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Braak Stage, Cerebral Amyloid Angiopathy, and Cognitive Decline in Early Alzheimer's Disease

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Abstract

The aim of this study was to determine the interaction between cerebral amyloid angiopathy (CAA) and Braak staging on cognition in the elderly. The study used a total of 141 subjects consisting of 72 non-cognitively impaired (NCI), 33 mild cognitive impairment (MCI), 36 Alzheimer's disease (AD) cases displaying Braak stages 0-II and III from the Rush Religious Order Study cohort. The association between Braak stage and CAA status and cognition was evaluated using a series of regression models that adjusted for age at death, sex, education, *APOE ε*4 status, and Consortium to Establish a Registry for Alzheimer's Disease (CERAD) neuropathological diagnosis. Individuals with CAA were more likely to be classified as Braak stage III relative to those without CAA [OR = 2.33, 95% CI (1.06, 5.14), $p = 0.04$]. A significant interaction was found between Braak stage and CAA status on a global cognitive score ($\beta = -0.58$, SE = 0.25, $p = 0.02$). Episodic memory also showed a significant association between Braak stage and CAA ($\beta = -0.75$, SE = 0.35, $p = 0.03$). These data suggest that there is a significant interaction between tau pathology and cerebrovascular lesions on cognition within the AD clinical spectrum.

Keywords

Alzheimer's disease; Braak stage; cerebral amyloid angiopathy; cognition; cognitive aging; mild cognitive impairment; neurofibrillary tangles

INTRODUCTION

Braak stages I to VI mark the progression of tau-based neurofibrillary tangle (NFT) pathology from least to greatest within the medial temporal lobe memory circuit in Alzheimer's disease (AD) [1]. Stages I and II display limited NFTs within the transentorhinal and entorhinal cortex and is often associated with normal cognitive and clinical profiles [1]. Braak stage III and IV display NFTs in the hippocampus and neocortex adjoining the transentorhinal cortex refers to the limbic phase when limited cognitive dysfunction is initially observed [2, 3]. Stages V and VI, labeled the neocortical phase,

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presents with the greatest number and extent of NFTs and is often associated with significant cognitive and functional impairment [2, 3]. While NFT pathology correlates well with cognitive decline and clinical status [3, 4], significant cognitive and clinical heterogeneity exists within the Braak stages [3, 5, 6]. Neuropathological analysis revealed a similar prevalence of Braak stage III in individuals with a clinical dementia rating (CDR) of 0 indicative of no cognitive impairment (55%) and those with a CDR of 0.5 corresponding to mild cognitive impairment (MCI; 56%) [3, 7], suggesting that other factors play a role in the transition from non-cognitively impaired (NCI) to MCI.

Given that many NCI individuals show significant AD pathology at autopsy in the absence of cognitive decline [8], the field has turned to the study of preclinical AD. For example, previous work by our group has shown that NCI individuals exhibit Braak stages ranging from I to V [9] and that an interaction between Braak stage, age, and *APOE ε*4 carrier status drives cognitive decline [10]. It has been suggested that Braak stage III represents an important transitional stage during the progression of AD [3]. However, the factors that precipitate cognitive decline among this group are unclear. Although inflammation [11], insulin resistance [12], and oxidative stress [13] have been proposed as additive variables contributing to cognitive impairment, the interaction between cerebrovascular factors and NFT pathology upon cognition remains an under-investigated area.

The role that cerebral amyloid angiopathy (CAA) plays in dementia is well established [14–17]. The presence of vascular CAA hastens the onset of AD clinical symptoms [18] and is associated with faster cognitive decline in NCI individuals [16, 18]. Although vascular dysregulation has been linked with amyloid pathology [19–21], there is increasing evidence that cerebrovascular damage is also associated with tau pathology. For example, focal ischemia is related with tau hyperphosphorylation [22, 23] and tau-dependent cerebrovascular repair mechanisms precede the development of CAA, which may contribute to downstream pathological events reported in AD animal models [24]. In human autopsy cases, hyperphosphorylated tau deposits were significantly more likely to be found in cerebral arteries displaying amyloid than those without [25]. The presence of CAA together with NFTs may also differentiate AD from primary age-related tauopathy (PART) [26]. Taken together, these data suggest that cerebrovascular factors moderate NFT pathology [27]. In this regard, positron emission tomography (PET) imaging has found that both the severity of small vessel cerebrovascular disease (SVCD) and amyloid binding (^{18}F-florbetaben uptake) correlated positively with tau binding (^{18}F-flortaucipir uptake) and these associations were independent of each other providing evidence for an interaction between ischemia and tau pathology [28]. Data derived from these studies support the hypothesis that cerebrovascular and NFT pathology interact to effect cognition during early Braak stages. Therefore, we investigated whether CAA plays a critical role in cognitive decline in cases that were neuropathologically categorized as Braak stage 0-II versus III.

