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Association of β-amyloid pathology with decision making and scam susceptibility

A Kapasi, Ph.D.[1,2], **L Yu, Ph.D.**[1,3], **CC Stewart, Ph.D.**[4], **JA Schneider, M.D.**[1,2,3], **DA Bennett, M.D.**[1,3], **PA Boyle, Ph.D.**[1,5]

[1]Rush Alzheimer's Disease Center, Rush University Medical Center, Chicago, IL

[2]Department of Pathology (Neuropathology), Rush University Medical Center, Chicago, IL

[3]Department of Neurological Sciences, Rush University Medical Center, Chicago, IL

[4]Department of Neurology, Indiana University School of Medicine, Indianapolis, IN

[5]Department of Behavioral Sciences, Rush University Medical Center, Chicago, IL

Abstract

Importance: Recent findings suggest that poor decision making and increased scam susceptibility are harbingers of Alzheimer's dementia and may be among the earliest behavioral manifestations of pathologic cognitive aging. However, the degree to which poor decision making and scam susceptibility reflect accumulating Alzheimer's disease (AD) pathology remains unclear.

Objective: To investigate the associations of AD pathology with decision making and scam susceptibility in older adults without dementia.

Methods: Data came from 198 deceased participants without clinical dementia (mean age at death =90 years; 69% women) from two ongoing studies of aging. All underwent annual clinical evaluations, completed assessments of healthcare and financial decision making and scam susceptibility, and brain donation. Neuropathologic evaluations quantified pathologic hallmarks of AD, β-amyloid and tau-tangles, Lewy body pathology, and TDP-43 proteinopathy.

Results: In linear regression models adjusted for demographics, β-amyloid pathology was associated with lower decision making (estimate = −0.35; SE = 0.16, $p = 0.03$), particularly healthcare decision making (estimate = −0.20; SE = 0.09, $p = 0.03$), as well as greater scam susceptibility (estimate = 0.12; SE = 0.04, $p = 0.003$); tau-tangle pathology was not related. Further, TDP-43 pathology was associated with greater scam susceptibility (estimate = 0.10; SE = 0.04; $p = 0.02$).

Conclusion: Accumulating AD pathology, particularly β-amyloid, is associated with poor decision making and increased scam susceptibility among older persons without overt cognitive

Contact Information for Corresponding Author: Alifiya Kapasi Ph.D., Rush Alzheimer's Disease Center, Rush University Medical Center, Jelke Building, 1750 W. Harrison St, Chicago, IL, 60612. Alifiya_Kapasi@rush.edu.

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impairment. These findings provide compelling evidence that decision making and scam susceptibility are sensitive to the earliest pathological changes of AD.

INTRODUCTION

Decision making, a complex behavior that requires cognitive, affective, and motivational resources, is central to health and wellbeing throughout life, but is especially critical in old age. Older individuals face a number of important health-related and financial decisions. While these decisions are especially challenging for older persons who suffer from multi-morbidity and cognitive impairment [1–3], evidence suggests that even those without overt cognitive impairment struggle with decision making. For example, in the United States alone, older individuals lose upwards of 35 billion dollars per year to financial scams and other forms of exploitation [4] and many victims are cognitively intact [5]. The problem of elder exploitation is worsening rapidly, as fraudsters increasingly target social security beneficiaries and those worried about their health, an issue that has come to the forefront in light of the dramatic influx of COVID-19 scams [6]. Compounding the economic challenge is a major public health problem, with financial exploitation leading to adverse health and social outcomes including depression, hospitalization, and early mortality [7–9]. Awareness of the public health implications recently spurred federal agencies such as the CDC to call for intense efforts to understand the basis and scope of older adults' heightened vulnerability [10].

Recent evidence shows that poor decision making and scam susceptibility in old age are harbingers of Alzheimer's dementia [2], mild cognitive impairment (MCI) [11], and cognitive decline [2] [12]. Further, even among those who are cognitively intact, subtle age-related deteriorations in cognition impairs decision making and increases scam susceptibility [13]. Alterations in these complex behaviors may be among the earliest manifestations of pathologic cognitive aging [2,13] and indicative of accumulating Alzheimer's disease (AD) pathology in the years before cognitive symptoms develop. Understanding the degree to which poor decision making and scam susceptibility reflect accumulating AD pathology may offer novel approaches to facilitate early detection of subclinical AD.

