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The role of clusterin in amyloid- β associated neurodegeneration

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Abstract

Importance—Converging evidence indicates that clusterin, a chaperone glycoprotein, influences Alzheimer's disease (AD) neurodegeneration. However, the precise role of clusterin in AD pathogenesis is still not well understood.

Objective—To elucidate the relationship between clusterin, amyloid- β (A β), p-tau, and rate of brain atrophy over time among non-demented older individuals.

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Dr. Linda K. McEvoy's spouse is CEO of CorTechs Labs, Inc.

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Design—A longitudinal cohort of cognitively normal older participants (HC) and individuals with mild cognitive impairment (MCI) assessed with baseline lumbar puncture and longitudinal structural MRI.

Setting—Research centers across the United States and Canada.

Participants—We examined 241 non-demented older individuals (91 participants with a Clinical Dementia Rating (CDR) of 0 and 150 individuals with a CDR of 0.5).

Main Outcome Measures—Using linear mixed effects models, we investigated interactions between CSF clusterin, CSF A β_{1-42} and CSF p-tau_{181p} on atrophy rate of the entorhinal cortex and hippocampus.

Results—Across all participants, we found a significant interaction between CSF clusterin and CSF A β_{1-42} on entorhinal cortex atrophy rate, but not on hippocampal atrophy rate. CSF clusterin was associated with entorhinal cortex atrophy rate among CSF A β_{1-42} positive individuals, but not among CSF A β_{1-42} negative individuals. In secondary analyses, we found significant interactions between CSF A β_{1-42} and CSF clusterin and CSF A β_{1-42} and CSF p-tau_{181p} on entorhinal cortex atrophy rate. We found similar results in subgroup analyses within the MCI and HC cohorts.

Conclusions and Relevance—In non-demented older individuals, A β -associated volume loss occurs in the presence of elevated clusterin. The effect of clusterin on A β -associated brain atrophy is not confounded or explained by p-tau. These findings implicate a potentially important role for clusterin in the earliest stages of the AD neurodegenerative process and suggest independent effects of clusterin and p-tau on A β -associated volume loss.

Introduction

Converging genetic, cellular, molecular and biomarker evidence indicates that clusterin, a chaperone glycoprotein also known as apolipoprotein J, influences Alzheimer's disease (AD) pathogenesis. Clusterin levels are increased in AD-affected brain regions¹⁻³ and elevated in the cerebrospinal fluid (CSF) of AD patients.⁴ Several genome-wide association studies have identified clusterin gene variants as AD susceptibility loci.⁵ Elevated plasma clusterin levels are associated with disease prevalence and severity of AD⁶ and with increased amyloid deposition and brain atrophy.⁷ Still, experimental findings suggest that clusterin increases both amyloid- β (A β) aggregation and clearance,⁵ raising the question of whether elevated clusterin levels are beneficial or harmful.

In humans, structural MRI and CSF biomarkers allow for the indirect assessment of cellular changes underlying AD *in vivo*. Structural MRI provides measures of brain atrophy, which includes loss of dendrites, synapses⁸ and neurons.⁹ Low CSF levels of A β strongly correlate with intracranial amyloid plaques and high concentrations of CSF phospho-tau (p-tau) correlate with tau-associated neurofibrillary tangles.¹⁰ Here, we investigated whether interactions between increased CSF clusterin and decreased CSF A β_{1-42} and increased CSF clusterin and increased CSF p-tau_{181p} are associated with increased brain atrophy over time in non-demented older individuals at risk for developing AD. Building upon recent evidence that A β -associated volume loss occurs in the presence of elevated p-tau,¹¹⁻¹⁵ we also examined the additive effect on volume loss of an interaction between increased CSF

clusterin and decreased CSF A β ₁₋₄₂ in the presence of an interaction between increased CSF p-tau_{181p} and decreased CSF A β ₁₋₄₂.

Subjects and Methods

A total of 313 non-demented older participants from the Alzheimer's Disease Neuroimaging Initiative (ADNI) underwent longitudinal MRI imaging and CSF lumbar puncture. Of these, we restricted analyses to 91 cognitively normal older adults (HC) and 150 individuals with amnesic mild cognitive impairment (MCI) who had quality-assured baseline and at least one follow-up MRI scan (6 months to 3.5 years, 4% with six month follow-up, 8% with twelve month follow-up, 11% with eighteen month follow-up, 42% with twenty-four month follow-up, and 35% with thirty-six month follow-up) (Table 1)(for additional details see Supplemental Material).

