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POSTER PRESENTATION

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Loneliness predicts stronger negative associations between cerebrovascular, but not Alzheimer's, pathology and cognition

Patrick J. Lao[1] | Christina B Young[2] | Ryan M Andrews[3] | Laura E Gibbons[4] | A.Zarina Kraal[1] | Indira C Turney[1] | Kacie D Deters[5] | Alexandra N Trelle[5] | Joshua T. Fox-Fuller[3] | Lex Minto[6] | Dominika Seblova[1] | Shubhabrata Mukherjee[4] | Vonetta M Dotson[6] | Jennifer J Manly[1] | Laura B. Zahodne[7]

[1]Columbia University Irving Medical Center, New York, NY, USA

[2]Stanford University School of Medicine, Stanford, CA, USA

[3]Boston University, Boston, MA, USA

[4]University of Washington, Seattle, WA, USA

[5]Stanford University, Stanford, CA, USA

[6]Georgia State University, Atlanta, GA, USA

[7]University of Michigan, Ann Arbor, MI, USA

Correspondence
Patrick J. Lao, Columbia University Irving Medical Center, New York, NY, USA.
Email: pjl2133@cumc.columbia.edu

Abstract

Background: Alzheimer's disease (AD) and cerebrovascular disease are the two most common pathologies underlying dementia. Loneliness is associated with faster cognitive decline and greater AD risk independent of pathology. Risk reduction efforts would benefit from knowing whether loneliness exacerbates the cognitive impact of pathology. Our objective was to characterize the interaction between loneliness and AD or cerebrovascular pathology on cognitive performance.

Methods: Participants with neuropathological data were drawn from the Religious Orders Study, the Memory and Aging Project, and the Minority Aging Research Study (Table 1). Loneliness was assessed with a modified version of the de Jong-Gierveld Loneliness Scale. Amyloid and tau pathology were assessed jointly with the NIA-Reagan scale as high/intermediate likelihood or low likelihood/no AD. Chronic infarcts and chronic microinfarcts were each assessed as present or not present. Composite domain scores for episodic memory, working memory, semantic memory, perceptual speed, and perceptual orientation were obtained from the study visit proximal to death. Separate general linear models were run for each domain and each pathology, including an interaction between loneliness and pathology and adjusting for covariates.

Results: Greater loneliness was associated with older age and lower education, and loneliness was greater in men compared to women, but not different by race or *APOE-ε4* (2). Loneliness was not associated with AD or cerebrovascular pathology (Table 3). Greater loneliness was independently associated with lower cognitive scores in all domains. Greater pathology was independently associated with lower episodic memory and semantic memory scores, while cerebrovascular disease was not independently associated with cognitive scores. We additionally found that negative associations between microinfarcts and cognitive scores in working memory, semantic memory, and perceptual orientation were stronger among individuals with greater (Table 4).

Conclusions: Negative associations between loneliness and cognition are apparent across domains and independent of pathology. While loneliness does not appear to

be related to AD or cerebrovascular pathology directly, it may increase susceptibility to cognitive impairment due to microinfarcts. Social support-based interventions may benefit optimal brain aging, particularly in older adults exposed to greater loneliness.

Variables	Distribution
N	960
Age at death [years]	90±6, 65.9 to 108.3
Sex	32% men, 68% women
Race	94% White, 6% Black
Education [years]	15±3, 5 to 28
Having at least one *APOE-ε4* allele	80% *APOE-ε4* non-carrier, 20% *APOE-ε4* carrier
Loneliness	2.4±0.6, 1 to 5
NIA-Reagan	44% low likelihood/no AD, 56% intermediate/high likelihood
Chronic Infarcts	65% not present, 35% present
Chronic Microinfarcts	69% not present, 31% present
Episodic Memory [average z-scores of 7 tests]	-0.53±1.1, -3.5 to 1.5
Working Memory [average z-scores of 3 tests]	-0.37±0.85, -3.4 to 1.9
Semantic Memory [average z-scores of 3 tests]	-0.66±1.1, -8.0 to 2.0
Perceptual Orientation [average z-scores of 2 tests]	-0.21±0.89, -3.2 to 1.7
Perceptual Speed [average z-scores of 4 tests]	-0.91±0.94, -3.2 to 1.3

Table 1. Distributions of demographics, loneliness, AD and cerebrovascular pathology, and cognitive z-scores.