In this study, we tested the hypothesis that AD pathology is associated with decision making (i.e., financial and health decision making) and scam susceptibility among a cohort of well-characterized, non-demented older adults who underwent autopsy. Because β-amyloid is thought to be the initiating pathologic change in AD and tau tangles develop later, analyses of these markers separately offer clues to the temporal cascade of AD and its behavioral impact.

METHODS

Participants

Participants were from one of two ongoing clinical-pathologic studies of aging, the Religions Orders Study (ROS) and the Rush Memory and Aging Project (MAP) [14]. Upon enrollment, participants consent to annual clinical evaluations and brain donation at the time of death. A decision making sub study, which includes annual assessments of healthcare and

financial decision making and scam susceptibility was added to ROS and MAP in 2010. ROS, MAP, and the decision making sub-study were approved by the Institutional Review Board of Rush University Medical Center. All subjects signed an informed consent and an Anatomical Gift Act for brain donation.

At the time of the present analyses, 3,652 older participants were recruited into ROS or MAP, of which 1,290 had completed the decision making sub study. Of these 1,290 participants, 392 died, 355 underwent autopsy, and 314 had complete neuropathologic data as required for these analyses. We excluded participants with clinical dementia (n = 116), leaving a final sample size of 198 older persons without dementia. Participants mean age-at-death was 90.2 years (SD 6.2; range 71.2–103.6), the mean level of education was 15.5 years (SD 3.2; range 0–27), and 68.7 % were women.

Clinical Diagnosis

Participants underwent structured annual clinical evaluation, as previously described [15]. Dementia was diagnosed using the criteria of the National Institute of Neurologic and Communicative Disorders and Stroke (NINCDS) and the Alzheimer's Disease and Related Disorders Association (ADRDA) [16]. Participants who had cognitive impairment but did not meet the criteria for dementia were classified as having MCI, and participants without any cognitive impairment were classified as no cognitive impairment (NCI). Clinical diagnoses were made blind to demographic information and postmortem data.

Assessment of Decision Making

Our healthcare and financial decision making measure was performance-based and consisted of 12 items in total (6 healthcare and 6 financial items) as described elsewhere [17]. Participants answered questions requiring comprehension and integration of tabulated information about health maintenance organization (HMO) plans (for healthcare items) or mutual funds (for financial items). Total decision making was quantified as the number of items answered correctly, which in turn, was averaged to generate a composite score for each participant (range 0–12, with lower scores indicating poorer decision making). Separate measures of healthcare decision making and financial decision making were quantified in an analogous fashion using the corresponding health and financial items (range 0–6), with lower scores indicating poorer decision making in those domains). All participants with a least one valid decision making assessment were included in the analyses. Of note, 26% of participants had at least one decision making assessment and 74% having two or more assessments (mean 3, SD=2.1). The mean interval between autopsy and last decision making assessment was 1.5 years (SD=1.49). For analyses, an average score for each decision making measure was derived from all assessments over time.

Scam Susceptibility

Our scam susceptibility measure consisted of 5 statements that participants rated along a 7-point scale ranging from strongly agree (1) to strongly disagree (7). The statements pertained to behaviors associated with vulnerability to fraud and scams and were developed based on findings from the American Association of Retired Persons (AARP) [18] and the Financial Industry Regulatory Authority (FINRA) Risk Meter [19], as previously described

[13]. Participants rated their level of agreement with each item using a Likert scale (1–7) and scam susceptibility was quantified as the average rating across the 5 items; higher scores indicate greater susceptibility. For analyses, an average score for scam susceptibility was derived from all assessments over time.

Neuropathology

Average post-mortem interval was 10.4 hours (SD=8.6), and brain removal and processing followed a standard protocol. Briefly, one hemisphere was cut into 1-cm coronal slabs and fixed in 4% paraformaldehyde for 48–72 hours.

Brain Regions ––—Tissue was taken from 8 brain regions; midfrontal, superior frontal, anterior cingulate, inferior temporal, entorhinal, inferior parietal, calcarine cortices, and mid-hippocampus at level of lateral geniculate nucleus, as previously described [20]. Additionally, 5 regions were added in those participants partaking in the decision making study; ventromedial frontal, anterior insular, amygdala, anterior caudate, and nucleus accumbens.