We examined baseline CSF clusterin levels derived from a multiplex-based immunoassay panel based on Luminex immunoassay technology developed by Rules Based Medicine (MyriadRBM).¹⁶ In brief, the ADNI Biomarker Core assessed CSF samples (159 analytes measured by the MyriadRBM) from a total of 327 individuals. These baseline CSF samples had matching aliquots from one year allowing evaluation of test-retest to determine analyte precision. For each analyte, a multi-step quality control procedure was implemented which included evaluation of CSF signal characteristics (high, medium and low), assessment for normality of distribution (not-normal values were transformed) and need for imputation (data with missing values and high/low values) (for additional details on CSF quality control procedures, please see reference 16). We used the quality-controlled values for CSF clusterin in all analyses. Using previously proposed CSF cutoffs¹⁷ we examined baseline CSF A β ₁₋₄₂ and p-tau_{181p} levels and classified participants based on low (<192 pg/ml, "positive") and high (>192 pg/ml, "negative") A β ₁₋₄₂ levels, and high (>23 pg/ml, "positive") and low (<23 pg/ml, "negative") p-tau_{181p} levels. As previously described,¹⁷ CSF A β ₁₋₄₂ and p-tau_{181p} were measured using the multiplex xMAP Luminex platform (Luminex Corp, Austin TX) with Innogenetics (INNOBIA AlzBio3, Ghent, Belgium) immunoassay kit-based reagents.

We analyzed 977 T₁-weighted MRI scans using a modified version of the FreeSurfer software package (<http://surfer.nmr.mgh.harvard.edu>). These analysis procedures have been applied, validated, and described in detail in a number of publications.¹⁸ The MRI scans were reviewed for quality, automatically corrected for spatial distortion due to gradient nonlinearity, registered and averaged to improve the signal to noise ratio. The cortical surface was automatically reconstructed and gray matter thickness measurements were obtained at each point across the cortical mantle. Here, we primarily focused on the entorhinal cortex and hippocampus, two medial temporal lobe regions that are affected in the earliest stages of AD¹⁹ (Figure 1). We additionally evaluated the amygdala and middle temporal gyrus, two temporal lobe regions that are also affected in AD.¹⁹ The entorhinal cortex and middle temporal gyrus were delineated using an automated, surface-based cortical parcellation atlas.²⁰ The hippocampus and amygdala were identified using an automated, subcortical segmentation atlas.²¹ For the analysis of the longitudinal gray matter volume change, we used Quarc (quantitative anatomical regional change), a recently

developed method from our laboratory.^{22,23} Briefly, each participant's follow-up image was affine-aligned to the baseline scan and locally intensity-normalized. Using nonlinear registration, a deformation field was then calculated to locally register the images with high fidelity for both large- and small-scale structures, including those with low boundary contrast. From the deformation field, a volume-change field (atrophy) can directly be calculated. Using the baseline subcortical and cortical ROIs, the volume-change field can be sampled at points across the cortical surface or averaged over subcortical regions to give the percent volume change for those ROIs (Figure 1).

We asked whether statistical interactions between CSF clusterin and CSF A β_{1-42} and between CSF clusterin and CSF p-tau_{181p} are associated with brain atrophy over time (Figure 2). Using a linear mixed effects model, we concurrently examined the main and interactive effects of CSF clusterin, CSF A β_{1-42} , and CSF p-tau_{181p} on atrophy rate of the temporal lobe regions (entorhinal cortex, hippocampus, amygdala, and middle temporal gyrus), co-varying for age, sex, carrier status for the $\epsilon 4$ allele of apolipoprotein E (APOE $\epsilon 4$), group status (MCI vs. HC), and disease severity (assessed using CDR-Sum of Boxes, a composite measure that characterizes six domains of cognitive and functional performance²⁴). Of note, the main effects of all variables (the three CSF analytes and all covariates) were also included in these analyses. For brevity, we focus below on the effects of interest. Specifically:

$$\begin{aligned} \Delta v = & \beta_0 + \beta_1 \Delta t + \beta_2 \text{CSF_clusterin} \times \Delta t \\ & + \beta_3 \text{CSF_A}\beta_{1-42}\text{-status} \times \Delta t \\ & + \beta_4 \text{CSF_p} \\ & \quad - \text{tau}_{181p}\text{-status} \times \Delta t \\ & + \beta_5 [\text{CSF_clusterin} \times \text{CSF_A}\beta_{1-42}\text{-status} \times \Delta t] + \beta_6 [\text{CSF_clusterin} \times \text{CSF_p} \\ & \quad - \text{tau}_{181p}\text{-status} \times \Delta t] + \text{covariates} \times \Delta t + \varepsilon \end{aligned} \tag{Equation 1}$$

where v = entorhinal cortex or hippocampal atrophy (millimeters³) and t = change in time from baseline MRI scan (years). Intercept and slope (β_0 and β_1) were entered as mixed effects.

