estimate (SE)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model 1: Time x ND+ and Time x Aβ+ as independent predictors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time</td>
<td>0.1084 (0.0183)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Time x Age</td>
<td>-0.0010 (0.0019)</td>
<td>0.592</td>
</tr>
<tr>
<td>Time x Male Sex</td>
<td>0.0072 (0.0218)</td>
<td>0.741</td>
</tr>
<tr>
<td>Time x Education</td>
<td>0.0051 (0.0041)</td>
<td>0.218</td>
</tr>
<tr>
<td>Time x ND+</td>
<td>-0.1060 (0.0246)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Time x Aβ+</td>
<td>-0.0915 (0.0240)</td>
<td>0.0002</td>
</tr>
<tr>
<td>Model 2: Time x Aβ+ x ND+ term added to Model 1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time x Aβ+ x ND+</td>
<td>-0.1080 (0.0522)</td>
<td>0.039</td>
</tr>
</tbody>
</table>

eTable: Longitudinal mixed models predicting global cognition. Age was centered at 74 years, and education at 16. Thus, the time term can be interpreted as the rate of change for a 74 year old female with 16 years of education that is Aβ- and ND-. 

© 2014 American Medical Association. All rights reserved. 10