Cortical β-amyloid and PHF-tau tangle pathology ––—Total 13 brain regions were assessed for β-amyloid and PHF-tau tangle densities, as previously described [20] (see Supplementary Material). Because the 5 additional brain regions have not been previously evaluated in ROS and MAP, we examined intercorrelations of cortical β-amyloid and PHF-tau tangle burden across all 13 brain regions. This analysis revealed strong positive correlations for cortical β-amyloid between all regions, while positive correlations for PHF-tau tangle pathology showed greater variation. For analyses, global composite measures for β-amyloid burden and PHF-tau tangle density were obtained by averaging the mean percentage area per region, across all 13 regions. Square root transformation was applied to cortical β-amyloid load and PHF tau-tangle density.

Lewy body pathology ––—Lewy body pathology was assessed using phosphorylated α-synuclein antibody (Zymed Labs; 1:100) in seven regions including substantia nigra, limbic and neocortical regions, as described previously [21].

TDP-43 pathology ––—Phosphorylated transactive response DNA-binding protein 43 (TDP-43) pathology was assessed by immunohistochemistry using a monoclonal antibody to phosphorylated TDP-43 (pS409/410; 1:100). TDP-43 was evaluated in 8 brain regions; amygdala, hippocampus, dentate gyrus, entorhinal cortex, anterior temporal pole, middle temporal gyrus, mid-frontal gyrus and orbitofrontal cortex, as described previously [22].

Statistical Analysis

We first examined bivariate associations of demographics with decision making and scam susceptibility, and examined bivariate associations of demographics, decision making, and neuropathologic characteristics in persons with and without a pathological diagnosis of AD. In separate multivariable linear regression models, we included terms for β-amyloid, tau tangle burden, as well as age, sex, and education, Lewy body pathology, and TDP-43, to examine associations of β-amyloid and tangle pathology with our measures of decision-

making outcomes (i.e. total, health, and financial). We used similar linear regression models to examine AD pathologic correlates for scam susceptibility. In subsequent analyses, to determine whether amyloid associations differ by presence of *APOE*-e4, MCI status, or sex, we augmented separate models by including a term for the interaction between β-amyloid and *APOE*-e4, a term for the interaction between β-amyloid and MCI status, and a term for the interaction between β-amyloid and sex. All models with interaction terms were adjusted for demographics and tangle pathology. We further included an interaction term between tangles and *APOE*-e4. Statistical significance for all analyses was determined at α level of 0.05.

RESULTS

Descriptive characteristics

Lower decision making was associated with older age ($r = -0.25$; $p<0.001$) and fewer years of education ($r = 0.40$; $p<0.001$), and men tended to perform better than women on decision making measures (total: $F_{1, 196}= 8.59$; $p=0.004$; healthcare: $p=0.02$; financial: $p=0.002$). Greater scam susceptibility was associated with older age ($r = 0.24$, $p<0.001$) but not education. Men and women did not differ in scam susceptibility ($p=0.70$).

It is now recognized that many individuals without clinical dementia meet criteria for a pathological diagnosis of AD, as was the case in this sample (58%). Those with a pathologic AD were older, more likely to have a diagnosis of MCI proximate to death, had lower decision making, and greater scam susceptibility. In the overall sample the mean burden of β-amyloid was 1.54-units (SD=1.20) and the mean burden of tangle pathology was 1.1-units (SD=0.80), among those with pathologic AD, the mean β-amyloid and tangle burdens were higher. In the overall group, Lewy body pathology was present in 22% of participants and TDP-43 pathology was present in 42% (Table 1).

Associations of β-amyloid and tangle pathology with decision making and scam susceptibility

We first examined associations of β-amyloid and tangles with total decision making score. In a linear regression model adjusted for age, sex, education, Lewy body, and TDP-43 pathology, we found that greater β-amyloid burden was associated with lower decision making (Table 2, Figure 1), while tangle pathology was not associated with decision making. More specifically, each additional unit in β-amyloid burden was associated with a 0.35-unit (95% CI: −0.67, 0.03) decrease in performance on the decision making measure. Next, in separate models we determined whether the association with β-amyloid pathology was driven by a specific decision making domain. In these models, β-amyloid burden was associated with lower health decision making, but the association with financial decision making did not quite meet the threshold for statistical significance. In analyses with scam susceptibility as the outcome, β-amyloid was associated with greater scam susceptibility, such that each additional unit of β-amyloid burden was associated with 0.12-unit (95% CI: 0.04, 0.20) increase in scam susceptibility (Figure 1). By contrast, tangle pathology was not associated with scam susceptibility. Interestingly, TDP-43 pathology was significantly associated with greater scam susceptibility (Table 2).