Prior findings from our laboratory indicate that A β -associated neurodegeneration occurs in the presence of elevated p-tau.¹¹⁻¹³ To test whether the effect of clusterin on A β -associated neurodegeneration is independent from the effect of p-tau on A β -associated neurodegeneration, we performed secondary analyses and fit the following linear mixed effects model:

$$\begin{aligned}
 \Delta v = & \beta_0 + \beta_1 \Delta t \\
 & + \beta \text{CSF_clusterin} \times \Delta t \\
 & + \beta \text{CSF_A}\beta_{1-42}\text{-status} \times \Delta t \\
 & + \beta \text{CSF_p} \\
 & - \text{tau}_{181p}\text{-status} \times \Delta t \\
 & + \beta [\text{CSF_clusterin} \times \text{CSF_A}\beta_{1-42}\text{-status} \times \Delta t] + \beta [\text{CSF_p} \\
 & - \text{tau}_{181p}\text{-status} \times \text{CSF_A}\beta_{1-42}\text{-status} \times \Delta t] + \text{covariates} \times \Delta t + \epsilon
 \end{aligned}
 \tag{Equation 2}$$

where v = entorhinal cortex or hippocampal atrophy (millimeters³) and t = change in time from baseline MRI scan (years). Intercept and slope (β_0 and β_1) were entered as mixed effects. We co-varied for age, sex, APOE $\epsilon 4$ carrier status, group status (MCI vs. HC), and CDR-Sum of Boxes. The main effects of all variables (the three CSF analytes and all covariates) were also included in these analyses.

To evaluate whether the above described effects of interest between CSF clusterin, CSF $A\beta_{1-42}$ status, and CSF p-tau_{181p} status were different between the MCI and HC cohorts, we performed additional analyses fitting group status (MCI vs HC) as an interaction with change in time from baseline MRI scan (t or time) and the main interactive effects. The main effects of all variables (the three CSF analytes and all covariates) were also included in these analyses.

Results

Results from the primary analyses revealed a significant three-way interaction between CSF clusterin, CSF $A\beta_{1-42}$ status and time ($\beta_5 = -0.032$, standard error (SE) = 0.01, $p = 0.01$) indicating that increased CSF clusterin and positive CSF $A\beta_{1-42}$ status were associated with an elevated entorhinal cortex atrophy rate. In contrast, the interaction between CSF clusterin, CSF p-tau_{181p} status and time was not significant ($\beta_6 = 0.01$, SE = 0.01, $p = 0.54$). With both of these three-way interaction terms in the model, only the effect of CSF $A\beta_{1-42}$ status by time was significantly associated with entorhinal atrophy cortex rate ($\beta_3 = 0.04$, SE = 0.02, $p = 0.02$); the effect of time by CSF clusterin and CSF p-tau_{181p} status was not associated with entorhinal cortex atrophy rate. None of the main effects of CSF clusterin, CSF $A\beta_{1-42}$ status and CSF p-tau_{181p} status were significant.

Follow-up analyses examining the three way interactions demonstrated that the CSF clusterin by time interaction was significantly associated with entorhinal cortex atrophy only among CSF $A\beta_{1-42}$ positive individuals (β -coefficient = -0.20, SE = 0.007, $p = 0.008$) but not among CSF $A\beta_{1-42}$ negative individuals (β -coefficient = 0.007, SE = 0.008, $p = 0.36$) (Figure 3a). In contrast, there was no significant CSF clusterin by time interaction on entorhinal cortex atrophy rate either among CSF p-tau_{181p} positive (β -coefficient = -0.01, SE = 0.01, $p = 0.28$) or among CSF p-tau_{181p} negative individuals (β -coefficient = 0.005, SE = 0.007, $p = 0.49$) (Figure 3b). Similar results were obtained when CSF p-tau_{181p} and CSF $A\beta_{1-42}$ were treated as continuous rather than categorical variables (see Supplemental Results).

To determine whether these effects differed by group status (MCI vs HC), we performed additional analyses fitting interactions between group status and the main effects of interest (for additional details see Subjects and Methods). These analyses showed a significant interaction between group status, time, CSF clusterin and CSF A β_{1-42} status on entorhinal cortex atrophy rate (β -coefficient = -0.031, SE = 0.009, p-value = 0.001). Follow-up subgroup analyses revealed that although both the MCI and HC cohorts demonstrated a significant three-way interaction of time, CSF clusterin and CSF A β_{1-42} status on entorhinal cortex atrophy rate, whereby entorhinal cortex volume loss was significantly associated with CSF clusterin only among CSF A β_{1-42} positive individuals, the slopes of change over time were steeper among the MCI cohort than the HC cohort (MCI: β -coefficient = -0.076, SE = 0.03, p = 0.008; HC: β -coefficient = -0.047, SE = 0.01, p = 0.001). The interaction between group status, time, CSF clusterin and CSF p-tau $_{181p}$ status was not significant. Similar results were obtained when CSF p-tau $_{181p}$ and CSF A β_{1-42} were treated as continuous rather than categorical variables (see Supplemental Results).

