Supplementary Material

Association of Loneliness with Functional Connectivity MRI, Amyloid-β PET, and Tau PET Neuroimaging Markers of Vulnerability for Alzheimer's Disease

Supplementary Table 1. Multivariable-Adjusted Models of Functional Connectivity MRI Measures as a Function of Conservative Loneliness Status [a]

	Model 1			Model 2			Model 3		
fcMRI Measures	**No. of participants**	**Estimate (SE)**	***p***	**No. of participants**	**Estimate (SE)**	***p***	**No. of participants**	**Estimate (SE)**	***p***
DMN-Intra	381	0.00 (0.02)	1.00	381	0.00 (0.02)	1.00	381	-0.004 (0.02)	0.85
Limbic-Intra		-0.02 (0.02)	0.27		-0.02 (0.02)	0.29		-0.02 (0.02)	0.28
Frontoparietal-Intra	381	-0.001 (0.02)	0.97	381	-0.001 (0.02)	0.96	381	-0.01 (0.02)	0.72
Dorsal Attention-Intra	381	0.003 (0.02)	0.89	381	0.002 (0.02)	0.91	381	0.00 (0.02)	0.96
Ventral Attention-Intra	381	-0.01 (0.02)	0.77	381	-0.01 (0.02)	0.79	381	-0.01 (0.02)	0.75
Somatomotor-Intra	381	-0.05 (0.05)	0.23	381	-0.06 (0.05)	0.22	381	-0.05 (0.05)	0.24
Visual-Intra	381	**0.03 (0.02)**	**0.07**	381	**0.03 (0.02)**	**0.07**	381	0.03 (0.02)	0.1
DMN to Limbic	381	0.001 (0.01)	0.86	381	0.001 (0.01)	0.85	381	0.001 (0.01)	0.82

DMN, Default Mode Network

[a] Predictor: Lonely (3+ days/week) versus not lonely (<3 days/week).

Supplementary Table 2. Multivariable-Adjusted Models of Functional Connectivity MRI Measures as a Function of Ordinal Loneliness Status [a]

	Model 1			Model 2			Model 3		
fcMRI Measures	**No. of participants**	**Estimate (SE)**	**p**	**No. of participants**	**Estimate (SE)**	**p**	**No. of participants**	**Estimate (SE)**	**p**
DMN-Intra	381	-0.001 (0.01)	0.87	381	-0.001 (0.01)	0.88	381	-0.003 (0.01)	0.63
Limbic-Intra	381	-0.01 (0.01)	0.13	381	-0.01 (0.01)	0.14	381	-0.01 (0.01)	0.12
Frontoparietal-Intra	381	0.003 (0.01)	0.68	381	0.003 (0.01)	0.69	381	-0.001 (0.01)	0.91
Dorsal Attention-Intra	381	0.002 (0.01)	0.78	381	0.002 (0.01)	0.79	381	0.00 (0.01)	0.99
Ventral Attention-Intra	381	-0.002 (0.01)	0.79	381	-0.002 (0.01)	0.82	381	-0.003 (0.01)	0.76
Somatomotor-Intra	381	-0.01 (0.02)	0.65	381	-0.01 (0.02)	0.64	381	-0.01 (0.02)	0.69
Visual-Intra	381	0.01 (0.01)	0.21	381	0.01 (0.01)	0.2	381	0.01 (0.01)	0.31
DMN to Limbic	381	0.00 (0.002)	0.94	381	0.00 (0.002)	0.96	381	0.00 (0.002)	0.99

DMN, Default Mode Network

[a] Predictor: Ordinal loneliness (<1 day, 1-2 days, 3-4 days, or 5-7 days/week).