MATERIALS AND METHODS

Data was derived from 141 older deceased and autopsied persons who died with a premortem clinical diagnosis of NCI (n = 72), MCI (n = 33), and AD (n = 46) and postmortem were classified as Braak stage 0 to III that were participants in the Rush

Religious Orders Study (RROS). The RROS participants had no coexisting clinical or neurological conditions judged to contribute to cognitive impairment at their last clinical evaluation [29, 30], agreed to an annual clinical evaluation, and signed an informed consent and an Anatomic Gift Act donating their brains at time of death. Data from these subjects have been used in numerous clinical pathological studies supported by our ongoing NIA program project grant entitled the “Neurobiology of Mild Cognitive Impairment in the Elderly” (P01AG14449). At the time of these studies, individuals were chosen from all available RROS participants that came to autopsy during a rolling admission (n = 663) [29]. In addition, those taking anticholinesterases or medication for depression were also excluded from this study. The Human Investigation Committee of Rush University Medical Center approved this study.

Clinical evaluation

Each of the participants underwent a uniform, structured, and clinical evaluation performed by a neurologist and a trained neuropsychological test technician [29, 31]. Medications used by the subjects within the previous fourteen days of the examination were reviewed and classified. A neurologist reviewed the medical history, medication use, neurologic examination, results of cognitive performance testing, and the neuropsychologist’s opinion of cognitive impairment and dementia. Each participant was evaluated in their home, emphasizing findings deemed clinically relevant. Clinical diagnostic classification was performed as described previously [31]. Petersen criteria [32] were used to diagnose MCI while NINCDS-ADRDA criteria were used to diagnose AD [33]. Individuals classified as NCI had cognitive test scores within normal limits for age and education and had no significant functional deficits. Among those who progressed to MCI, 12 were classified as amnestic and 21 were classified as non-amnestic. Previous work by our group has shown that plaque and tangle pathology does not differ significantly between amnestic and non-amnestic MCI subjects in this cohort [34].

Tissue preparation and neuropathological diagnosis

Brain accruement and processing was described in previous publications [31, 35, 36]. Briefly, each brain was cut into 1 cm thick coronal slabs using a brain slice apparatus and hemisected. One hemisphere was immersion fixed in 4% paraformaldehyde (24–72 h) and cryoprotected (10% glycerol and 2% dimethyl sulfoxide in phosphate buffer solution) until processing for immunohistochemistry.

Diagnostic blocks (mid-frontal, superior temporal, entorhinal cortex, hippocampus, inferior parietal cortex, basal ganglia, thalamus, and substantia nigra) from the opposite hemisphere were paraffin embedded and sectioned at 6 μm. Examination for cerebral infarctions was conducted as described previously [37]. Bielschowsky silver stain was used to visualize neuritic plaques (NPs), diffuse plaques (DPs), and NFTs. Sections were also immunostained for Aβ using antibody M0872 (1:100; Dako, CA) raised against $A\beta_{1–40}$ and $A\beta_{1–42}$. Paired helical filament tau (AT8; 1:800, Covance) immunohistochemistry was also used to label NFTs. Neuropathological diagnoses were determined according to CERAD [38] and Braak staging [1] as recommended by the NIA-Reagan criteria [39]. Exclusion criteria included mixed dementias, Parkinson’s disease, frontotemporal dementia,

argyrophilic grain disease, vascular dementia, hippocampal sclerosis, stroke, and Lewy body disease. Cortical and subcortical Lewy body pathology was detected using α-synuclein (αSyn) immunohistochemistry as previously described [40] and scored semi-quantitatively according to the severity and anatomical distribution, separating brainstem predominant, limbic/transitional and diffuse neocortical types, depending on the anatomical distribution of αSyn-positivity [41, 42].

