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Related amyloid burden and cortical atrophy in individuals with subtle cognitive decline

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Abstract

Background and Purpose: Subtle cognitive decline represents a stage of cognitive deterioration in which pathological biomarkers may be present, including early cortical atrophy and amyloid deposition. Using individual items from the Montreal Cognitive Assessment and k-modes cluster analysis, we previously identified three clusters of individuals without overt cognitive impairment: (1) High Performing (no deficits in performance), (2) Memory Deficits (lower memory performance), and (3) Compound Deficits (lower memory and executive function performance). In this study, we sought to understand the relationships found in our clusters between cortical atrophy on MR and amyloid burden on PET.

Methods: Data were derived from the Alzheimer's Disease Neuroimaging Initiative and comprised individuals from our previous analyses with available MR and amyloid PET scans (n=272). Using multiple group structural equation modeling, we regressed amyloid standardized uptake value ratio on volumetric regions to simultaneously evaluate unique associations within each cluster.

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Disclosure

The authors claim no competing interests or conflicts of interest in relation to this work.

Results: In our Compound Deficits cluster, greater whole cerebral amyloid burden was significantly related to right entorhinal cortical and left hippocampal atrophy, $r_s = -0.412$ ($p=0.005$) and -0.304 ($p=0.049$), respectively. Within this cluster, right entorhinal cortical atrophy was significantly related to greater amyloid burden within multiple frontal regions.

Conclusions: The Compound Deficits cluster, which represents a group potentially at higher risk for decline, was observed to have significantly more cortical atrophy, particularly within the entorhinal cortex and hippocampus, associated with whole brain and frontal lobe amyloid burden. These findings point to a pattern of early pathological deterioration that may place these individuals at risk for future decline.

Keywords

Amyloid burden; cortical atrophy; Montreal Cognitive Assessment; subtle cognitive decline; Alzheimer's disease

Introduction

Subtle cognitive decline, which represents a period of slow cognitive worsening before one reaches the level of mild cognitive impairment (MCI), continues to be studied in the context of Alzheimer's disease (AD) and other dementias.[1,2] Pathological AD biomarkers may be present below clinical thresholds in those with subjective cognitive decline before they present with overt cognitive deterioration, including MR atrophy and PET amyloid deposition.[3–5] In patients with MCI, global amyloid deposition is related to regional atrophy in the hippocampus, medial frontal and parietal areas, and lateral temporoparietal cortex; regional amyloid is correlated to atrophy in areas of high amyloid deposition.[6] Baseline levels of amyloid deposition and cortical atrophy can also predict time to progression from MCI to dementia.[7] Therefore, it is valuable to examine these pathologies in pre-clinical AD populations.

In our previous work, we used individual items of the Montreal Cognitive Assessment (MoCA) to identify three distinct cognitive clusters among individuals without cognitive impairment: (1) the High Performing cluster showed no deficits in performance, (2) the Memory Deficits cluster displayed lower memory performance, and (3) the Compound Deficits cluster displayed lower performance on memory and executive function items.[8,9] The Compound Deficits cluster represents a group with subtle cognitive decline who may be at higher risk for deterioration. AD biomarker changes have been shown to be present in individuals with a similar pattern of decline to that of our Compound Deficits cluster, thus suggesting that this group also may show subclinical biomarker changes.[3,5–7]

In this study, we set out to understand the relationships in cortical atrophy and amyloid deposition in individuals with subtle cognitive decline.[8] We hypothesized that cortical volume and amyloid PET burden may vary as a function of cluster membership. These findings will help identify which brain areas might undergo pathologic changes before an individual develops overt cognitive impairment.

Methods

Data were originally collected as part of the Alzheimer's Disease Neuroimaging Initiative (ADNI, www.adni.loni.usc.edu), described previously.[8] At enrollment in ADNI, all participants gave informed consent. Inclusion criteria for our previous work with this cohort are described previously.[8] Three clusters of individuals without objective cognitive impairment were previously derived using k-modes cluster analysis: (1) High Performing (n = 282) had a modal MoCA score of 30/30, (2) Memory Deficits (n = 228) had a modal MoCA score of 25/30 with deficits in memory items, and (3) Compound Deficits (n = 89) had a modal MoCA score of 24/30 with deficits in memory items and cube drawing.[8]