Supplementary Table 3. Multivariable-Adjusted Models of PET Measures as a Function of Conservative Loneliness Status [a]

	Model 1			Model 2			Model 3		
PET Measures[b]	**No. of participants**	**Estimate (SE)**	**p[c]**	**No. of participants**	**Estimate (SE)**	**p[c]**	**No. of participants**	**Estimate (SE)**	**p[c]**
Amyloid, FLR	415	0.00 (0.02)	0.98	415	0.00 (0.02)	0.98	368	0.00 (0.02)	0.98
Amyloid, Precuneus	416	0.00 (0.03)	0.98	416	0.00 (0.03)	0.98	369	-0.01 (0.03)	0.98
Tau, Amygdala	321	-0.05 (0.03)	0.35	321	-0.04 (0.03)	0.40	287	-0.04 (0.03)	0.47
Tau, Entorhinal	321	-0.04 (0.02)	0.35	321	-0.03 (0.02)	0.37	287	-0.04 (0.03)	0.35
Tau, Rhinal	314	-0.05 (0.03)	0.33	314	-0.05 (0.03)	0.33	282	-0.06 (0.03)	0.33
Tau, Inferior Temporal	321	-0.02 (0.02)	0.47	321	-0.02 (0.02)	0.47	287	-0.02 (0.02)	0.47
Tau, Parahippocampus	321	-0.04 (0.02)	0.33	321	-0.04 (0.02)	0.33	287	-0.03 (0.02)	0.35
Tau, Precuneus	321	-0.02 (0.02)	0.47	321	-0.02 (0.02)	0.47	287	-0.01 (0.02)	0.78
Tau, Medial Orbitofrontal	321	-0.03 (0.02)	0.40	321	-0.03 (0.02)	0.47	287	-0.02 (0.02)	0.63

FLR, Frontal, lateral parietal and lateral temporal, and retrosplenial cortices

[a] Predictor: Lonely (3+ days/week) versus not lonely (<3 days/week).

[b] PET measurements provided as Partial-Volume Uncorrected values.

[c]Model 1: Age, age-squared, sex, time interval between loneliness assessment and PET camera (binary variable: HR+ vs. Smoothed Discovery GE)

[d]Model 2: + Level of educational achievement (three-level variable)

[e]Model 3: + Modified CES-D (continuous, logarithm of CES-D excluding loneliness item)

[f]FDR-corrected p-value.

Supplementary Table 4. Multivariable-Adjusted Models of PET Measures as a Function of Ordinal Loneliness Status [a]

	Model 1			Model 2			Model 3		
PET Measures[b]	**No. of participants**	**Estimate (SE)**	***p*[c]**	**No. of participants**	**Estimate (SE)**	***p*[c]**	**No. of participants**	**Estimate (SE)**	***p*[c]**
Amyloid, FLR	415	0.00 (0.01)	0.79	415	0.00 (0.01)	0.79	368	0.00 (0.01)	0.79
Amyloid, Precuneus	416	-0.01 (0.01)	0.76	416	-0.01 (0.01)	0.76	369	-0.01 (0.01)	0.76
Tau, Amygdala	321	-0.01 (0.01)	0.57	321	-0.01 (0.01)	0.70	287	-0.01 (0.01)	0.78
Tau, Entorhinal	321	-0.01 (0.01)	0.57	321	-0.01 (0.01)	0.57	287	-0.01 (0.01)	0.57
Tau, Rhinal	314	-0.01 (0.01)	0.57	314	-0.01 (0.01)	0.57	282	-0.02 (0.01)	0.57
Tau, Inferior Temporal	321	-0.01 (0.01)	0.76	321	0.00 (0.01)	0.76	287	0.00 (0.01)	0.76
Tau, Parahippocampus	321	-0.01 (0.01)	0.57	321	-0.01 (0.01)	0.57	287	-0.01 (0.01)	0.57
Tau, Precuneus	321	-0.01 (0.01)	0.57	321	-0.01 (0.01)	0.57	287	0.00 (0.01)	0.78
Tau, Medial Orbitofrontal	321	-0.01 (0.01)	0.57	321	-0.01 (0.01)	0.57	287	-0.01 (0.01)	0.76

FLR, Frontal, lateral parietal and lateral temporal, and retrosplenial cortices

[a] Predictor: Ordinal loneliness (<1 day, 1-2 days, 3-4 days, or 5-7 days/week).

