

Supplementary Online Content

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eTable 1. Alzheimer's Disease Neuroimaging Initiative (ADNI) Inclusion and Exclusion Criteria

eTable 2. Breakdown and Classification of Psychosis Symptoms at Baseline (n = 32)

eFigure 1. Participant Selection Flow Chart

eTable 3. Comparison Between Remaining Sample and Participant Excluded Due to Poor Scan Quality

eTable 4. Binary Logistic Regression Modeling to Predict Presence of Delusions at Baseline

eTable 5. Region of Interest Analysis Model Diagnostics

eFigure 2. Voxel-Based Morphometry (VBM) Design Orthogonality Matrices

eTable 6. Comparison of Volume in Identified Regions of Interest Between Those With Delusions at Baseline and the Control Group

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

eTable 1. Alzheimer’s Disease Neuroimaging Initiative (ADNI) Inclusion and Exclusion Criteria

<i>General Criteria</i>
Hachinski less than or equal to 4
Age between 55-90
Stability of Permitted Medications for 4 weeks (see https://adni.loni.usc.edu/methods/documents/ for permitted medication list)
Geriatric Depression Scale less than 6
Study partner with 10+ hr/wk contact (can be in person and telephone), accompanies to visits
Visual and auditory acuity adequate for neuropsychological testing
Good general health with no diseases precluding enrollment
Women must be sterile or two years past childbearing potential
Willing and able to complete a 3 year imaging study (2 years for AD subjects)
6 grades education or work history
Must speak English/Spanish fluently
Commitment to Neuroimaging and no medical contraindications to MRI
Agrees to DNA for ApoE testing and banking
Agrees to Blood and Urine for Biomarkers
Not enrolled in other trials or studies
<i>Group specific criteria: Cognitively normal</i>
No Memory Complaints aside from those common to other normal subjects of that age range.
Normal memory function documented by scoring at specific cutoffs on the Logical Memory II subscale (delayed Paragraph Recall) from the Wechsler Memory Scaled - Revised (the maximum score is 25): a) greater than or equal to 9 for 16 or more years of education b) greater than or equal to 5 for 8-15 years of education c) greater than or equal to 3 for 0-7 years of education.
Mini-Mental State Exam score between 24 and 30 (inclusive) (Exceptions may be made for subjects with less than 8 years of education at the discretion of the project director).
Clinical Dementia Rating = 0. Memory Box score must be 0.
Cognitively normal, based on an absence of significant impairment in cognitive functions or activities of daily living.
<i>Group specific criteria: Mild Cognitive Impairment</i>
Memory complaint by subject or study partner that is verified by a study partner.
Abnormal memory function documented by scoring below the education adjusted cutoff on the Logical Memory II subscale (Delayed Paragraph Recall) from the Wechsler Memory Scale – Revised (the maximum score is 25): a) less than or equal to 8 for 16 or more years of education b) less than or equal to 4 for 8-15 years of education c) less than or equal to 2 for 0-7 years of education.
Mini-Mental State Exam score between 24 and 30 (inclusive) (Exceptions may be made for subjects with less than 8 years of education at the discretion of the project director).
Clinical Dementia Rating = 0.5. Memory Box score must be at least 0.5.
General cognition and functional performance sufficiently preserved such that a diagnosis of Alzheimer disease cannot be made by the site physician at the time of the screening visit.

Group specific criteria: Alzheimer disease

Memory complaint by subject or study partner that is verified by a study partner.

Abnormal memory function documented by scoring below the education adjusted cutoff on the Logical Memory II subscale (Delayed Paragraph Recall) from the Wechsler Memory Scale – Revised (the maximum score is 25):

- a) less than or equal to 8 for 16 or more years of education
- b) less than or equal to 4 for 8-15 years of education
- c) less than or equal to 2 for 0-7 years of education.

MMSE between 20 and 26 (inclusive) (Exceptions may be made for subjects with less than 8 years of education at the discretion of the protocol PI).