A board-certified neuropathologist or trained technician, blinded to clinical diagnosis, counted number of NPs and DPs revealed by Bielschowsky silver stain and tau immunohistochemistry using the phosphorylated paired helical filament tau AT8 marker for NFTs, respectively, in one square mm area (100x magnification) per cortical region [32, 43]. CAA was assessed using a semiquantitative summary [16, 44] from the angular gyrus, inferior temporal gyrus, midfrontal gyrus, and the calcarine cortices. Paraffin-embedded sections were immunostained for Aβ using 1 of 3 monoclonal anti-human antibodies: 4G8 (1:9000; Covance Labs, Madison, WI), 6F/3D (1:50; Dako North America Inc., Carpinteria, CA), and 10D5 (1:600; Elan Pharmaceuticals, San Francisco, CA). In the group of RROS subjects used in this study, the 6F/3D antibody was used for all cases. For each region, meningeal and parenchymal vessels were assessed for amyloid deposition and scored from 0 to 4, where: 0 = no deposition, 1 = scattered segmental but no circumferential deposition, 2 = circumferential deposition up to 10 vessels, 3 = circumferential deposition up to 75% of the region, 4 = circumferential deposition over 75% of the total region. CAA score for each region was the maximum of the meningeal and parenchymal CAA scores. Scores were averaged across regions and summarized as a continuous measure of CAA pathology. CAA severity was then converted to a semi-quantitative summary and graded on a 0 to 3 scale based on the neuropathologist's examination (0 = None, 1 = Mild, 2 = Moderate, 3 = Severe) [16].

Cognitive composite scores

Composite scores are based on the results of 17 cognitive tests categorized into five domains of cognition [45, 46]. Mini-Mental State Examination (MMSE) was used to describe the cohort, but was not used in the composite scores. Briefly, episodic memory was evaluated with tests including immediate and delayed recall of Story A from Logical Memory and of the East Boston Story, and Word List Memory, Recall, and Recognition from the Consortium to Establish a Registry for AD (CERAD). Semantic memory was assessed with three tests including a 15-item version of the Boston Naming Test, Verbal Fluency, which involves naming examples of semantic categories (i.e., animals, vegetables) in 1-min trials; and a reading test that involves reading single words aloud and a 10-item reading test. Working memory was assessed using Digit Span Forward and Backward and Digit Ordering. Two tests of perceptual speed included Symbol Digit Modalities Test, and Number Comparison. Finally, two tests of visuospatial ability included a 15-item version of Judgment of Line Orientation and a 9-item version of Ravens Standard Progressive Matrices [46]. For each test, raw scores were converted into z-scores based on the mean and standard deviation of the sample. The z-scores from the individual tests were averaged to create individual domain composite scores. The Global Composite Score (GCS) is an average of the 17 individual test z-scores.

Statistical analysis

Between-group frequency differences for categorical variables were analyzed using the Chi-square test while between-group differences for continuous variables were compared with the independent two-sample *t*-test procedure. CAA was converted to a dichotomous variable (CAA-Absent = None; CAA-Present = Mild, Moderate, Severe). Braak stage was also dichotomized into the following groups: 0 – II and III. Logistic regression was used to estimate the odds of being in the Braak stage III group given the presence of CAA after adjusting for age at death, sex, years of education, *APOE ε*4 status, and CERAD diagnosis. Linear regression models were used to test whether the interaction of CAA status and Braak stage was significantly associated with measures of cognition. Separate analyses with the same type of model were carried out for the GCS, Episodic Memory, Semantic Memory, Working Memory, Perceptual Speed, and Visuospatial domains. Each model adjusted for age at death, sex, years of education, *APOE ε*4 status, and CERAD diagnosis. Group differences for DP and NP counts were analyzed using the Mann-Whitney test due to their highly skewed distributions. Follow-up analyses for the DP and NP group differences used negative binomial regression models that adjusted for age at death, sex, years of education, *APOE ε*4 status, clinical diagnosis, and CAA status. p value was set at 0.05.