[b] PET measurements provided as Partial-Volume Uncorrected values.

[c]Model 1: Age, age-squared, sex, time interval between loneliness assessment and PET camera

[d]Model 2: + Level of educational achievement (three-level variable)

[e]Model 3: + Modified CES-D (continuous, logarithm of CES-D excluding loneliness item)

[f]FDR-corrected p-value.

Supplementary Table 5. Interaction Models with Functional Connectivity MRI Measures as a Function of Loneliness Status [a]

FcMRI Measures	Interaction variable	*p*
DMN-Intra	Age<60	0.52
	APOE4	0.29
	Sex	0.71
	BDNF [b]	0.67
	BDNF Quartile [c]	0.31
	IGF-1 [d]	0.71
	IGF-1 Quartile [e]	0.26
Limbic-Intra	Age<60	0.92
	APOE4	0.97
	Sex	0.79
	BDNF	0.52
	BDNF Quartile	0.73
	IGF-1	0.75
	IGF-1 Quartile	0.82
Frontoparietal-Intra	Age<60	0.49
	APOE4	0.53
	Sex	0.4
	BDNF	0.99
	BDNF Quartile	0.62
	IGF-1	**0.05**
	IGF-1 Quartile	0.01
Dorsal Attention-Intra	Age<60	0.62
	APOE4	0.64
	Sex	0.45
	BDNF	**0.08**
	BDNF Quartile	**0.06**
	IGF-1	0.42
	IGF-1 Quartile	0.24
Ventral Attention-Intra	Age<60	0.9
	APOE4	1
	Sex	0.8
	BDNF	0.82
	BDNF Quartile	0.99
	IGF-1	0.5
	IGF-1 Quartile	0.16
Somatomotor-Intra	Age<60	0.76
	APOE4	0.91
	Sex	0.94
	BDNF	0.15
	BDNF Quartile	0.13

	IGF-1	0.68
	IGF-1 Quartile	0.93
Visual-Intra	Age<60	0.82
	APOE4	**0.09**
	Sex	0.61
	BDNF	0.86
	BDNF Quartile	0.8
	IGF-1	0.72
	IGF-1 Quartile	0.53
DMN to Limbic	Age<60	0.76
	APOE4	0.98
	Sex	0.55
	BDNF	0.34
	BDNF Quartile	0.4
	IGF-1	0.25
	IGF-1 Quartile	0.36

DMN, Default Mode Network; *APOE4*, Apolipoprotein E4; BDNF, Brain-derived neurotrophic factor; IGF-1-1, Insulin-like growth factor 1

[a] Predictor: Lonely (1+ days/week) versus not lonely (<1 days/week).

[b] BDNF, defined continuously

[c] BDNF, divided into quartiles

[d] IGF-1, defined continuously

[e] IGF-1, divided into quartiles

Supplementary Table 6. Stratified Models of fcMRI Measures as a Function of Loneliness Status [a] (where significant)

FcMRI Measures	Stratum	*p*
Visual-Intra	*APOE4* negative	0.16
	APOE4 positive	0.25

[a] Predictor: Lonely (1+ days/week) versus not lonely (<1 days/week).

Supplementary Table 7. Interaction Models with Functional Connectivity MRI Measures as a Function of Conservative Loneliness Status [a]