To determine whether similar associations could be observed in other temporal lobe areas affected later in the disease process, we repeated these analyses using atrophy rates of the hippocampus, amygdala, and middle temporal gyrus. Results revealed no significant interactions of CSF clusterin, CSF A β_{1-42} status, and time on atrophy rate of the hippocampus (β -coefficient = -0.013, SE = 0.01, p = 0.33), amygdala (β -coefficient = -0.015, SE = 0.01, p = 0.24) and middle temporal gyrus (β -coefficient = -0.009, SE = 0.01, p = 0.39). As observed for entorhinal cortex atrophy rate, the interaction of CSF clusterin, CSF p-tau $_{181p}$ status and time was not significant for atrophy rate of the hippocampus (β -coefficient = 0.004, SE = 0.01, p = 0.74), amygdala (β -coefficient = 0.005, SE = 0.01, p = 0.74) and middle temporal gyrus (β -coefficient = 0.016, SE = 0.01, p = 0.18).

To determine whether the effect of clusterin on A β -associated neurodegeneration is independent from the previously observed effect of p-tau on A β -associated neurodegeneration,¹¹⁻¹³ we included interaction terms with CSF p-tau $_{181p}$ status (for additional details see Subjects and Methods and Equation 2). These analyses on the full cohort revealed significant interactions between CSF clusterin, CSF A β_{1-42} status, and time (β -coefficient = -0.026, SE = 0.01, p = 0.01) and CSF p-tau $_{181p}$ status, CSF A β_{1-42} status and time (β -coefficient = -0.010, SE = 0.004, p = 0.01) on entorhinal cortex atrophy indicating independent effects of CSF clusterin and CSF p-tau $_{181p}$ on CSF A β_{1-42} associated volume loss. As in the primary analyses, with the interaction terms in the model, only the effect of CSF A β_{1-42} status by time was significant (β -coefficient = 0.04, SE = 0.01, p = 0.009); the effects of time by CSF clusterin and CSF p-tau $_{181p}$ status were not significant. The main effects of CSF clusterin, CSF A β_{1-42} status or CSF p-tau $_{181p}$ status were not significant.

Additional interaction analyses with group status demonstrated significant interactions between group status, time, CSF clusterin and CSF A β_{1-42} status (β -coefficient = -0.020, SE = 0.003, p-value = 0.01) and between group status, time, CSF p-tau $_{181p}$ status and CSF A β_{1-42} status (β -coefficient = -0.008, SE = 0.003, p-value = 0.009) on entorhinal cortex atrophy rate. Subgroup analyses showed that within the MCI cohort, interactions between both CSF clusterin, CSF A β_{1-42} status, and time (β -coefficient = -0.047, SE = 0.02, p = 0.01)

and CSF p-tau_{181p} status, CSF A β ₁₋₄₂ status, and time (β -coefficient = -0.014, SE = 0.007, p = 0.048) on entorhinal cortex atrophy were significant. Within the HC cohort, only the interaction between CSF clusterin, CSF A β ₁₋₄₂ status, and time on entorhinal cortex atrophy was significant (β -coefficient = -0.032, SE = 0.01, p = 0.02); the interaction between CSF p-tau_{181p} status, CSF A β ₁₋₄₂ status and time on entorhinal cortex atrophy was not significant (β -coefficient = -0.005, SE = 0.004, p = 0.23).

Comment

Here, we show that in non-demented older individuals, A β -associated entorhinal cortex atrophy occurs in the presence of elevated clusterin. We also found that the effect of clusterin on A β -associated entorhinal cortex atrophy is not confounded or explained by p-tau. Taken together, this implicates a potentially important role for clusterin in the earliest stages of the Alzheimer's neurodegenerative process and suggests independent effects of clusterin and p-tau on A β -associated volume loss (Figure 4).

Though a number of studies have evaluated the relationship between A β , tau and p-tau on volume loss in the earliest stages of AD,¹¹⁻¹⁵ the role of clusterin in modulating this relationship is still unknown. Our findings demonstrate that non-demented older individuals with elevated CSF clusterin and decreased A β (i.e. increased intracranial A β deposition) experience increased volume loss suggesting that clusterin may accelerate progression from amyloid deposition to neurodegeneration. These results also indicate that a biomarker profile incorporating CSF clusterin, CSF A β ₁₋₄₂ and CSF p-tau_{181p} levels may better identify those older individuals who are at an elevated risk of progressing to dementia than any of these biomarkers by themselves.

These findings provide novel insights into the preclinical stage of AD. Though prior research suggests that clusterin by itself may not represent a marker of presymptomatic AD,⁶ our work indicates that the presence of clusterin may represent a critical link between A β deposition and entorhinal cortex degeneration in preclinical AD. Furthermore, in secondary analyses among HC participants, we found a significant interaction on volume loss only between clusterin and A β whereas among MCI individuals we noted concurrent interactions of A β with both clusterin and p-tau suggesting that the clusterin related effects on A β -associated neurodegeneration may precede tau related effects. Finally, in contrast to p-tau-related atrophy within the later-affected hippocampus or other temporal lobe regions, we found clusterin-associated effects only for the entorhinal cortex, a region selectively affected in the earliest stages of AD.¹⁹ Considered together, these findings indicate that the interaction between clusterin and A β may provide an important window into the earliest stages of the Alzheimer's neurodegenerative process.