Patients were administered both PET and MR for quantification of amyloid burden (measured as standardized uptake value ratio [SUVR]) and cortical atrophy (measured as volume), respectively. For these analyses, subjects were included if they had available MR data within 18 months of previously identified PET data. Amyloid burden was quantified according to SUVR.[10] For PET acquisition, 370 MBq Florbetapir was administered, after which 3D PET images of four 5-minute frames were acquired.[11] Cortical atrophy was quantified utilizing 1.5T or 3T MR scans.[12] MRI acquisition and scanning parameters have been described previously in ADNI documentation.[13] Image data was preprocessed at the Mayo Clinic and by ADNI-approved vendors; on-scanner non-uniformity correction was included for all images.[13]

SUVR and atrophy were calculated using Freesurfer (version 5.3.0) regions, with whole cerebellum as reference for SUVR, at the University of California at Berkeley as part of the ADNI study.[14] Volume measurements were derived from the following Freesurfer regions, according to previous literature regarding atrophy in AD: entorhinal cortex, hippocampus, superior frontal, middle frontal (rostral and caudal), parahippocampal gyrus, temporal (superior, medial, inferior, and transverse), fusiform, precuneus, parietal (superior and inferior), supramarginal, and cingulate (rostral anterior, caudal anterior, posterior, and isthmus).[6,7,15] MRI volumes were normalized 1:1000 to match SUVR order of magnitude. The following SUVR regions were utilized in these analyses: orbitofrontal (lateral and medial), superior frontal, middle frontal (rostral and caudal), superior temporal, precuneus, supramarginal, and cingulate (rostral anterior, caudal anterior, and posterior).[16,17]

The relationship between atrophy and amyloid burden was first assessed for correlations across the entire sample, regardless of cluster membership, and then within each cluster among several brain regions of interest. Results were reported as standardized correlation coefficient (Spearman, r) and p-value (with and without correction for multiple comparisons).

We then sought to understand the significance of these relationships across clusters by examining related regions using multiple-group structural equation modeling (SEM). This method facilitates the examination of group-specific coefficients among variables by fitting a SEM in which separate parameters are simultaneously estimated for each group.[18] In other words, the multiple group approach fits a single model that provides a direct comparison of subgroup-specific parameter estimates. Thus, we sought to compare the association between

cortical volume and amyloid burden across three groups comprised of the High Performing, Memory Deficits, and Compound Deficits clusters described previously in Cersonsky et al.[8] To test whether associations were consistent across clusters, we fit a three-group model in which whole brain SUVR was regressed on cortical volume based on MR; model coefficients were obtained for each cluster. Separate models were subsequently fit for several specific brain sub-regions in which SUVR of different cortical areas (rather than whole brain SUVR) was regressed on cortical volumes. All analyses were conducted using R software (version 4.0.2); SEM was conducted using lavaan 0.6–6.

Results

Of the 599 subjects previously separated into clusters, 272 had complete PET and MR data: 132 in the High Performing cluster, 102 in the Memory Deficits cluster, and 38 in the Compound Deficits cluster.

There were no strong correlations ($|r| > 0.3$) between volume and SUVR across the entire study group, nor were there significant correlations found in the High Performing or Memory Deficits clusters. However, in the Compound Deficits cluster, lower right entorhinal cortex volumes were associated with higher amyloid burden in multiple areas; this robust association is shown in Table 1. Additionally, within this cluster, lower left superior frontal volumes were associated with higher amyloid burden in the right entorhinal cortex ($r = -0.320$, $p = 0.049$).

The relationship between whole cerebral SUVR and cortical volume loss was most pronounced in the Compound Deficits cluster, particularly in relation to right entorhinal cortex and left hippocampal volumes (Table 2). A significant relationship was also found within the High Performing and Memory Deficits clusters between whole cerebral SUVR and bilateral superior frontal and left medial orbitofrontal volumes, though these regression estimates were small ($|r| < 0.2$).

We further evaluated right entorhinal cortex volume and amyloid burden in areas found to be correlated in the Compound Deficits cluster. The relationship between these neuroimaging findings was pronounced in SEM analyses (Table 1).

Discussion

We investigated the relationships between cortical atrophy and amyloid deposition across brain regions of interest in three clusters of individuals at risk for future cognitive decline. Within the Compound Deficits cluster, which was considered to be highest risk due to lower MoCA scores in both executive function and memory, higher whole cerebral amyloid deposition was associated with more atrophy in the right entorhinal cortex and left hippocampus.[8] Furthermore, lower right entorhinal cortex volume was associated with more amyloid deposition in multiple areas, including bilateral lateral and medial orbitofrontal lobes, superior temporal lobes, supramarginal cortex, and cingulate cortex.