RESULTS

Table 1 shows the demographic and neuropathologic characteristics of the cases evaluated. Braak stage III subjects had significantly older ages at death relative to stages 0-II ($p < 0.001$), but did not differ on years of education ($p = 0.50$). The proportion of *APOE ε*4 carriers was similar between the Braak stage 0-II and stage III groups ($p = 0.58$). There was no difference in the frequency of clinical diagnoses between groups ($p = 0.12$), although it was noted that the prevalence of clinical AD in the Braak stage III group was twice that of the Braak stage 0-II group ($n = 24$ versus $n = 12$). Postmortem interval ($p = 0.18$), duration between last clinical assessment and autopsy ($p = 0.35$), and brain weight at autopsy ($p = 0.17$) were not significantly different between stage 0-II and III cases. DP load was not a significantly different ($p = 0.23$), but NP load was significantly higher in the Braak stage III group ($p < 0.001$). NP difference between groups remained significant even after adjusting for age at death, sex, education, CERAD diagnosis, *APOE ε*4 status, and CAA ($\beta = 0.77$, SE = 0.38, $p = 0.04$; Fig. 1) while the adjusted group difference for DPs was not statistically significant ($\beta = 0.35$, SE = 0.38, $p = 0.36$). CAA presence was also similar among the three clinical groups ($p = 0.31$). However, the presence of CAA was significantly higher in Braak stage III ($p = 0.01$) even after adjusting for CERAD diagnosis, age at death, sex, education, and *APOE ε*4 status [OR = 2.33, 95% CI (1.06, 5.14), $p = 0.04$]. A separate analysis using CAA scores from the inferior temporal gyrus alone yielded a similar result [OR = 3.16, 95% CI (1.26, 7.93), $p = 0.01$].

For the cognitive variables, the Braak stage III group had significantly lower GCS ($p = 0.02$), episodic memory ($p = 0.03$), semantic memory ($p = 0.01$), and perceptual speed ($p = 0.03$) scores relative to the Braak stage 0-II group, while working memory ($p = 0.11$) and the visuospatial domain ($p = 0.81$) were not significantly different (Table 2). After adjusting for age at death, sex, education, *APOE ε*4 status, and CERAD diagnosis, the interaction

between Braak stage and CAA status was statistically significant for GCS (β = −0.58, SE = 0.25, $p = 0.02$). Groupwise comparisons of this interaction found that among those with CAA, the Braak stage III group had significantly lower performance than Braak stage 0-II individuals ($p = 0.04$; Fig. 2). The episodic memory domain also showed a significant effect for Braak by CAA interaction (β = −0.75, SE = 0.35, $p = 0.03$). However, the Braak stage and CAA interaction was not significant for semantic memory ($p = 0.13$), working memory ($p = 0.12$), visuospatial function ($p = 0.13$), and perceptual speed ($p = 0.33$). A separate analysis revealed no significant association of the Braak stage by CAA interaction with GCS and episodic memory using CAA scores from the inferior temporal gyrus (GCS: (β = −0.51, SE = 0.28, $p = 0.07$); Episodic Memory: (β = −0.51, SE = 0.34, $p = 0.13$). When the clinical groups were analyzed separately, the CAA by Braak stage interaction was not significantly associated with the GCS (NCI: [β = −0.08, SE = 0.16, $p = 0.61$]; MCI: [β = 0.11, SE = 0.31, $p = 0.73$]; AD: [β = −1.05, SE = 0.67, $p = 0.13$]).

DISCUSSION

We found that individuals with CAA were significantly more likely to be classified postmortem as Braak stage III. This was independent of *APOE ε*4 status, demographic characteristics, and CERAD diagnosis. We also found that Braak stage III individuals with CAA had significantly lower global cognition and episodic memory scores compared to Braak stage 0-II individuals with CAA, which was independent of plaque load, *APOE ε*4 status, and demographic characteristics. Others have reported similar results showing that the presence of both tau and vascular pathologies are associated with lower delayed recall memory scores among NCI individuals [47]. We also demonstrated that Braak stage III is heterogeneous in terms of clinical diagnosis [3, 5, 6] suggesting that this tau pathological phase is transitional both neuropathologically and cognitively. Although amyloid deposition plays a key role in CAA, it is possible that CAA induces downstream ischemic events that trigger tau hyperphosphorylation resulting in a greater NFT burden in these individuals [22–24].