Cellular and molecular evidence suggests that an interaction between clusterin and A β potentiates neurotoxicity. Though prior experimental²⁵ and plasma-based human studies suggest that elevated clusterin levels may represent a non-etiological, neuroprotective response,^{6,26} the molecular mechanism by which clusterin effects AD pathology is still not well understood. Recent experimental evidence indicates that knockdown of clusterin protects against A β -induced apoptosis whereas neuronal treatment with A β increases

intracellular clusterin (and decreases extracellular clusterin), resulting in wnt/Dickkopf-1-induced neurotoxicity.²⁷ Importantly, this clusterin-dependent, wnt/Dickkopf-1-induced apoptotic effect is specific to A β and is not observed with tau or other cytotoxic agents.²⁷ As a chaperone, clusterin has also been shown to bind with A β , thus increasing the rate of fibrillar amyloid deposition and neuritic dystrophy²⁸ and potentiating A β oligomeric neurotoxicity.²⁹ Consistent with these experimental results, our human findings suggest that clusterin may affect AD neurodegeneration primarily via A β -associated mechanisms.

A limitation of our study is its observational nature, which precludes conclusions regarding causation. Our results cannot differentiate whether elevated clusterin causes, results from, or is simply correlated with amyloid deposition and entorhinal cortex atrophy. Additionally, our findings require further validation on a larger, independent population-based cohort.

From a translational perspective, though considerable efforts have focused on A β and tau, comparatively little is known about other proteins influencing Alzheimer's neurodegeneration. Our findings implicate the involvement of clusterin in the earliest stages of AD. Using experimental models, it will be essential to better delineate the differential mechanistic aspects of intracellular from extracellular clusterin. In humans, it would be helpful to understand whether CSF and plasma clusterin levels correspond to experimentally derived intracellular or extracellular clusterin. It will also be important to determine whether interactions between clusterin and other factors modulate A β -associated neurotoxicity. Along with our current findings, the results from these studies could provide valuable insights into whether modifying clusterin levels or blocking clusterin/A β interactions are likely to represent viable therapeutic approaches for individuals in the earliest phases of the disease process.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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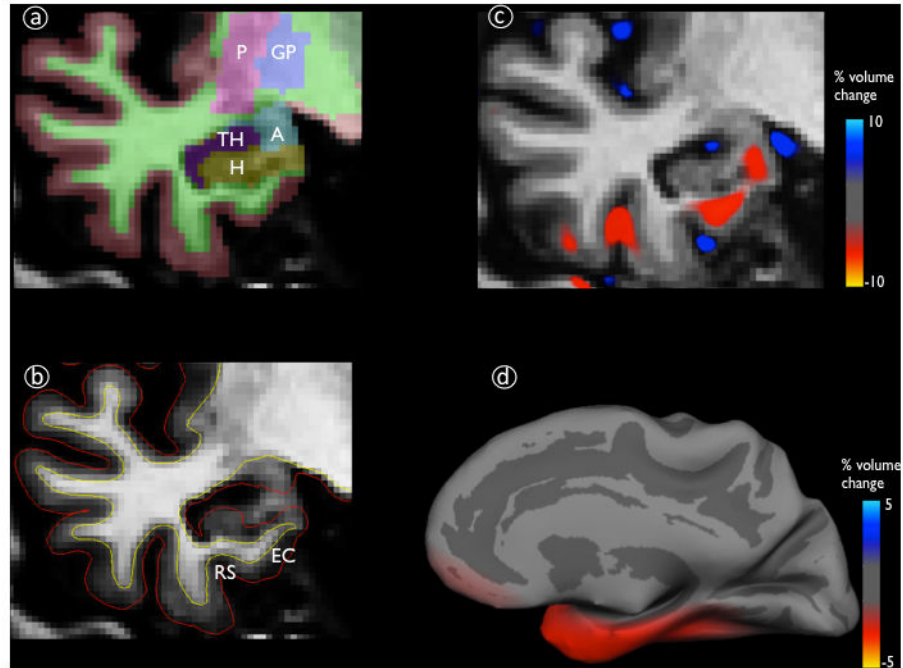


Figure 1.

T1-weighted MRI images in the coronal dimension and a medial semi-inflated gray matter cortical surface depicting the entorhinal cortex and hippocampus (a and b) and 1-year volume change fields (c and d) for an MCI participant at the median for entorhinal cortex and hippocampal volume loss (annualized percent change) who was $A\beta$ positive, p-tau positive and demonstrated elevated clusterin levels. (a) Automated segmentation of the baseline, structural MRI with subcortical structures (including the hippocampus) depicted in various colors. (b) The red overlay shows the gray matter/CSF boundary, the white overlay depicts the gray/white matter boundary and the distance between these surfaces represents the cortical thickness. Here, we were primarily interested in evaluating longitudinal thinning of the entorhinal cortex. (c) Heat map representation of the voxel-wise estimates of volumetric change at 1-year. Note that volumetric change is most pronounced in the medial temporal lobe. (d) Semi-inflated gray matter cortical surface (medial hemisphere) with a heat map representation of cortical volumetric change at 1-year. Note that volumetric change is most pronounced in the medial temporal and temporopolar cortices. H= hippocampus, A = amygdala, TH = temporal horn lateral ventricles, P = putamen, GP = globus pallidus, EC = entorhinal cortex, RS = rhinal sulcus.