Atrophy of the right entorhinal cortex was related to amyloid deposition throughout the cerebrum and in several cortical regions in the Compound Deficits cluster. Annual shrinkage

of the entorhinal cortex is predictive of memory decline in non-cognitively impaired adults, and has been shown to atrophy at a higher rate than the hippocampus.[15,19] Accordingly, this pattern of atrophy is consistent with the cognitive deficiencies observed in the Compound Deficits cluster, as the entorhinal atrophy correlates with memory deficits, and linked amyloid deposition in frontal lobe regions correlates with executive function deficits.[20,21] Thus, the regions identified in these analyses as having related pathologies are consistent with neuropsychological changes observed in this cluster.

These findings have implications for assessment of patients without cognitive impairment. Indeed, while previous studies have confirmed that atrophy and amyloid deposition are present at pre-MCI stages of cognitive decline, our study has identified areas that show related degeneration in a group of individuals distinguished only by their performance on a single, easy-to-administer neuropsychological test, the MoCA.[5] Given the associations between baseline cortical atrophy and amyloid deposition and future degeneration, these findings suggest that the Compound Deficits group is indeed at higher risk of future cognitive decline.[22] As we suggested previously, this group, identified by their performance on the MoCA, may benefit from early interventions that would improve quality of life and decrease the financial burden associated with cognitive decline; our findings here further underscore this need, as these individuals have significant relationships in brain pathologies that may indicate future decline as well. These related pathologies should be investigated further and correlated to clinical findings on comprehensive neuropsychological testing in order to validate such a relationship.

There are limitations to this work, in addition to those previously mentioned.[8] Though there are established cutoffs for whole cerebral amyloid burden in the literature, there are no cutoffs available for isolated cortical regions, which prevents us currently from identifying those who have clinically significant amyloid deposition in a certain area of the brain without reaching whole cerebral positivity. The same is true for atrophy; therefore, we can investigate the relationships between amyloid burden and cortical atrophy but cannot surmise if the burden in our clusters meets any clinical threshold.

In this study, we identified brain regions in which individuals with subtle cognitive decline show related atrophy and amyloid deposition. In those with deficits in memory and executive function (our “Compound Deficits” cluster), atrophy of the right entorhinal cortex was associated with amyloid deposition across the whole cerebrum and in several frontal lobe areas. These results are consistent with the neuropsychological performance of these individuals and also underscore the need for early assessment of those with particular deficits in neuropsychological testing, even on a global test such as the MoCA. Future studies will attempt to identify a threshold for this relationship between atrophy and amyloid deposition that may serve as a cutoff for pathologic decline.

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Table 1:

Right entorhinal cortex volume versus cortical SUVR – correlations and structural equation modeling

			Correlations (Compound Deficits Cluster)		Structural equation modeling		
			Coefficient (r_s)	**p-Value [1]**	**High Performing [2]**	**Memory Deficits [2]**	**Compound Deficits [2]**
Standardized uptake value ratio (SUVR, PET)	Whole cerebral		–0.437	0.006*	–0.030 (0.73)	0.008 (0.94)	–0.412 (0.005)
	Total temporal		–0.394	0.014*			
	Superior temporal	Left	–0.420	0.009*	–0.020 (0.73)	–0.025 (0.73)	–0.396 (0.008*)
		Right	–0.443	0.005*	–0.044 (0.49)	–0.047 (0.49)	–0.407 (0.006*)
	Caudal middle frontal	Left	–0.355	0.029*	–0.090 (0.30)	–0.017 (0.86)	–0.475 (0.001**)
		Right	–0.345	0.034*	–0.088 (0.31)	–0.039 (0.70)	–0.437 (0.003*)
	Rostral middle frontal	Left	–0.435	0.006*	–0.099 (0.25)	–0.019 (0.85)	–0.498 (<0.001**)
		Right	–0.411	0.010*	–0.116 (0.18)	–0.006 (0.95)	–0.495 (<0.001**)
	Lateral orbitofrontal	Left	–0.285	0.08	–0.049 (0.47)	–0.046 (0.47)	–0.377 (0.012*)
		Right	–0.285	0.08	–0.061 (0.36)	–0.057 (0.36)	–0.406 (0.006*)
	Medial orbitofrontal	Left	–0.381	0.018*	–0.007 (0.92)	–0.006 (0.92)	–0.421 (0.004*)
		Right	–0.381	0.018*	–0.007 (0.92)	–0.006 (0.92)	–0.421 (0.004*)
	Superior frontal	Left	–0.348	0.032*	–0.046 (0.60)	–0.019 (0.85)	–0.458 (0.002**)
		Right	–0.333	0.041*	–0.056 (0.52)	–0.030 (0.76)	–0.435 (0.003*)
	Precuneus	Left	0.200	0.10	–0.011 (0.87)	–0.011 (0.87)	–0.291 (0.06)
		Right	0.155	0.20	–0.026 (0.69)	–0.026 (0.69)	–0.316 (0.040*)
	Supramarginal	Left	0.067	0.58	–0.031 (0.60)	–0.038 (0.60)	–0.400 (0.007*)
		Right	0.050	0.68	–0.052 (0.40)	–0.057 (0.40)	–0.509 (<0.001**)
	Rostral anterior cingulate	Left	0.128	0.29	–0.013 (0.85)	–0.013 (0.85)	–0.421 (0.004*)
		Right	0.109	0.37	–0.025 (0.70)	–0.025 (0.70)	–0.387 (0.010*)
	Caudal anterior cingulate	Left	0.119	0.33	–0.025 (0.69)	–0.027 (0.69)	–0.444 (0.002**)