However, it is possible that other vascular pathologies such as atherosclerosis, superficial siderosis, arteriosclerosis, and white matter rarefaction may also trigger ischemic-related tau hyperphosphorylation. Regardless of which vascular pathology underlies an increase in tau pathology, there is an opportunity to intervene in the pathogenesis of AD that is not focused primarily on amyloid. Although previous studies [48–51], including our own [52, 53], have shown that increases in cortical amyloid are associated with decreases in cognition among NCI individuals, evidence suggesting that brain vascular dysregulation precedes and initiates amyloid deposition [21] highlights the need to include cerebrovascular damage prevention in conjunction with current treatment approaches [54–57]. Although the amyloid cascade hypothesis for AD serves as the rationale for many current therapeutic approaches [58], previous failures of amyloid-based therapies in symptomatic AD has spurred the development of tau-based therapies, since tau pathologies are better correlates of cognitive decline than amyloid lesions [59]. Given the associations between cerebrovascular and tau pathology reported here, tau-directed therapies might be augmented by interventions that ameliorate or prevent cerebral vascular damage.

The present findings offer additional insight into the interaction between the cerebrovascular system and tau pathology in AD. A weakness of most hypotheses of AD pathogenesis is the need to define the pathogenic factors that precede amyloid and tau deposition. Although vascular dysfunction may be just one of several possible mechanisms that trigger or interact with amyloid, here we have shown that cerebrovascular lesions are associated with NFTs, which is supported by experimental evidence showing that CAA-induced tau phosphorylation and misfolding leads to tau-associated neurotoxicity [60]. This raises the possibility that cerebrovascular pathologies influence the progression of NP and NFT pathology during the course of AD. In fact, there is evidence suggesting that increased tau load is the result of a synergistic relationship between vascular factors and amyloid pathology [61]. Previous findings have demonstrated a main effect of CAA on cognitive decline in NCI older adults [16]; however, our findings show that CAA is a moderating factor in the association between Braak stage and cognition. Others have found that vascular factors are not related to amyloid load, but are significantly associated with tau load [62, 63]. Whether CAA interacts with amyloid and/or tau and its effect on cognition remain an under-investigated area in the field of AD.

The role that cognitive reserve (CR) plays in the differences in cognition seen between Braak stage 0-II and stage III groups remains to be determined. In particular, CR likely plays a role in the heterogeneity of clinical diagnoses seen in Braak stage III. Neuroimaging results have shown that CR mitigates the negative effect of white matter hyperintensities on cognition suggesting that CR confers protection against cerebrovascular lesions [61] in the same way that it is thought to mitigate the effects of NP and NFT lesions [64]. In our sample, fifty Braak stage III individuals also had CAA, of which 21 (42%) were NCI suggesting a mitigating effect of CR upon both AD and vascular pathology resulting in the maintenance of normal cognition.

A limitation of this study is its cross-sectional design, which prevents temporal associations from being investigated, particularly as they relate to progression from early to late Braak stages. It is also important to consider that CAA is just one of several vascular lesions that may influence the pathogenesis and cognitive outcomes of people with AD [65]. It is important to consider that age of biological disease onset for AD, which may be earlier for *APOE ε*4 carriers, may result in greater CAA and NFT burdens for these individuals. Another caveat is the relatively small number of *APOE ε*4 carriers, particularly homozygous individuals, which may affect the associations reported here. Future studies with a greater balance of *APOE ε*4 carriers and non-carriers are needed to extend these findings. The cases examined here were from a community-based cohort of highly educated retired clergy who had excellent health care and nutrition and were used in multiple clinical pathological [66, 67] and epidemiological investigations [30, 32, 35]. Individuals who volunteer may introduce bias by decreasing pathology but this is partially mitigated by high follow-up and autopsy rates of the RROS [36]. Strengths include uniform premortem clinical and postmortem pathological evaluation and that final the pathologic classification was performed without knowledge of the clinical evaluation.

The results of this study show that Braak stage III is heterogeneous with respect to clinical diagnosis and represents an important transition stage of AD disease progression. We have

also shown that cerebrovascular factors are associated with both the neuropathological and clinical progression of AD and should be given greater consideration in the development of therapeutic strategies.

