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Alzheimer pathology does not mediate the association between depressive symptoms and subsequent cognitive decline

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Abstract

Background—Depressive symptoms in non-demented persons appear to hasten the conversion from Mild Cognitive Impairment (MCI) to clinical Alzheimer's disease (AD) and doubles the risk of incident AD. However, the mechanism(s) by which depression might effect this risk has not been well established. The purpose of this analysis is to test the hypothesis that progression of AD pathology mediates depression's apparent effect on the risk of dementia conversion using longitudinally collected psychometric testing and autopsy data from the Honolulu-Asia Aging Study (HAAS).

Methods—Latent factor variables representing AD, cortical Lewy body (CLB) and ischemic neuropathology were tested as potential mediators of the Centers for Epidemiological Studies depression scale (CES-D)'s significant association with the 10-year prospective rate of cognitive decline, adjusted for baseline cognition, age, education, total number of medications and brain weight at autopsy.

Results—CES-D scores, neurofibrillary tangle (NFT) counts, CLB counts and ischemic lesions each made significant independent contributions to cognitive decline. However, CES-D scores were not significantly associated with any pathological variable, which thus were not mediators of its effect.

Conclusions—We can confirm that subsyndromal depressive symptoms are significantly associated with subsequent cognitive decline. Although the effect is relatively modest, it is stronger than that of amyloid-related neuropathologies, and independent of that of NFT, CLB and ischemic lesions. Our results argue against AD-related neuropathology as a mediator of

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depression's effects on cognitive decline, but cannot rule out a significant mediation effect in a subset of cases, perhaps with greater baseline depressive symptoms.

Keywords

aging; Alzheimer's; depression; dementia; longitudinal; neuropathology

1. Introduction

Depression in non-demented persons has been identified as a possible risk factor for incident Alzheimer's disease (AD) [1,2]. In a recent meta-analysis, depression appeared to double the risk of AD [3]. Depressive symptoms are common in Mild Cognitive Impairment (MCI) [4] and appear to hasten conversion from MCI to clinical AD [5]. It has been suggested that depressive symptoms in AD may reflect a specific syndrome of "depression in AD" (dAD) [6].

The mechanism(s) by which depression might effect this risk has not been well established. However, depression is associated with widespread structural brain changes, including hippocampal atrophy [7] and with metabolic dysfunction in the orbitofrontal, and mesiofrontal cortex [8]. The latter structures are affected by AD pathology at about a Braak stage of V /VI [9].

Clinicians seldom diagnose dementia at earlier stages in AD's evolution, and hippocampal AD pathology is not associated with clinical dementia independently of neocortical lesions [10]. Thus, depressive symptoms may act as a proxy for preclinical AD lesions, or for conditions (inflammation, stress?) that favor AD pathology or its progression. However, these scenarios would also imply that progression of AD pathology mediates depression's apparent effect on the risk of dementia conversion.

The purpose of this analysis is to test that hypothesis using longitudinally collected psychometric testing and autopsy data from the Honolulu-Asia Aging Study (HAAS). If depression increases the risk of dementia conversion via an association with or an effect on the AD process itself, then the association between baseline depressive symptoms and subsequent cognitive change should be mediated by AD-related neurodegenerative changes.

2. Methods

2.1 HAAS

Autopsy tissue and clinical data were obtained from HAAS [11]. HAAS began in 1991 as an add-on to the Honolulu Heart Program (HHP). It is a longitudinal study of heart disease and stroke established in 1965 with the examination of 8006 Japanese-American men born 1900-1919. Brain autopsy and cognitive exams have been performed continuously since 1991.

2.2 HAAS autopsy material

838 autopsies had been performed prior to May, 2010. These represent approximately 20% of HAAS deaths since 1991. Although a diagnosis of dementia increased the likelihood that

family members would contact the HAAS and /or agree to autopsy at the time of death, previous analyses indicate a general comparability across the two groups (demented and non-demented) with regard to clinical and demographic features [12]. The current analyses are limited to autopsies obtained between 1991 and 2001. Microscopic examinations performed since 2001 have been done by a different team of neuropathologists, and have not yet been pooled for common analyses. Complete microscopic data generated by the first team are available in 493. 436 of those with complete microscopic data also have premorbid clinical information related to dementia and neuropsychological test performance.