	Association with loneliness B [95% CI], p-value
Age at death [years]	0.02 [0.01, 0.03], p=0.00005
Men	0.14 [0.03, 0.25], p=0.009
Black	0.03 [-0.18, 0.24], p=0.81
Education [years]	-0.03 [-0.05, -0.01], p=0.002
Having at least one *APOE-ε4* allele	0.03 [-0.09, 0.15], p=0.61

Table 2. Multivariate associations of demographic variables with loneliness.

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Model	Association with loneliness B [95% CI], p-value
NIA-Reagan	-0.006 [-0.11, 0.10], p=0.91
Chronic Infarcts	0.04 [-0.06, 0.14], p=0.41
Chronic Microinfarcts	-0.02 [-0.12, 0.08], p=0.65

Table 3. Associations of AD or cerebrovascular pathology with loneliness in three models, all adjusted for age at death, sex, race, years of education, and having at least one *APOE-ε4* allele.

Model	Episodic memory	Working memory	Semantic memory	Perceptual Orientation	Perceptual Speed
Loneliness	-0.27 [-0.45, -0.09], p=0.003	-0.23 [-0.37, -0.09], p=0.001	-0.38 [-0.56, -0.20], p=0.00004	-0.28 [-0.43, -0.13], p=0.0002	-0.40 [-0.55, -0.25], p=0.0000003
NIA-Reagan	-0.86 [-1.47, -0.25], p=0.006	-0.35 [-0.84, 0.14], p=0.16	-0.64 [-1.26, -0.02], p=0.046	-0.31 [-0.82, 0.20], p=0.23	-0.50 [-1.02, 0.02], p=0.06
Loneliness X NIA-Regan	0.09 [-0.15, 0.33], p=0.45	0.05 [-0.15, 0.25], p=0.63	0.07 [-0.18, 0.32], p=0.59	0.04 [-0.16, 0.24], p=0.70	0.09 [-0.12, 0.30], p=0.38
Loneliness	-0.22 [-0.38, -0.06], p=0.007	-0.19 [-0.31, -0.07], p=0.003	-0.30 [-0.45, -0.15], p=0.0002	-0.20 [-0.33, -0.07], p=0.002	-0.32 [-0.45, -0.19], p=0.000002
Chronic Infarcts	0.009 [-0.67, 0.69], p=0.98	0.04 [-0.49, 0.57], p=0.89	0.17 [-0.51, 0.85], p=0.62	0.48 [-0.07, 1.03], p=0.08	0.23 [-0.34, 0.80], p=0.42
Loneliness X Infarcts	-0.05 [-0.32, 0.22], p=0.71	-0.08 [-0.29, 0.13], p=0.45	-0.17 [-0.44, 0.10], p=0.21	-0.20 [-0.42, 0.02], p=0.07	-0.12 [-0.34, 0.10], p=0.28
Loneliness	-0.16 [-0.31, -0.01], p=0.03	-0.16 [-0.28, -0.04], p=0.008	-0.27 [-0.42, -0.12], p=0.0003	-0.20 [-0.21, -0.19], p=0.0009	-0.31 [-0.43, -0.19], p=0.000001
Chronic Microinfarcts	0.55 [-0.17, 1.27], p=0.13	0.49 [-0.07, 1.05], p=0.09	0.54 [-0.17, 1.25], p=0.14	0.52 [-0.05, 1.09], p=0.08	0.32 [-0.27, 0.91], p=0.29
Loneliness X Microinfarcts	-0.27 [-0.55, 0.01], p=0.06	-0.23 [-0.45, -0.01], p=0.046	-0.34 [-0.62, -0.06], p=0.02	-0.26 [-0.49, -0.03], p=0.03	-0.19 [-0.43, 0.04], p=0.11

Table 4. Associations of variables of interest (loneliness, AD or cerebrovascular pathology, and their interaction) with each cognitive domain score. All models adjusted for age at death, sex, race, years of education, and having at least one *APOE-ε4* allele.