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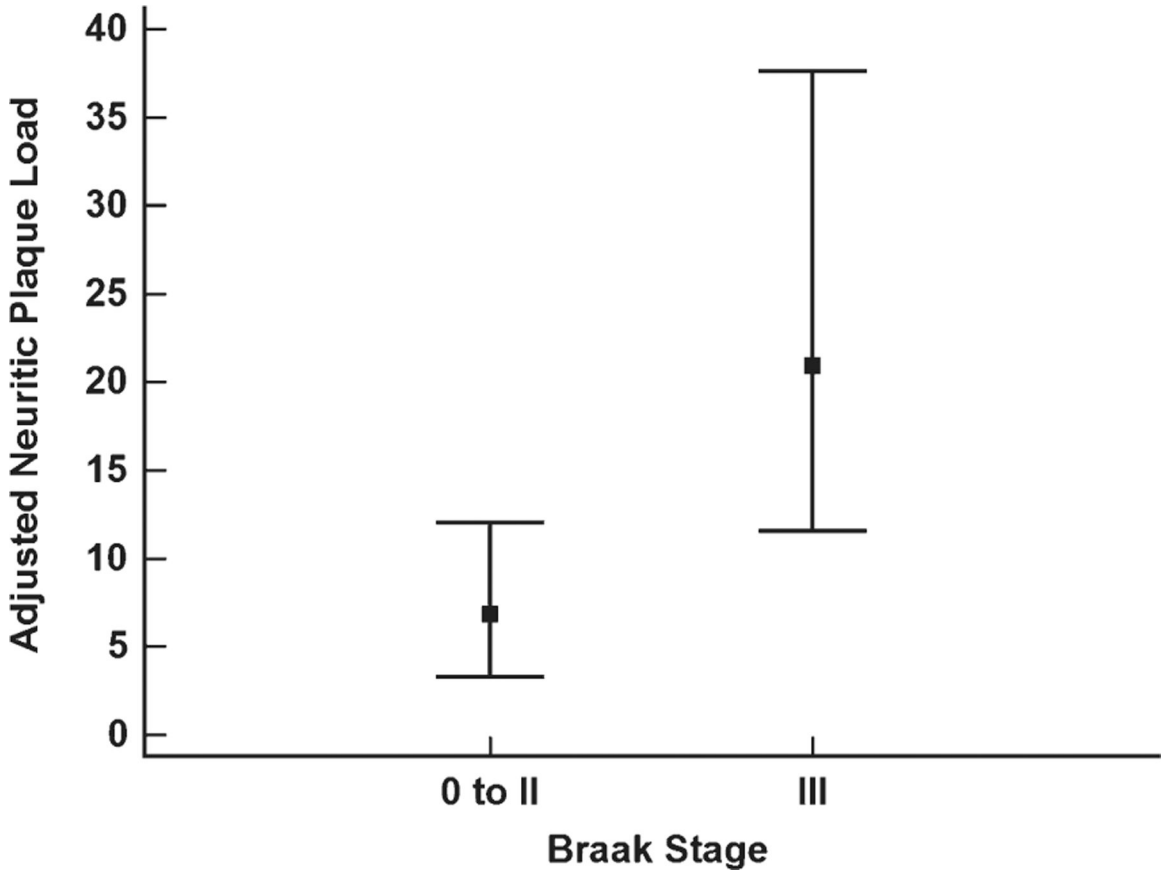

Fig. 1.

Adjusted neuritic plaque load differences for braak stage 0 to II and III. Braak stage 0-II and Braak stage III group difference for adjusted neuritic plaque load. Boxes represent the median and error bars are the 25th and 75th percentiles. Neuritic plaque load was adjusted age at death, education, sex, *APOE ε*4 carrier status, clinical diagnosis, and CAA status.