The gross exams include external measurements and examination of 1 cm thick coronal sections of the entire brain for lacunes and large infarcts. The microscopic exam includes multiple stains for each of 38 tissue blocks from the brainstem and left hemisphere [13]. These are typically stained using Hematoxylin and Eosin (H&E) staining, Bielschowsky, Gallyus, and anti-A β . Anti- α -synuclein staining was done on isocortical sections from brains in which Lewy bodies were observed in H & E stained sections from the substantia nigra and /or locus ceruleus, and on a sample of brains in which no brainstem Lewy bodies were observed.

Microscopic AD pathology data include neurofibrillary tangle (NFT) counts, neuritic and diffuse (non-neuritic) amyloid plaque densities, vascular amyloid indices, substantia nigra neuronal counts, and anti- α -synuclein assessments of isocortical Lewy bodies. Focal ischemic lesions assessed included large cortical infarctions, small grey and white matter lacunes and “microinfarcts” (i.e., ischemic lesions visible only on light microscopy).

2.3 Pathological materials

Brains were fixed by submersion in 10% neutral formalin. Tissue samples were embedded in paraffin. Slides were cut at 8 micron thicknesses and stained as mentioned. Modified Bielschowsky, Gallyus and α -synuclein-stained slides were examined to quantify diffuse plaques (DP), neuritic plaques (NP), NFT, cortical Lewy bodies (CLB), and to determine Braak stage. NP were defined as extracellular accumulations of abnormal agyrophilic and anti-amyloid staining aggregates containing a central amyloid core and identifiable neurites (abnormal dark, coarse, tangled or irregular neuritic processes). DP were defined as unformed and amorphous plaques that lack identifiable neurites. NFT were defined by intraneuronal, cytoplasmic dense accumulations of agyrophilic (Bielschowsky or Gallyus stain) filamentous material that may be globoid, circumferential or flame-shaped. Extracellular or “tombstone” neurofibrillary tangles were interpreted as indicating that the neuron in which the NFT had developed had died and deteriorated. CLB were defined by round to oval, single or multiple intraneuronal, cytoplasmic accumulations of synuclein immunoreactive material.

NP, DP, and NFT were enumerated in 5 fields for each anatomical region, with post-assessment adjustment to produce counts standardized to areas of 1 square millimeter. Fields with the highest counts (2-dimensional densities) were selected for either the total plaque count (neuritic plus diffuse) or the total NFT count. Mean NP, DP, and NFT counts were calculated across 20 isocortical fields, from the right frontal, parietal, temporal, and occipital lobes. Total CLBs were counted in defined segments of the cortical gray ribbon of the four

main lobes, plus the insula and anterior cingulate cortex, in order to create a total cortical Lewy body score and a standard McKeith Lewy body score [14].

2.4 Clinical Assessments

2.4.1 Centers for Epidemiological Studies depression scale (CES-D)[15]—

Depressive symptoms were assessed using the CES-D. This scale rates self-reported frequency of 11 depression-related symptoms over the previous week. The CES-D's psychometric characteristics are well known. Gerety et al., [16] report that the CES-D score performs well as a screen for clinical depression in elderly patients [sensitivity (0.89), specificity (0.77), and area under the receiver operating curve (ROC) (0.91)] relative to blind expert structured clinical assessment.

2.4.2 Cognitive Abilities Screening Instrument (CASI)—The CASI was developed by merging an expanded MMSE (the 3MS) with the Hasegawa dementia scale [17,18]. The resulting measure has been rescaled to 100 points (higher score is better), and contains items addressing 9 cognitive domains, including long-term and short-term memory, attention, concentration, orientation, visuospatial abilities, judgment and abstract thinking, word fluency and language.