			Correlations (Compound Deficits Cluster)		Structural equation modeling		
			Coefficient (r_s)	p-Value [1]	High Performing [2]	Memory Deficits [2]	Compound Deficits [2]
		Right	0.194	0.11	–0.029 (0.66)	–0.030 (0.66)	–0.446 (0.002**)
	Posterior cingulate	Left	0.120	0.32	–0.032 (0.60)	–0.037 (0.60)	–0.385 (0.010*)
		Right	0.166	0.17	–0.015 (0.81)	–0.017 (0.81)	–0.385 (0.010*)

[1] Correlations considered significant without correction (*) if <0.05; significant with Bonferroni correction (**) if <0.002.

[2] Standard regression estimates calculated from structural equation modeling utilizing various cortical standardized uptake value ratios (with whole cerebellum as reference) and right entorhinal cortex volume as parameters. Values are given as coefficient (p-Value, significant without correction [*] if <0.05, with Bonferroni correction [**] if <0.002).

Table 2:

Structural equation modeling of whole cerebral SUVR vs. cortical volumes

			Whole cerebral standardized uptake value ratio (SUVR)		
			High Performing [1]	**Memory Deficits** [1]	**Compound Deficits** [1]
Cortical volume (MR)	Entorhinal cortex	Left	−0.055 (0.42)	−0.050 (0.42)	−0.236 (0.13)
		Right	−0.015 (0.83)	−0.014 (0.83)	−0.412 (0.005*)
	Hippocampus	Left	−0.115 (0.08)	−0.112 (0.08)	−0.304 (0.049*)
		Right	−0.114 (0.09)	−0.106 (0.09)	−0.095 (0.56)
	Superior frontal	Left	−0.184 (0.006*)	−0.168 (0.006*)	−0.038 (0.82)
		Right	−0.153 (0.025*)	−0.134 (0.025*)	−0.049 (0.76)
	Caudal middle frontal	Left	−0.011 (0.89)	−0.088 (0.89)	−0.142 (0.38)
		Right	−0.005 (0.95)	−0.004 (0.95)	−0.256 (0.10)
	Rostral middle frontal	Left	−0.116 (0.09)	−0.101 (0.09)	−0.074 (0.65)
		Right	−0.092 (0.18)	−0.079 (0.18)	0.025 (0.88)
	Lateral orbitofrontal	Left	−0.007 (0.61)	−0.007 (0.61)	−0.009 (0.82)
		Right	−0.004 (0.82)	−0.004 (0.82)	−0.002 (0.97)
	Medial orbitofrontal	Left	−0.035 (0.030*)	−0.035 (0.030*)	0.007 (0.91)
		Right	−0.024 (0.20)	−0.024 (0.20)	−0.022 (0.66)

[1]Standard regression estimates calculated from structural equation modeling utilizing whole cerebral standardized uptake value ratio (with whole cerebellum as reference) and various cortical volumes as parameters. Values are given as coefficient (p-Value, significant without correction [*] if <0.05).