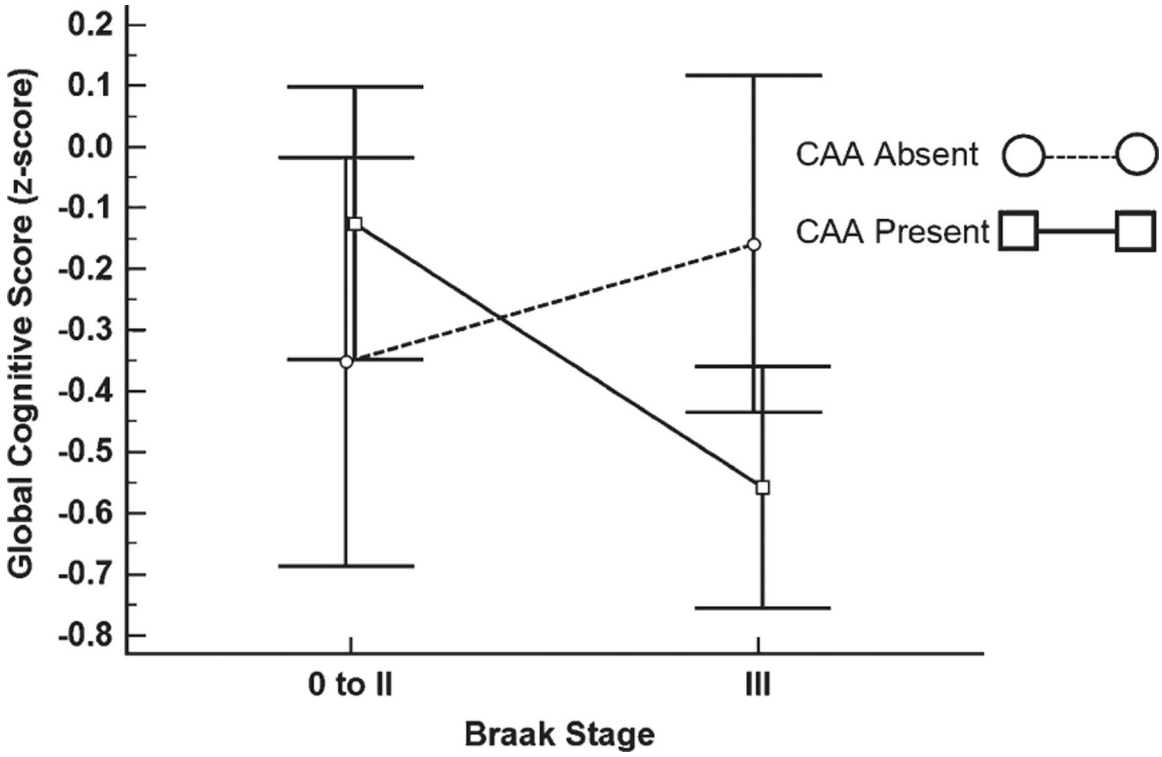

Fig. 2.

CAA-dependent global cognitive score differences for braak stage 0 to II and III. Global cognitive score stratified by Braak stage and CAA status. Squares and circles represent the mean and error bars are 95% confidence intervals. Dashed line represents the CAA Absent group and the solid line represents the CAA Present group.

Table 1

Demographic and neuropathological characteristics by braak stage

	Braak 0 – II (*n* = 66)	**Braak III (*n* = 75)**	***p***
Age at death (years)	82.25 ± 6.56	86.43 ± 5.70	<0.001
Sex (M/F)	41/25	37/38	0.13
Education (y)	18.27 ± 4.03	17.83 ± 3.74	0.50
APOE ε4 (Carrier/Non-Carrier)	11/54	10/64	0.58
Clinical diagnosis (NCI/MCI/AD)	39/15/12	33/18/24	0.12
Postmortem interval (hours)	7.01 ± 4.07	6.03 ± 3.77	0.18
Duration between last clinical assessment and autopsy (y)	0.73 ± 0.64	0.64 ± 0.49	0.35
Brain weight at autopsy (g)	1,256.28 ± 151.55	1,222.82 ± 133.93	0.17
Cerebral amyloid angiopathy (present/absent)	32/29	50/18	0.01
Neuritic plaque count	0 (0–11)	10 (0–37)	<0.001
Diffuse plaque count	4 (0–38)	21.50 (0–60)	0.23

Mean ± standard deviation; median (25th %ile, 75th %ile).

Table 2

Cognitive score differences by braak stage

	Braak 0 – II (*n* = 66)	**Braak III (*n* = 75)**	***p***	**Cohen's *d***
MMSE	26.54 ± 4.65	24.78 ± 5.91	0.05	0.33
Global cognitive score	−0.22 ± 0.76	−0.53 ± 0.81	0.02	0.39
Episodic memory	−0.04 ± 1.01	−0.42 ± 1.09	0.03	0.36
Semantic memory	−0.05 ± 0.85	−0.47 ± 0.95	0.01	0.47
Working memory	−0.32 ± 0.74	−0.53 ± 0.79	0.11	0.27
Perceptual speed	−0.65 ± 1.13	−1.04 ± 0.99	0.03	0.37
Visuospatial	−0.45 ± 0.81	−0.48 ± 0.80	0.81	0.04

Mean ± standard deviation; z-scores are reported for all cognitive variables except the MMSE.