FcMRI Measures	**Interaction variable**	*p*
DMN-Intra	Age<60	0.14
	APOE4	0.91
	Sex	0.28
	BDNF [b]	0.77
	BDNF Quartile [c]	0.91
	IGF-1 [d]	0.63
	IGF-1 Quartile [e]	0.41
Limbic-Intra	Age<60	0.13
	APOE4	0.82
	Sex	0.27
	BDNF	0.5
	BDNF Quartile	0.81
	IGF-1	0.86
	IGF-1 Quartile	0.54
Frontoparietal-Intra	Age<60	0.54
	APOE4	0.41
	Sex	0.56
	BDNF	0.84
	BDNF Quartile	0.92
	IGF-1	0.84
	IGF-1 Quartile	0.7
Dorsal Attention-Intra	Age<60	**0.05**
	APOE4	0.81
	Sex	0.78
	BDNF	0.85
	BDNF Quartile	0.89
	IGF-1	0.56
	IGF-1 Quartile	0.87
Ventral Attention-Intra	Age<60	0.29
	APOE4	0.61
	Sex	0.34
	BDNF	**0.01**
	BDNF Quartile	**0.04**
	IGF-1	0.41
	IGF-1 Quartile	0.15
Somatomotor-Intra	Age<60	0.99
	APOE4	0.73
	Sex	0.64
	BDNF	0.45
	BDNF Quartile	0.5

	IGF-1	0.42
	IGF-1 Quartile	0.31
Visual-Intra	Age<60	0.25
	APOE4	0.82
	Sex	0.52
	BDNF	0.86
	BDNF Quartile	0.73
	IGF-1	0.2
	IGF-1 Quartile	0.23
DMN to Limbic	Age<60	0.8
	APOE4	0.85
	Sex	0.55
	BDNF	0.29
	BDNF Quartile	0.35
	IGF-1	0.24
	IGF-1 Quartile	0.24

DMN, Default Mode Network; *APOE4*, Apolipoprotein E4; BDNF, Brain-derived neurotrophic factor; IGF-1-1, Insulin-like growth factor 1

[a] Predictor: Lonely (3+ days/week) versus not lonely (<3 days/week).

[b] BDNF, defined continuously

[c] BDNF, divided into quartiles

[d] IGF-1, defined continuously

[e] IGF-1, divided into quartiles

Supplementary Table 8. Stratified Models of fcMRI Measures as a Function of Conservative Loneliness Status [a] (where significant)

FcMRI Measures	Stratum	*p*
Dorsal Attention- Intra	<57	0.19
	>57	0.13

[a] Predictor: Lonely (3+ days/week) versus not lonely (<3 days/week).

Supplementary Table 9. Interaction Models with Functional Connectivity MRI Measures as a Function of Ordinal Loneliness Status [a]

FcMRI Measures	Interaction variable	*p*
DMN-Intra	Age<60	0.57
	APOE4	0.29
	Sex	0.58
	BDNF [b]	0.7
	BDNF Quartile [c]	0.38
	IGF-1 [d]	0.58
	IGF-1 Quartile [e]	0.24
Limbic-Intra	Age<60	0.57
	APOE4	0.88
	Sex	0.93
	BDNF	0.52
	BDNF Quartile	0.8
	IGF-1	0.94
	IGF-1 Quartile	0.56
Frontoparietal-Intra	Age<60	0.73
	APOE4	0.36
	Sex	0.79
	BDNF	0.98
	BDNF Quartile	0.74
	IGF-1	0.14
	IGF-1 Quartile	0.05
Dorsal Attention-Intra	Age<60	**0.22**
	APOE4	0.8
	Sex	0.59
	BDNF	0.17
	BDNF Quartile	0.13
	IGF-1	0.72
	IGF-1 Quartile	0.44
Ventral Attention-Intra	Age<60	0.75
	APOE4	0.83
	Sex	0.73
	BDNF	**0.17**
	BDNF Quartile	**0.32**
	IGF-1	0.3
	IGF-1 Quartile	0.08
Somatomotor-Intra	Age<60	0.72
	APOE4	0.91
	Sex	0.98
	BDNF	0.19
	BDNF Quartile	0.2

	IGF-1	0.45
	IGF-1 Quartile	0.57
Visual-Intra	Age<60	0.42
	APOE4	0.15
	Sex	0.97
	BDNF	0.89
	BDNF Quartile	0.93
	IGF-1	0.48
	IGF-1 Quartile	0.41
DMN to Limbic	Age<60	0.56
	APOE4	0.9
	Sex	0.53
	BDNF	0.29
	BDNF Quartile	0.24
	IGF-1	0.15
	IGF-1 Quartile	0.21

DMN, Default Mode Network; *APOE4*, Apolipoprotein E4; BDNF, Brain-derived neurotrophic factor; IGF-1-1, Insulin-like growth factor 1

[a] Predictor: Ordinal loneliness (<1 day, 1-2 days, 3-4 days, or 5-7 days/week).