2.5 Statistical approach

2.5.1. Mediation models—Following the approach of MacKinnon et al. [19], we first modeled change in CASI scores (dCASI), as estimated by the slope parameter of a latent growth curve (LGC) model, adjusted for its intercept. In contrast to multiwave autoregressive models, which estimate interindividual rates of change across measurements, LGC models estimate the full trajectory of change across each individual's measurement points [20]. The residual variances were constrained to be equal across time, and their intercorrelations were determined empirically so as to achieve an acceptable fit. Then we used exploratory factor analysis to develop latent variables (factors) representing the shared variance in NP, DP, NFT, CLB counts, and ischemic lesions, across multiple regions of interest.

Next, we assessed the significance of the “direct” path between baseline CES-D and dCASI (b1). If this path was significant, we next tested each neuropathology factor as an independent predictor of the dCASI performance (b2) in separate models. Figure 1, for example, presents the mediation model for NFT. If the neuropathology factor in question was also significant, we then tested the indirect path (b2 + b3) as a mediator of the “direct” path b1. Finally, we built a single omnibus model of all the pathological factors as potential independent mediators. All models were adjusted for baseline age, education, total number of medications and brain weight at autopsy.

According to Kraemer et al. [21], the timing of the variables relative to each other is also important. For a true mediation effect, the mediator should occur between the predictor and the outcome, not coincidentally with the predictor. Thus, any AD pathology at the time of depression screening would be irrelevant to the mediation effect, although it could confound the analysis as it would be difficult to distinguish from salient incident lesions.

Technically, autopsy always follows both baseline depression scores and any intervening premorbid cognitive change. Thus, the path $b_2 > b_3$ in Figure 1 does not appear to be a classical mediation path. However, we have independently shown by a separate analysis in the same HAAS cohort that the AD pathology seen at autopsy must have developed during the period of CASI surveillance, and neither before nor after [22]. Thus, the development of this pathology was arguably contemporaneous with the observed change in CASI scores, and is therefore a potential formal mediator. The incident development of AD lesions between CASI /CES-D baseline and death /autopsy is also supported by 1) the observed normal mean CASI at baseline and impaired mean last CASI before death (Table 1) and 2) recent radiocarbon dating of AD lesions that date the pathology to the onset of cognitive decline [23].

2.52 Missing data—3734 subjects were available with a valid CASI score at wave 4 (ca 1991-1993). However, autopsy data are available only in a subset (436). Thus, there may be a high degree of missingness in models that combine autopsy and clinical variables.

All analyses were performed using Analysis of Moment Structures (AMOS) software [24]. AMOS uses Full Information Maximum Likelihood (FIML) methods to address missing data. FIML uses the entire observed data matrix to estimate parameters with missing data. In contrast to listwise or pairwise deletion, FIML yields unbiased parameter estimates, preserves the overall power of the analysis, and is currently the accepted state-of-the-art method in addressing issues of missing data [25,26]. Thus, the analysis is not limited to autopsied decedents with complete cases but instead employs the entire sample.

3. Results

Sample characteristics are presented in Table 1. Variable means are provided both for autopsied decedents and the entire cohort. Pathology factor loadings by anatomical region are presented in Table 2. Table 3 presents a LGM model of CASI scores. CASI scores were in the normal range at baseline (estimated mean = 82.32) and declined linearly in time (estimate $-11.32 = -1.1$ CASI points /year). There was significant variability about the baseline estimate and rate of decline in CASI scores, suggesting subsets within the cohort with discriminable rates of cognitive change.

CES-D scores were significantly associated with rate of decline in CASI scores ($r = -0.07$; $p < 0.001$), independently of its intercept, which, together with covariates, explained 30% of its variance. Age, medications and brain weight at autopsy were significant independent predictors of dCASI.