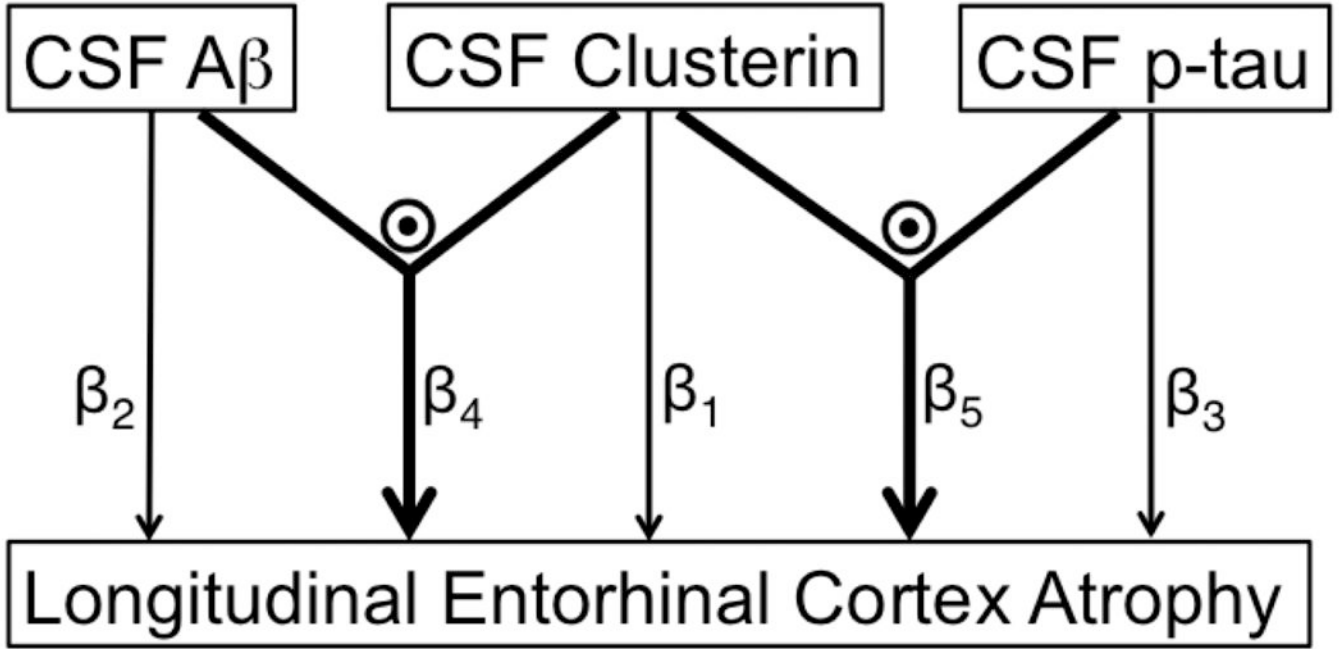


Figure 2. Diagrammatic representation of the primary hypotheses evaluated in the current study where the primary outcome was longitudinal entorhinal cortex atrophy: (β_1) main effect of clusterin, (β_2) main effect of $A\beta_{1-42}$, (β_3) main effect of p-tau, (β_4 and \odot) an interactive effect between clusterin and $A\beta_{1-42}$, and (β_5 and \odot) an interactive effect between clusterin and p-tau.

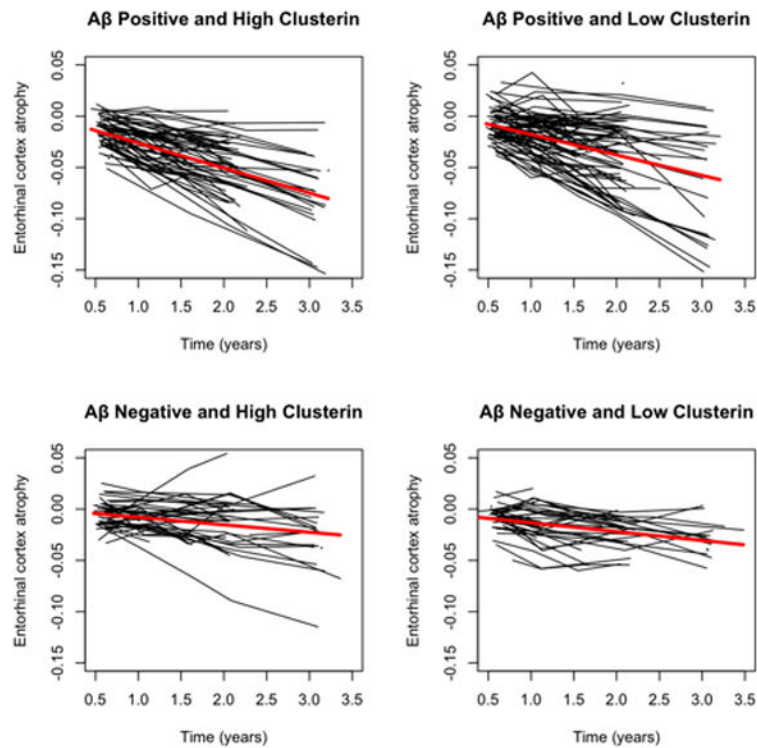


Figure 3.