Because neurofibrillary tangle pathology has a stereotypical pattern of accumulation in the brain, we examined the association of mesial temporal tangle burden as well as neocortical tangle burden with decision making and scam. In linear regression models adjusted for demographics and amyloid, neither mesial temporal tangle burden nor neocortical tangle burden were related to decision making [(estimate = 0.08; 95% CI : −0.16 – 0.31) and (estimate = −0.18, 95% CI: −0.69 – 0.33), respectively] or to scam susceptibility [(estimate = −0.01; 95% CI: −0.07 −0.05) and (estimate = −0.06; 95% CI: −0.19 – 0.07), respectively].

In a sensitivity analysis, we excluded persons (n=20) with long intervals between the last decision making assessment and autopsy (>3 years). Associations with β-amyloid with both decision making (estimate = −0.41; 95% CI: −0.73, −0.09.; p= 0.01) and scam susceptibility (estimate = 0.12; 95 CI: 0.04, 0.20; p=0.003) remained statistically significant.

Modifying factors

Given that APOE-e4 is thought to manifest clinically via amyloid deposition, we conducted additional analyses to test whether APOE-E4 status modified the relationship of β-amyloid pathology with decision making and scam susceptibility. We did not find any evidence of an interaction for either total decision making (estimate = −0.10; 95% CI: −1.10, 0.90; p=0.84) or scam susceptibility (estimate = −0.03; 95% CI: −0.28, 0.22; p=0.81). We further tested whether APOE-e4 status modified the relationship between tau-tangles with decision making. We did not find significant interactions for either decision making (estimate = −0.14; 95% CI: 1.45, 1.16; p=0.83) or scam susceptibility (estimate = 0.10; 95% CI: −0.22, 0.43; p=0.54). We also did not find any significant interaction between β-amyloid and tau-tangles with decision making (estimate = −0.25; 95% CI: −0.78, 0.28; p=0.35) or scam (estimate = −0.02; 95% CI: −0.15, 0.12; p=0.80). Additionally, to determine whether the primary results were driven by persons with emerging cognitive impairment, we examined whether the associations with β-amyloid differed by MCI status. We did not find any evidence of interaction for either decision making or scam susceptibility [(estimate= −0.15; 95% CI: −0.78 – 0.48; p=0.65); (estimate= 0.06; 95% CI: −0.10 – 0.23; p=0.45)]. Lasty, we did not find any evidence of an interaction between β-amyloid and sex with decision making (estimate= −0.42; 95% CI: −1.03 – 0.22; p=0.20) or scam susceptibility (estimate= 0.01; 95% CI: −0.15 – 0.17; p=0.85).

DISCUSSION

In a community-based sample of nearly 200 participants free of dementia, we found that β-amyloid pathology was associated with poor decision making and increased scam susceptibility, while tangle pathology was not. Further, we found that non-AD proteinopathies, TDP-43 pathology, is also associated with greater scam susceptibility. These data provide novel and compelling evidence that poor decision making and vulnerability to scams among older adults without dementia reflect accumulating neurodegenerative pathology, specifically β-amyloid pathology, the first pathologic change in the AD continuum.

We previously reported that decision making and scam susceptibility are not only associated with an increased risk for Alzheimer’s dementia and its precursor, MCI, but also related

to subtle changes in cognition over time even in individuals without any detectable cognitive impairment [2,12,13]. Our current study extends these findings to show that poor decision making and scam susceptibility reflect accumulating neurodegenerative pathology, particularly β-amyloid pathology in the earliest stages of the disease process (i.e., before the onset of overt cognitive impairment). supporting the notion that amyloid pathophysiologic mechanisms impact behavior [23]. This study is novel in that very little is known about AD and non-AD pathologic changes that underlie poor decision making and scam susceptibility in old age, especially among those without dementia, and offers new insights into the scope of behaviors affected by β-amyloid and TDP-43 pathology. In addition, this study for the first time examined pathologic correlates with both financial and healthcare decision making, domains of decision making that are particularly relevant to the aging population. In conjunction with our prior work showing that decision making and scam susceptibility are associated with the risk of dementia, MCI, and cognitive decline in older individuals, our findings strongly support the conclusion that changes in these behaviors signal a very early manifestation of accumulating neurodegenerative proteinopathies, specifically β-amyloid pathology. Notably, we did not find a significant interaction between MCI and amyloid in relation to decision making, suggesting that the relationship may not differ by cognitive status. We conceptualize decision making as a higher order function relative to traditional cognitive measures and our prior work suggests that alterations in decision making may occur prior to overt cognitive syndromes (i.e., MCI). Thus, elevated β-amyloid burden may impact decision making prior to cognitive function but the effect of amyloid with decision making may not vary by cognitive status. We hypothesize that additional physical and lifestyle factors contribute to poor decision making in old age, and further work exploring the role of chronic illness, physical disabilities, and mental health status with neuropathological pathways and decision making is ongoing.