NFT counts added additional variance to the model ($R = 0.36$), but did not attenuate CES-D's effect ($r = -0.08$; $p = 0.002$) (Table 4). CES-D scores also were not significantly associated with NFT counts at autopsy. Thus, NFT did not mediate CES-D scores' significant association with the rate of decline in CASI scores.

In the omnibus model, CES-D scores, NFT counts, CLB counts and ischemic lesions each made significant independent contributions to the rate of decline in CASI scores (Table 5). 45.6% of the variance in dCASI was explained by these predictors. CES-D's effect remained

significant ($r = -0.06$; $p = 0.04$). However, CES-D scores were not significantly associated with any pathological variable and thus none were mediators of its effect.

In ancillary analyses (data not shown) we repeated the omnibus model after limiting the sample to cases with autopsy data ($N = 436$). The CES-D was no longer significantly associated with dCASI, although the pathological predictors retained their effects. We also shortened the period of CASI surveillance to six years, to see whether a shorter follow-up strengthened the association between CES-D and dCASI. It did not, although baseline CES-D retained its significant but weak association with dCASI, independent of the pathological predictors (in all subjects; $N = 3734$).

4. Discussion

We have confirmed that depressive symptoms, in fact *subsyndromal* depressive symptoms, are significantly associated with subsequent cognitive decline, *over up to 10 years*. Although this effect is relatively modest, it is independent of cognition's intercept.

The association between depressive symptoms and cognitive change might have been stronger had we been able to regress longitudinal change in CES-D scores onto cognitive change. Unfortunately, HAAS did not conduct serial depression screening. The association between depressive symptoms and cognitive change might also have been stronger had a more sophisticated cognitive battery been available. We recently showed that subsyndromal depressive symptoms can be related to incident changes in attention and executive function in initially non-demented persons [27]. Similarly, Goveas et al. [28] have found that subsyndromal CES-D scores can be associated with structural grey matter atrophy, particularly in the frontal lobes. Thus, the association between depressive symptoms and cognition is potentially mediated by structural brain changes.

However, Goveas et al. speculated that these changes reflect pre-clinical AD neuropathology. On the contrary, we found that baseline depressive symptoms in non-demented persons had no effect on subsequent memory test performance [27]. We argued that this precluded AD-related neuropathology as the mediator, as memory loss precedes executive impairment in that condition.

Our conclusion is confirmed in the present analysis. Here we have shown that the significant effect of depressive symptoms on cognitive change is independent of NFT, CLB, and ischemic pathology. Diffuse and neuritic amyloid plaques had no significant effects on cognitive change independently of CES-D scores and the other lesions. Thus, the association between depressive symptoms and subsequent cognitive decline does not appear to be mediated through any of these HAAS-rated neurodegenerative changes. This confirms a similar finding in the Religious Orders Study [29].

We have only considered the possibility of a mediation effect. Two risk factors for an outcome (e.g., clinically diagnosed "AD") can have other relationships that do not invoke causality [21]. Depression might moderate the independent effect of neuropathology on dementia status. It might overlap with the independent effect of neuropathology on dementia status. It might be a proxy for the independent effect of neuropathology on dementia status.

However, in the absence of a mediation effect, depression does not serve as an element in the causal chain of events that leads to neuropathology and hence to AD-related dementia, or the portion of a case's dementia status that is AD-related.

In truth, neuropathology appears to explain only a modest fraction of the observed variance in cognitive performance [30]. In our analysis, CES-D scores, NFT, CLB and ischemic lesions together explained only about 15% of the variance in the rate of change in cognitive performance. This suggests the potential for depressive symptoms to affect cognition via pathological changes that were not assessed by HAAS (i.e., regional atrophy, white matter change or synaptic density). Goveas' study [28] implicates depression-related frontal atrophy. However, such atrophy cannot be mediated by AD lesions, or in fact any of the neurodegenerative processes surveyed by HAAS. This raises the possibility of a true “dementia of depression”, independent of those pathologies. Alternatively, depressive symptoms may lead to lifestyle changes, nutritional changes, or drug exposures that can affect later cognitive declines. Finally, depression may affect a subject's motivation or capacity to engage in subsequent cognitive testing.