(a) Spaghetti plots illustrating atrophy of the entorhinal cortex among all non-demented older participants classified as $A\beta_{1-42}$ positive and high clusterin (based on median value of clusterin) (top left panel), $A\beta_{1-42}$ positive, and low clusterin (top right panel), $A\beta_{1-42}$ negative and high clusterin (bottom left panel), and $A\beta_{1-42}$ negative and low clusterin (bottom right panel). The red line indicates the mean atrophy rate for the four respective groups (i.e. $A\beta_{1-42}$ positive and high clusterin, $A\beta_{1-42}$ positive and low clusterin, $A\beta_{1-42}$ negative and high clusterin and $A\beta_{1-42}$ negative and low clusterin). As illustrated in the top panel, the slopes of the red lines between the $A\beta_{1-42}$ positive and high clusterin and $A\beta_{1-42}$ positive and low clusterin individuals are significantly different corresponding to the significant interaction between CSF $A\beta_{1-42}$, CSF clusterin and time (please see text for further details).

(b) Spaghetti plots illustrating atrophy of the entorhinal cortex among all non-demented older participants classified as p-tau positive and high clusterin (based on median value of CSF clusterin) (top left panel), p-tau positive, and low clusterin (top right panel), p-tau negative and high clusterin (bottom left panel), and p-tau negative and low clusterin (bottom right panel). The red line indicates the mean atrophy rate for the four respective groups (i.e. p-tau positive and high clusterin, p-tau positive and low clusterin, p-tau negative and high clusterin and p-tau negative and low clusterin). As illustrated in the top panel, the slopes of the red lines between the p-tau positive and high clusterin and p-tau positive and low clusterin individuals are not significantly different corresponding to the non-significant interaction between CSF p-tau, CSF clusterin, and time (please see text for further details).