[b] BDNF, defined continuously

[c] BDNF, divided into quartiles

[d] IGF-1, defined continuously

[e] IGF-1, divided into quartiles

Supplementary Table 10. Interaction Models with Functional Connectivity MRI Measures as a Function of Persistent Loneliness Status [a]

FcMRI Measures	**Interaction variable**	*p*
DMN-Intra	Age<60	0.35
	APOE4	0.26
	Sex	0.76
	BDNF [b]	NA[f]
	BDNF Quartile [c]	NA
	IGF-1 [d]	NA
	IGF-1 Quartile [e]	NA
Limbic-Intra	Age<60	0.77
	APOE4	0.35
	Sex	1
	BDNF	NA
	BDNF Quartile	NA
	IGF-1	NA
	IGF-1 Quartile	NA
Frontoparietal-Intra	Age<60	0.62
	APOE4	0.55
	Sex	0.78
	BDNF	NA
	BDNF Quartile	NA
	IGF-1	NA
	IGF-1 Quartile	NA
Dorsal Attention-Intra	Age<60	**0.09**
	APOE4	0.38
	Sex	0.52
	BDNF	NA
	BDNF Quartile	NA
	IGF-1	NA
	IGF-1 Quartile	NA
Ventral Attention-Intra	Age<60	0.11
	APOE4	0.1
	Sex	0.98
	BDNF	NA
	BDNF Quartile	NA
	IGF-1	NA
	IGF-1 Quartile	NA
Somatomotor-Intra	Age<60	0.32
	APOE4	0.75
	Sex	0.91
	BDNF	NA
	BDNF Quartile	NA

	IGF-1	NA
	IGF-1 Quartile	NA
Visual-Intra	Age<60	0.44
	APOE4	0.85
	Sex	0.85
	BDNF	NA
	BDNF Quartile	NA
	IGF-1	NA
	IGF-1 Quartile	NA
DMN to Limbic	Age<60	0.27
	APOE4	0.8
	Sex	0.79
	BDNF	NA
	BDNF Quartile	NA
	IGF-1	NA
	IGF-1 Quartile	NA

DMN, Default Mode Network; *APOE4*, Apolipoprotein E4; BDNF, Brain-derived neurotrophic factor; IGF-1-1, Insulin-like growth factor 1

[a] Predictor: four-level exposure variable, persistent/incident/recovered/absent.

[b] BDNF, defined continuously

[c] BDNF, divided into quartiles

[d] IGF-1, defined continuously

[e] IGF-1, divided into quartiles

Supplementary Table 11. Stratified Models of fcMRI Measures as a Function of Persistent Loneliness Status [a] (where significant)

Dorsal Attention- Intra	Age<57	Incident	0.84
		Persistent	0.12
		Recovered	0.14
		Absent	Ref
	Age > 57	Incident	0.84
		Persistent	0.66
		Recovered	0.1
		Absent	Ref

[a] Predictor: four-level exposure variable, persistent/incident/recovered/absent.