This analysis also confirms data from the HAAS [31] and elsewhere [30,32] which indicate that age-related cognitive changes are “overdetermined”, by independent and additive risk factors. Since the effect of depressive symptoms was independent of each of the pathologies modeled, it is also arguably a determinant of the observed dementia status.

In fact, the independent effect of depressive symptoms was comparable in size to that of DP and NP (i.e., amyloid-related lesions) (data not shown), and unlike these lesions, its effect survives adjustment for comorbid lesions (Table 5). The significance of this is that only depressive symptoms are known to be reversible with currently available pharmacotherapy. While anti-amyloid interventions are currently in development, all recent clinical trials of such interventions have failed to significantly improve cognition. These data suggest that increased attention to depressive symptoms may offer an alternative approach [33]. They also suggest that even subsyndromal depressive symptoms may be worthy of intervention, as successful treatment might slow cognitive decline and postpone or prevent conversion to dementia, despite the presence of comorbid neuropathologies.

Our analysis is well powered to detect an effect of depressive symptoms on dCASI. CES-D and CASI data are available on over 3,700 HAAS subjects at baseline, and we have 10 years of serial CASI surveillance. In contrast, autopsy data are available only in a fraction of cases. Our ability to detect a significant effect along the critical mediation path labeled b3 in Figure 1 may have been disadvantaged by missing data relative to our power to detect a significant effect along b1. Nevertheless, limiting the analysis to complete cases failed to attenuate dCASI's association with pathological predictors, which had only slightly stronger associations with dCASI than the CES-D. If our analysis has missed a significant mediation effect along b3, it must have been very weak and would not offer meaningful support for a “depression of AD”.

Limiting the analysis to the first six years of cognitive follow-up (to strengthen the CES-D's association with dCASI) did not appreciably change the results. Nevertheless, there is

significant variability about CES-D scores at baseline, and it may yet be that neuropathology acts as a mediator in the subset of cases with more severe depressive symptomatology at baseline. Growth Mixture Models may help identify any such subsets in this cohort.

In summary, we can confirm that subsyndromal depressive symptoms are significantly associated with subsequent cognitive decline. Although the effect is relatively modest, it is stronger than that of amyloid-related neuropathologies, and independent of that of NFT, CLB and ischemic lesions. Our results argue against AD-related neuropathology as a mediator of depression's effects on cognitive decline, but cannot rule out a significant mediation effect in a subset of cases, perhaps with greater baseline depressive symptoms.

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Figure 1. Latent Growth Curve Model of NFT Formation

CA1 = cornu ammonis area 1; CASI = Cognitive Abilities Screening Instrument; CESD = Center for Epidemiological Studies Depression scale; FRNT = frontal lobe; NFT = neurofibrillary tangles; PAR = parietal lobe; OCC = occipital lobe; TEMP = temporal lobe. Significant associations in bold.

Table 1
Demographic Features

	N	N*	Mean	SD
Baseline Age (yrs)	3734		77.8	4.7
Baseline Age (yrs)		436	79.6	5.1
Education (yrs)	3734		10.5	3.2
Education (yrs)		436	10.4	3.4
Baseline CASI Score	3734		82.2	16.4
Baseline CASI Score		436	76.7	21.3
Baseline CES-D Score	3203		3.7	3.7
Baseline CES-D Score		504	4.0	3.9
Medications	2701		2.9	2.0
Last CASI Score Before Death		436	61.6	29.1
Age at Death (yrs)		436	85.9	5.3
Braak Stage		393	3.7	1.3
Brain Weight (g)		435	1229.9	120.8

* Autopsied subset

Table 2
Pathological Factor Loadings[†]

NFT	Factor Loading	p
CA1	0.63	<0.001
Subiculum	0.49	<0.001
Temporal	0.85	<0.001
Parietal	0.80	<0.001
Frontal	0.72	<0.001
Occipital	0.59	<0.001