The present findings have important implications regarding the very early functional consequences of accumulating AD. Accumulation of β-amyloid is considered to be the initial pathogenic event in the development of AD, occurring over years or decades prior to onset of any clinical symptoms, and amyloid is indeed abundant in older individuals with no cognitive impairment [24–26]. Accumulation of tau initially occurs in the mesial temporal lobe, followed by the neocortex [27]. Interestingly, in the current study, we found no relationship between mesial temporal or neocortical tau pathology with decision making or scam susceptibility. This suggests that decision making is an early behavioral change associated with accumulation of β-amyloid, the initiating event in the AD cascade, and not tau pathophysiological changes thought to be downstream of amyloid accumulation and proximal to cognitive changes. Tau can also accumulate in the brainstem, often preceding cortical tau pathology [28,29]. Prior studies have shown tau pathology in the brainstem to be associated with neuropsychiatric symptoms [30,31]. Furthermore, neural inputs from specific brainstem nuclei play a pivotal role in decision making [32]. We are actively collecting tau pathology data in brainstem nuclei, and future work exploring tau pathology in these regions will be important.

The reasons why decision making and scam susceptibility are sensitive to early neurodegenerative pathologies are unclear. Accumulation of β-amyloid, even in early stages of disease, occurs in highly connected brain regions and impacts neurotransmission and

neural activity. We conceptualize decision making and scam susceptibility as complex behaviors that involve integration and coordination of diverse cognitive, affective, and socioemotional resources, and we suspect that elevated burden of β-amyloid pathology in old age impacts multiple brain networks linked to socio-emotional processing that support these complex abilities [33–38]. The finding that TDP-43 pathology was also associated with increased scam susceptibility is of particular interest, suggesting that other pathologic factors are at play and that functional networks that may not be related to AD pathology may also be crucial in maintaining complex decision making [39]. Further pathologic-neuroimaging studies are needed to examine the relationship between neurodegenerative pathologies, brain network degeneration, and decision making, and this work is ongoing.

Within the biomarker field, preeminence is given to β-amyloid pathology given its importance as the earliest marker of AD [40]. Therefore, identifying changes in behaviors associated with β-amyloid pathology, especially in prodromal AD, is highly relevant. While future work incorporating β-amyloid biomarkers (PET, CSF, or plasma) will be crucial and necessary to validate associations between β-amyloid and decision making, our current findings suggest that assessments of complex behaviors such as decision making and scam susceptibility offers high potential to facilitate identification of individuals with accumulating β-amyloid pathology and those at greatest risk for subsequent cognitive decline. The measure used here was developed for use in an epidemiologic study and our measure alone is not suitable to predict β-amyloid burden at an individual level. However, appropriately validated measures to assess decision making and scam susceptibility in clinical settings may offer very important diagnostic tools.

To our knowledge, this is the first study showing that β-amyloid pathology is associated with both decision making and scam susceptibility in older persons without dementia. This study has multiple strengths. Data came from a group of well-characterized, community-based, older persons without dementia. We used well validated measures of decision making that assess domains that are highly relevant for the older and the most vulnerable populations, particularly healthcare and financial decision making and scam susceptibility. We were also able to assess measures of β-amyloid and tau tangle burden from a diverse range of brain regions. A limitation is that this study included primarily non-Latino white and highly educated participants, limiting generalizability. Future work is needed to assess the neuropathologic correlates of change in decision making using formal longitudinal modeling approaches and to examine potential terminal decline in decision making as sufficient longitudinal data accrue. In addition, more work is needed to explore pathological signatures that impact functional and structural connectivity related to decision making in older adults, providing important information to advance our understanding of neural underpinnings of early signs of pathologic aging.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Data Availability

Raw data are available by request through the Rush Alzheimer's Disease Center (RADC) Research Resource Sharing Hub https://www.radc.rush.edu/