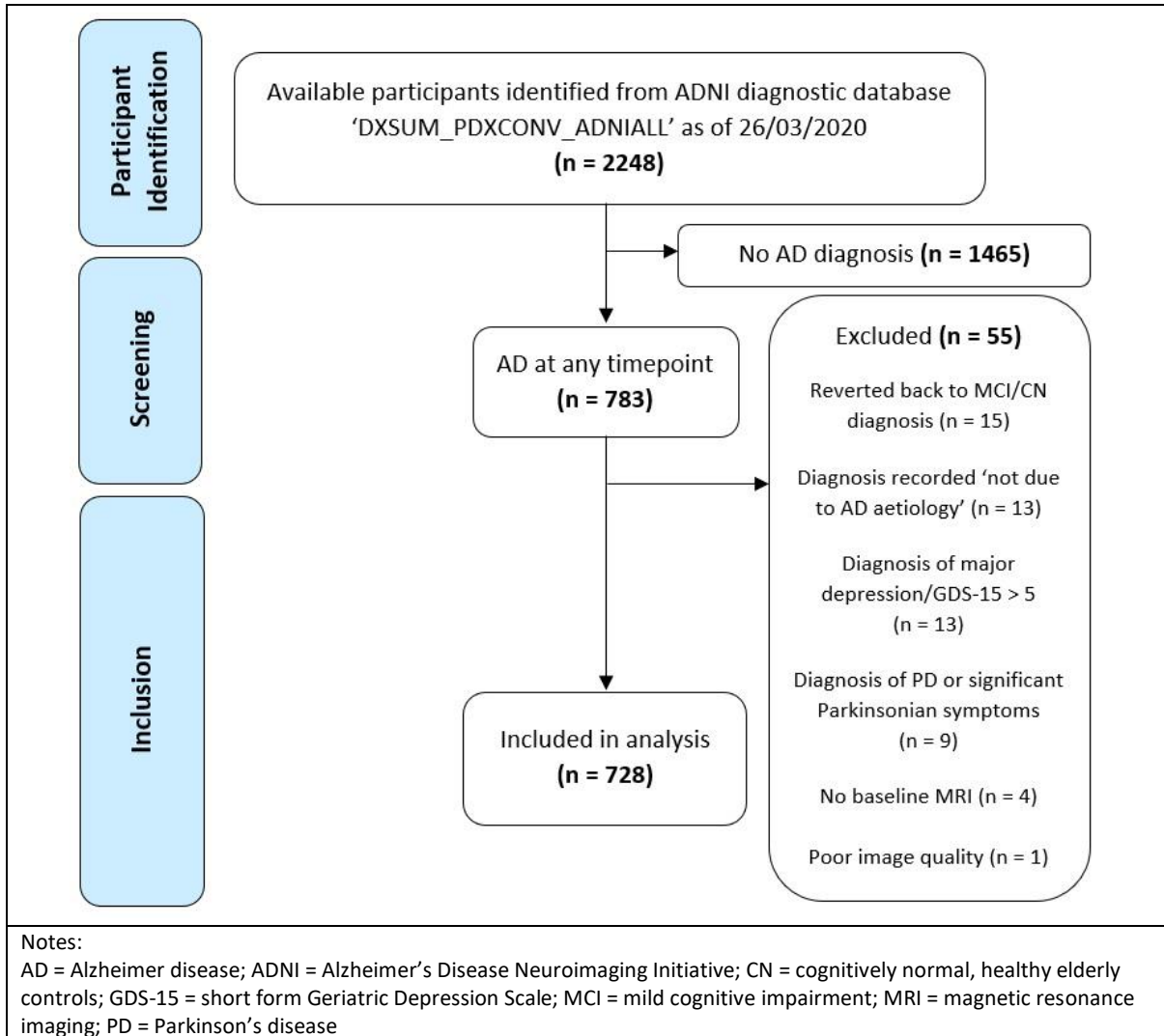
Clinical Dementia Rating = 0.5, 1.0

NINCDS/ADRDA criteria for probable AD.

eTable 2. Breakdown and Classification of Psychosis Symptoms at Baseline (n = 32)