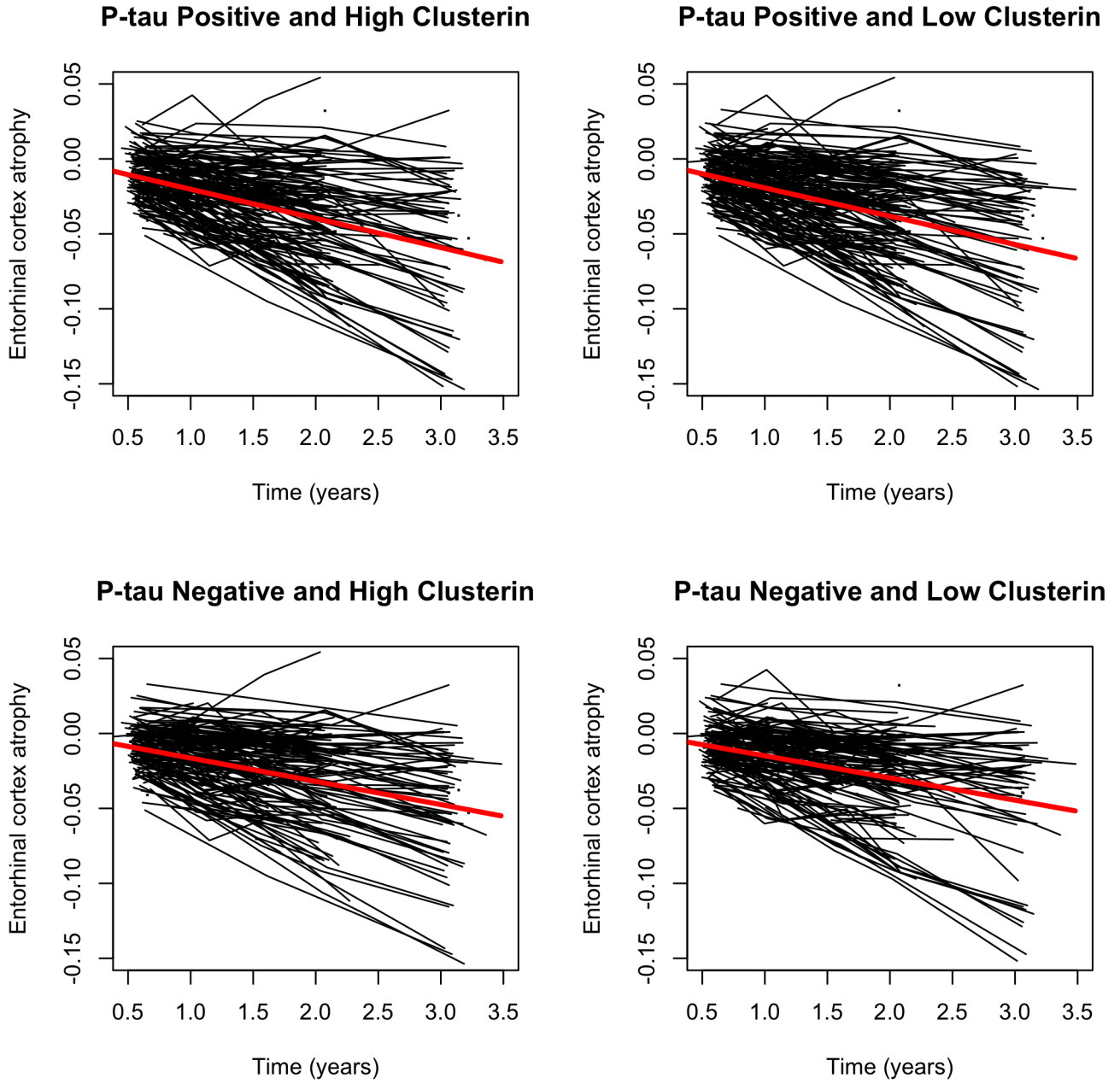


Figure 4. Results from our linear mixed effects model demonstrating independent effects of clusterin and p-tau on A β -associated volume loss in non-demented older individuals (please see text for details). \odot illustrates an interactive effect and the arrow demonstrates a main effect of A β .

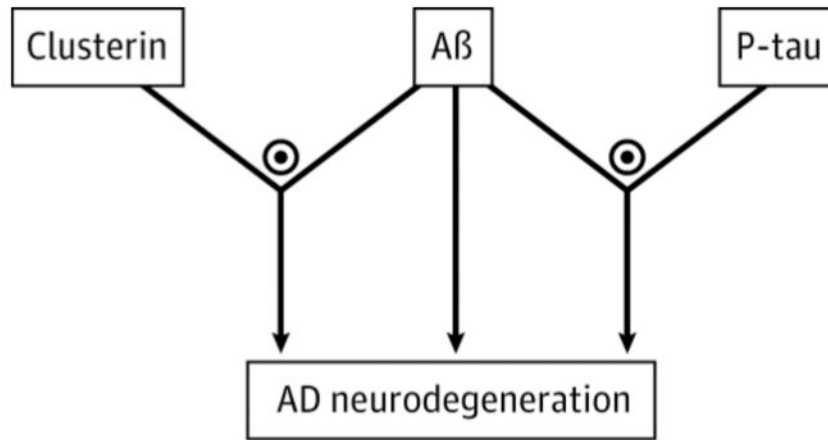


Figure 5.

Table 1

Demographic, clinical, and imaging data for all participants in this study. MCI = mild cognitive impairment, HC = cognitively normal older adults, MMSE = Mini-mental status exam, CDR-SB = Clinical Dementia Rating-Sum of Boxes score, APC = Annualized Percent Change, SE = Standard error of the mean, MRI = magnetic resonance imaging, LP-MRI interval = time in months between baseline lumbar puncture (LP) and baseline MRI, Years between MRI scans = time between baseline and last available MRI

| | HC (n = 91) | MCI (n = 150) |
|--|--------------|---------------|
| Age, Mean (SE) | 76.0 (0.6) | 75.1 (0.7) |
| Female, % | 51 | 33 |
| Education Years, Mean (SE) | 15.6 (0.3) | 16.1 (0.2) |
| MMSE, Mean (SE) | 29.1 (0.1) | 26.7 (0.1) |
| CDR-SB, Mean (SE) | 0.03 (0.01) | 1.5 (0.07) |
| APOE ϵ 4 carriers (%) | 24 | 54 |
| CSF Clusterin level (μ g/ml), Mean (SE) | 1.39 (0.02) | 1.42 (0.01) |
| CSF A β ₁₋₄₂ level (pg/ml), Mean (SE) | 207.8 (5.6) | 157.5 (4.1) |
| CSF p-tau _{181p} level (pg/ml), Mean (SE) | 24.7 (1.4) | 36.8 (1.3) |
| LP-MRI interval (months), Mean (SE) | 0.07 (0.007) | 0.08 (0.006) |
| Years between MRI scans, Mean (SE) | 2.37 (0.08) | 2.17 (0.05) |
| Entorhinal cortex APC, Mean (SE) | -0.84 (0.11) | -2.37 (0.12) |
| Hippocampus APC, Mean (SE) | -0.95 (0.08) | -2.42 (0.13) |
| Amygdala APC, Mean (SE) | -0.99 (0.10) | -2.65 (0.15) |
| Middle Temporal Gyrus, Mean (SE) | -0.70 (0.09) | -1.97 (0.12) |