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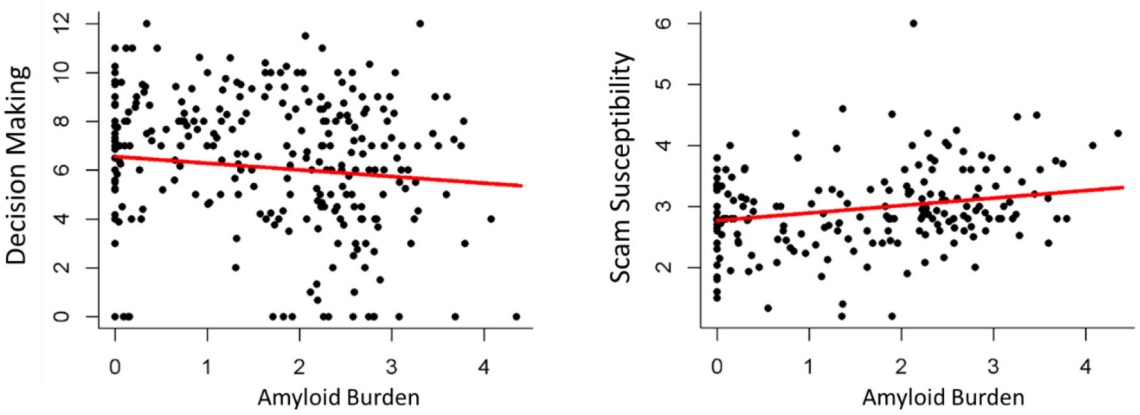

Figure 1–. Association of β-amyloid burden with decision making and scam susceptibility.
Associations between β-amyloid with total decision making and scam susceptibility, adjusted for demographics and PHF-tau tangles. Each black circle represents data from a single individual.

Table 1.

Characteristics of participants without dementia

	Overall (N=198)	With a Pathological diagnosis of AD (N=115)	Without a pathological diagnosis of AD (N=83)	*p*-value
Demographics, Mean (SD) or N (%)				
Age-at-death	90.2 (6.19)	91.6 (5.71)	88.3 (6.34)	<0.001
Sex, Women	136 (68.7%)	80 (69.6%)	56 (67.5%)	0.75
Education	15.5 (3.18)	15.1 (3.12)	16.0 (3.20)	0.06
APOE-e4 *	33 (17.2%)	24 (21.8%)	9 (4.7%)	0.05
Clinical, N (%)				
No Cognitive Impairment	123 (62.1%)	57 (28.8%)	66 (33.3%)	<0.001
Mild Cognitive Impairment	75 (37.9%)	58 (29.3%)	17 (8.6%)	<0.001
Decision Making, Mean (SD)				
Overall Decision making	6.86 (2.82)	6.5 (2.95)	7.4 (2.56)	0.04
Financial Decision Making	3.2 (1.39)	3.0 (1.46)	3.5 (1.24)	0.04
Health Decision Making	3.7 (1.59)	3.5 (1.65)	3.9 (1.48)	0.07
Scam Susceptibility	2.9 (0.67)	3.0 (0.70)	2.8 (0.59)	0.008
Neuropathologic, Mean (SD) or N(%)				
Cortical β-Amyloid density	1.5 (1.20)	2.3 (0.87)	0.5 (0.80)	<0.001
NFT-Tau Tangle density	1.1 (0.80)	1.4 (0.86)	0.7 (0.41)	<0.001
Lewy body pathology	44 (22.2%)	26 (22.6%)	18 (21.7%)	0.88
TDP-43 pathology	84 (42.4%)	55 (47.8%)	29 (23.1%)	0.09

* Missing data for 6 participants. Abbreviations: SD-standard deviation, NFT-neurofibrillary tangles

Table 2.

Association of neurodegenerative pathologies with decision making and scam susceptibility.

	Total Decision Making	Financial Decision Making	Healthcare Decision Making	Scam Susceptibility
β-Amyloid	**−0.35 (0.16,0.03)**	−0.15 (0.08,0.06)	**−0.20 (0.09,0.03)**	**0.12 (0.04,0.003)**
PHF-tau tangles	−0.07 (0.25,0.79)	−0.03 (0.13,0.80)	−0.04 (0.15,0.81)	−0.07 (0.06,0.28)
Lewy bodies	0.01 (0.44,0.98)	0.07 (0.22,0.74)	−0.06 (0.25,0.80)	0.19 (0.11,0.08)
TDP-43	0.15 (0.18,0.41)	0.08 (0.09,0.39)	0.07 (0.10,0.49)	**0.10 (0.04,0.02)**

Estimates in each cell were obtained from 4 linear regression models with separate outcomes, adjusted for demographics and pathologic indices. Cell values represent β-coefficient (SE, *p*-value)