Supplementary Online Content

Donovan NJ, Okereke OI, Vannini P, Amariglio RE, Rentz DM, Marshall GA, Johnson KA, Sperling RA. Higher cortical amyloid is associated with loneliness in cognitively normal older adults

eText. Supplemental descriptions of Harvard Aging Brain study criteria for inclusion of participants in Year 1 and Year 4 (Participants), clinical assessments at Year 4 (Measures), and analyses and results pertaining to secondary analyses (Statistical Analysis and Results).

eReferences.

eTable. Medical conditions, health behaviors and psychiatric characteristics for the study participants

This supplementary material has been provided by the authors to give readers additional information about their work.

eText

Methods

Participants

Participants in this study were undergoing fourth year clinical and neuroimaging assessments as part of the Harvard Aging Brain Study. When originally enrolled in Year 1, exclusion criteria included serious and unstable medical, neurological or psychiatric illness, history of traumatic brain injury, extensive cerebrovascular disease visualized on magnetic resonance imaging, and a Modified Hachinski score $\geq$ 4. Participants with stable, treated vascular risk factors such as hypertension, hyperlipidemia or cardiovascular disease were not excluded. During Year 1, individuals with a history of schizophrenia, schizoaffective disorder or bipolar disorder, moderate or severe major depression or substance abuse (within the past two years), determined by psychiatric history, were excluded. A self-reported history of depression adequately treated with selective serotonin reuptake inhibitors (SSRI) or dual serotonin-norepinephrine reuptake inhibitors (SNRI), bupropion or nortriptyline was allowed. While participants with mild depression, defined by scores of 11 or greater on the 30-item Geriatric Depression Scale (GDS),[1] were excluded from the cohort at the beginning of the study, there were no exclusions related to GDS or to psychiatric conditions at subsequent yearly visits.

Measures

The year 4 clinical assessment involved a comprehensive review of participants' medical, neurological and psychiatric health**.** This included a survey of health behaviors and medical conditions, a general physical and neurological exam performed by the study physician, vital signs and laboratory tests. Medical and psychiatric history were based on participant self-report of life-time (including current) clinically significant symptoms and treatment. Self-reported medical and psychiatric problems and medication use were corroborated, if necessary, by medical record review. Depression and Anxiety Disorders were not classified according to DSM diagnoses.

The 3-item UCLA loneliness scale is a validated instrument, adapted from the 20-item UCLA-revised loneliness scale, with which it is strongly correlated r=0.82).[2,3] Both scales have good convergent and discriminant validity and internal consistency (for the 3-item UCLA loneliness scale, the Cronbach $\alpha = 0.72$; $\alpha = 0.73$ in this sample).[3] The 3-item UCLA loneliness scale was developed for application to aging research and has been implemented in international cohort studies such as the US Health and Retirement Study,[4] the English Longitudinal Study of Ageing,[5] and the German Socio-Economic Panel Study[6]

Statistical Analyses

T-tests and the Kruskal-Wallis test were used to evaluate UCLA-loneliness scores in relation to medical conditions (hypertension, hyperlipidemia, diabetes, TIA/stroke, coronary artery disease (CAD)), history of depression or use of SSRI-SNRI medication. In a series of secondary analyses, we evaluated whether CAD diagnosis, depressive disorder or SSRI-SNRI use were significant predictors of UCLA-loneliness adjusting for age, sex, Hollingshead score, PiB, GDS, HADS-anxiety and social network scores.

Additional sensitivity analyses were performed in subsamples that excluded participants scoring above the cutoff for mild anxiety (HADS-anxiety$\geq$8) or those scoring above the cutoff for mild depression (GDS$\geq$11).

To further characterize the relationship between UCLA-loneliness score and PiB retention, we performed a reciprocal linear regression model for UCLA-loneliness predicting PiB, co-varying for age, sex, APOEe4, Hollingshead, GDS, HADS-anxiety and social network scores. Finally, a reciprocal logistic regression model was conducted for the dichotomous loneliness variable predicting the amyloid-positive group, controlling for all covariates.

Results

Vascular risk factors and CAD

Data regarding vascular risk factor profile and morbidity for the sample are shown in eTable 1. There was no difference in mean loneliness score across groups based on hypertension (t=1.3, p=0.4), hyperlipidemia (t=0.3, p=0.9), diabetes (t=0.4, p=0.7), TIA/stroke (t=0.1, p=0.9) or CAD (t=-0.4, p=0.7). In a post-hoc multiple linear regression model, CAD diagnosis was not a significant predictor of UCLA-loneliness controlling for age, sex, PiB, Hollingshead score, GDS, HADS-anxiety and social network. Inclusion or exclusion of this variable did not alter the association of PiB and UCLA-loneliness (data not shown).