Supplementary Table 12. Interaction Models with PET Measures as a Function of Loneliness Status [a]

		Model 1
PET Measures[b]	**Interaction variable**	***p***
Amyloid, FLR	Age<60	0.49
	APOE4	0.34
	Sex	0.40
	Modified CES-D<20	0.78
Amyloid, Precuneus	Age<60	0.44
	APOE4	**0.07**
	Sex	0.85
	Modified CES-D<20	0.65
Tau, Amygdala	Age<60	0.54
	APOE4	0.68
	Sex	0.74
	Modified CES-D<20	0.39
Tau, Entorhinal	Age<60	0.91
	APOE4	0.46
	Sex	0.41
	Modified CES-D<20	0.85
Tau, Rhinal	Age<60	0.33
	APOE4	0.63
	Sex	0.91
	Modified CES-D<20	0.68
Tau, Inferior Temporal	Age<60	0.94
	APOE4	0.48
	Sex	0.51
	Modified CES-D<20	0.72
Tau, Parahippocampus	Age<60	0.72
	APOE4	0.95
	Sex	0.88
	Modified CES-D<20	0.52
Tau, Precuneus	Age<60	0.93
	APOE4	0.35
	Sex	0.80
	Modified CES-D<20	0.90
Tau, Medial Orbitofrontal	Age<60	0.55
	APOE4	0.58
	Sex	0.40
	Modified CES-D<20	0.32

FLR, Frontal, lateral parietal and lateral temporal, and retrosplenial cortices

[a] Predictor: Lonely (1+ days/week) versus not lonely (<1 days/week).

[b] PET measurements provided as Partial-Volume Uncorrected values

Supplementary Table 13. Stratified Models of PET Measures as a Function of Loneliness Status [a] (where significant)

	Model 1			
PET Measures[b]	**Stratum**	**No. of participants**	**Estimate (SE)**	***p***
Amyloid, Precuneus	*APOE4+*	93	-0.07 (0.04)	0.07
	APOE4-	310	0.00 (0.02)	0.92

FLR, Frontal, lateral parietal and lateral temporal, and retrosplenial cortices

[a] Predictor: Lonely (1+ days/week) versus not lonely (<1 days/week).

[b] PET measurements provided as Partial-Volume Uncorrected values

		Model 1, Offspring Cohort			**Model 1, 3rd Generation Cohort**		
PET Measures[b]	**Stratum**	**N**	**Estimate (SE)**	***p***	**N**	**Estimate (SE)**	***p***
Amyloid, FLR	*APOE4+*	15	NA		78	-0.02 (0.02)	0.49
	APOE4-	50	-0.01 (0.06)	0.82	259	-0.01 (0.01)	0.61
Amyloid, Precuneus	*APOE4+*	15	NA		78	-0.06 (0.03)	0.10
	APOE4-	50	0.00 (0.10)	0.99	260	0.002 (0.02)	0.91
Tau, Amygdala	*APOE4+*	8	NA		68	-0.01 (0.04)	0.78
	APOE4-	20	NA		215	-0.01 (0.02)	0.48
Tau, Entorhinal	*APOE4+*	8	NA		68	-0.004 (0.04)	0.91
	APOE4-	20	NA		215	-0.02 (0.02)	0.24
Tau, Rhinal	*APOE4+*	8	NA		65	-0.01 (0.04)	0.75
	APOE4-	20	NA		213	-0.01 (0.02)	0.42
Tau, Inferior Temporal	*APOE4+*	8	NA		68	0.00 (0.03)	0.99
	APOE4-	20	NA		215	-0.01 (0.01)	0.55
Tau, Parahippocampus	*APOE4+*	8	NA		68	-0.03 (0.03)	0.33
	APOE4-	20	NA		215	-0.01 (0.01)	0.28
Tau, Precuneus	*APOE4+*	8	NA		68	-0.04 (0.02)	0.10
	APOE4-	20	NA		215	0.00 (0.01)	0.81
Tau, Medial Orbitofrontal	*APOE4+*	8	NA		68	-0.01 (0.03)	0.64
	APOE4-	20	NA		215	-0.02 (0.02)	0.26

FLR, Frontal, lateral parietal and lateral temporal, and retrosplenial cortices

[a] Predictor: Lonely (1+ days/week) versus not lonely (<1 days/week).

[b] PET measurements provided as Partial-Volume Uncorrected values

NA, not applicable, too few observations (n<=20)