NP	Factor Loading	p
Temporal	0.93	<0.001
Parietal	0.97	<0.001
Frontal	0.88	<0.001
Occipital	0.86	<0.001
CA1	0.56	<0.001
Subiculum	0.58	<0.001

DP	Factor Loading	p
Temporal	0.91	<0.001
Parietal	0.92	<0.001
Frontal	0.47	<0.001
Occipital	0.72	<0.001
CA1	0.44	<0.001
Subiculum	0.66	<0.001

CLB	Factor Loading	p
Anterior cingulate	0.95	<0.001
Frontal	0.92	<0.001
Temporal	0.94	<0.001
Insula	0.83	<0.001
Parietal	0.86	<0.001
Occipital	0.71	<0.001

Ischemic Lesions	Factor Loading	p
Total lacunes	0.59	<0.001
Hemorrhagic & large infarcts	0.46	<0.001
Microvascular lesions: BG & thal	0.46	<0.001
Microvascular lesions: Cortical grey matter	0.37	<0.001
Microvascular lesions: Cortical white matter	0.15	<0.001

[†]From Omnibus Model

Table 3
Latent Growth Model of Change in CASI scores over 10 years (R = 0.30)

Estimated means		p
dCASI	-11.32	<0.001
Baseline CASI	82.32	<0.001
CES-D	3.73	<0.001
Age	77.82	<0.001
Medications	2.93	<0.001
Education	10.51	<0.001
Brain weight	1225.16	<0.001

Standardized Regression Weights	p	
Baseline CASI > dCASI	0.42	<0.001
CES-D > dCASI (b1)	-0.07	<0.001
Age > dCASI	-0.30	<0.001
Medications > dCASI	-0.05	0.05
Education > dCASI	-0.07	0.19
Brain weight > dCASI	0.15	0.004

Table 4
NFT Mediation Model of Change in CASI scores over 10 years (R = 0.36)

Estimated Means		p
dCASI	-11.32	<0.001
Baseline CASI	82.32	<0.001
CES-D	3.73	<0.001
NFT	1.45	<0.001
Age	77.82	<0.001
Medications	2.93	<0.001
Education	10.51	<0.001
Brain weight	1224.90	<0.001

Standardized Regression Weights		p
Baseline CASI > dCASI	0.41	<0.001
CES-D > dCASI (b1)	-0.08	0.002
NFT > dCASI (b2)	-0.27	<0.001
CES-D > NFT (b3)	-0.02	0.70
Age > dCASI	-0.30	<0.001
Medications > dCASI	-0.05	0.04
Education > dCASI	-0.07	0.19
Brain weight > dCASI	0.14	0.006

Table 5
Omnibus Mediation Model of Change in CASI scores over 10 years (R = 0.46)

Estimated Means		p
dCASI	-11.32	<0.001
Baseline CASI	82.32	<0.001
CES-D	3.73	<0.001
NFT	1.55	<0.001
NP	1.78	<0.001
DP	1.56	<0.001
CLB	0.16	0.62
Ischemic Lesions	1.75	<0.001
Age	77.82	<0.001
Medications	2.93	<0.001
Education	10.51	<0.001
Brain weight	1224.24	<0.001

*Standardized Regression Weights	p	
Baseline CASI > dCASI	0.40	<0.001
CES-D > dCASI	-0.06	0.04
NFT > dCASI	-0.23	<0.001
NP > dCASI	-0.09	0.20
DP > dCASI	-0.12	0.08
CLB > dCASI	-0.22	<0.001
Ischemic Lesions > dCASI	-0.22	0.003
CES-D > NFT	-0.03	0.57
CES-D > NP	-0.07	0.181
CES-D > DP	0.01	0.84
CES-D > CLB	0.08	0.12
CES-D > Ischemic Lesions	0.001	0.98
Age > dCASI	-0.3	<0.001
Medications > dCASI	-0.05	0.03
Education > dCASI	-0.08	0.13
Brain weight > dCASI	0.13	0.01