Depressive disorder and SSRI-SNRI use

Fourteen percent of the sample endorsed a lifetime history of depression, 3% a lifetime history of anxiety disorder and 8% were taking SSRI-SNRI medication (eTable 1). Depressive Disorder, as a dichotomous variable, was not associated with UCLA-loneliness adjusting for age, sex, Hollingshead score, HADS-anxiety, social network in models with or without GDS. Inclusion of this variable did not impact the association of PiB and UCLA-loneliness. Similarly, SSRI/SNRI use, as a dichotomous variable, was not associated with UCLA-loneliness in analogous models with or without GDS and did not alter the association of PiB and UCLA-loneliness (data not shown).

Samples excluding high GDS or HADS-anxiety values

We re-estimated the relation of PiB to UCLA-loneliness controlling for age, sex, APOEε4, Hollingshead, GDS, HADS-anxiety and social network in two separate models excluding subjects with either HADS-anxiety scores or GDS scores above the cutoff values of 8 and 11 respectively. In the model excluding participants with high HADS-anxiety scores, the results were not significantly changed from the primary model (for PiB β =3.5, p=0.003; for the model, R^2=0.31, adjusted R^2=0.22, p=0.003). Higher GDS and younger age were significant predictors in this model, consistent with prior findings (for age, β = -0.1, p=0.003; for GDS, β=0.2, p=0.009). In the model excluding high GDS scores, PiB and younger age remained as significant predictor of UCLA-loneliness (for PiB, β =3.0, p=0.01, for age, β= -0.1, p=0.007) but the relation of GDS to UCLA-loneliness became non-significant (for GDS, β=0.2, p=0.13; for the model R^2=0.24, adjusted R^2=0.13, p=0.03).

Reciprocal models for UCLA-loneliness predicting PiB

In a reciprocal linear regression model for UCLA-loneliness predicting PiB, using the full set of covariates, greater UCLA-loneliness, older age, APOEε4 positive status, and higher anxiety were significant predictors of PiB (for UCLA loneliness ß=0.04, p=0.002; for age ß=0.008, for APOEε4 ß=0.2, p<0.001, for HADS-anxiety ß=0.02, p=0.05; for the model F=4.6, p<0.001, df=64, R^2=0.36, adjusted R^2=0.28). *Lower* GDS was a marginal predictor of PiB (ß= -0.01, r= -0.23, p-0.07). Thirty-six percent of the variance for PiB was explained by the model, 28% adjusted for all predictors. The partial correlation of UCLA-loneliness and PiB was 0.36, the semi-partial correlation was 0.32.

In a reciprocal logistic regression model for UCLA-loneliness predicting amyloid-positive group, controlling for all covariates, the odds ratio for being amyloid-positive was 6.5 for the lonely compared to the non-lonely (for lonely, OR=6.5 (95% CI 1.4, 29.6) p=0.01; for the model p= 0.007).

eReferences

1. Yesavage JA, Brink TL, Rose TL, et al. Development and validation of a geriatric depression screening scale: a preliminary report. *J Psychiatr Res.* 1982;17(1):37-49.
2. Russell DW. UCLA Loneliness Scale (Version 3): reliability, validity, and factor structure. *J Pers Assess.* 1996;66(1):20-40.
3. Hughes ME, Waite LJ, Hawkley LC, Cacioppo JT. A Short Scale for Measuring Loneliness in Large Surveys: Results From Two Population-Based Studies. *Res Aging.* 2004;26(6):655-672.
4. Perissinotto CM, Stijacic Cenzer I, Covinsky KE. Loneliness in older persons: a predictor of functional decline and death. *Arch Intern Med.* 2012;172(14):1078-1084.
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eTable 1: Medical conditions, health behaviors and psychiatric characteristics

	N	Value	Range	SD
Age (years)	79	76.4	68, 89	6.2
Sex (% male)	79	45.6		
Hypertension, n (%)	79	40 (51)		
Hyperlipidemia, n (%)	79	42 (53)		
Diabetes, n (%)	79	5 (6)		
TIA or stroke, n (%)	79	5 (6)		
Coronary Artery Disease, n (%)	79	7 (9)		
Self-reported smoking (current), n (%)	79	1 (1)		
Self-reported alcohol intake, n (%)	79			
0 (none)		16 (20)		
1 (<1 drink per day)		40 (51)		
2 (1-2 drinks per day)		21 (27)		
3 (3-4 drinks per day)		2 (3)		
4 (>4 drinks per day)		0		
Depressive Disorder, n (%)	79	11 (14)		
Anxiety Disorder, n (%)	79	2 (3)		
Use of antidepressant (SSRI/ SNRI)	79	6 (8)		

Abbreviations: TIA (Transient Ischemic Attack), SSRI (Selective Serotonin Reuptake Inhibitor) SNRI (Serotonin-Norephinephrine Reuptake Inhibitor)