	Content	N (%)
<i>Persecutory</i>		
Delusions	In danger/others are planning to hurt him/her	5 (15.6)
	Others are stealing from him/her	12 (37.5)
	Spouse is having an affair	1 (3.1)
	Family members plan to abandon him/her	3 (9.4)
<i>Misidentification</i>		
Delusions	Unwelcome guests are staying in his/her house	4 (12.5)
	His/her spouse or others are not who they claim to be	3 (9.4)
	His/her house is not his/her own	2 (6.3)
	Television/magazine figures are present in his/her home	1 (3.1)
Hallucinations	He/she can hear voices	5 (15.6)
	Talks to people who are not there	3 (9.4)
	Seeing things not seen by others	7 (21.9)
<i>Other</i>		
Delusions	Any other unusual beliefs	11 (34.4)
Hallucinations	Smells odours not smelled by others	-
	Feels things on his/her skin	3 (9.4)
	Tastes without known cause	1 (3.1)
	Any other unusual sensory experiences	4 (12.5)
Notes: In total seven participants experienced persecutory symptoms alone, nine misidentification symptoms alone, eight had mixed persecutory and misidentification symptoms and the remaining eight had other psychosis symptoms.		

eFigure 1. Participant Selection Flow Chart



eTable 3. Comparison Between Remaining Sample and Participant Excluded Due to Poor Scan Quality

	Remaining sample (n = 728) [†]	Excluded participant (n = 1)
Age, mean (SD), years	74.8 (7.4)	82
No. (%) female	317 (43.5)	1 (100)
No. (%) right handed	673 (92.4)	1 (100)
Education, mean (SD), years	15.5 (2.9)	14
No. (%) delusions at baseline	42 (5.8)	0 (0)
No. (%) hallucinations at baseline	24 (3.3)	0 (0)
<i>Race</i>		
No (%) Asian	16 (2.2)	-
No (%) Black	25 (3.4)	-
No. (%) White	681 (93.5)	1 (100)
No. (%) Multiple races [‡]	6 (0.8)	-
<i>Diagnosis</i>		
No. (%) cognitively normal	27 (3.7)	-
No. (%) amnesic MCI	315 (43.3)	1 (100)
No. (%) Alzheimer disease	386 (53.0)	-
<i>Medication</i>		
No. (%) ChEI/Memantine	523 (71.8)	0 (0)
No. (%) antidepressant	251 (34.5)	1 (100)
No. (%) antipsychotic	10 (1.4)	0 (0)
<i>Screening Assessments</i>		
NPI-Q, median (IQR), score	2 (0 – 4)	1
MMSE, mean (SD), score	25.1 (2.9)	30
GDS-15, median (IQR), score	1 (1 – 2)	4
Category fluency, mean (SD), score	14.0 (5.2)	12
Notes: MCI = mild cognitive impairment; ChEI = cholinesterase inhibitor; GDS-15 = short form Geriatric Depression Scale; MMSE = Mini Mental State Examination; NPI-Q = Neuropsychiatric Inventory Questionnaire. [†] Whole sample n = 727 for Medication and Category fluency. [‡] Indicates that participant self-reported as 'more than one race' when demographic details were collected by ADNI researchers.		

eTable 4. Binary Logistic Regression Modeling to Predict Presence of Delusions at Baseline

4a. Binary logistic regression modeling to predict presence of delusions at baseline, with false recognition on ADAS-Cog 13 as false memory measure (n = 589)

Covariates	Odds ratio (95% CI)	P Value
Total false recognition on ADAS-Cog 13	1.060 (.950, 1.183)	.298
Age	1.024 (.979, 1.070)	.309
Gender	.888 (.450, 1.753)	.733
Years of education	1.060 (.937, 1.199)	.353
ChEI	.983 (.427, 2.264)	.967
MMSE	.864 (.756, .987)	.032
Category fluency	.950 (.884, 1.021)	.161

4b. Binary logistic regression modeling to predict presence of delusions at baseline, with false recognition on RAVLT as false memory measure (n = 588)

Covariates	Odds ratio (95% CI)	P Value
Total false recognition on RAVLT	1.048 (.930, 1.181)	.442
Age	1.022 (.977, 1.069)	.339
Gender	.865 (.440, 1.700)	.673
Years of education	1.058 (.936, 1.196)	.365
ChEI	.971 (.421, 2.235)	.944
MMSE	.859 (.752, .981)	.025
Category fluency	.949 (.883, 1.019)	.149

Notes:
 ADAS-Cog 13 = Alzheimer’s Disease Assessment Scale–Cognitive Subscale, 13 item; ChEI = cholinesterase inhibitor prescription; MMSE = Mini Mental State Examination; RAVLT = Rey’s Auditory Verbal Learning Test. Category fluency for animals only.

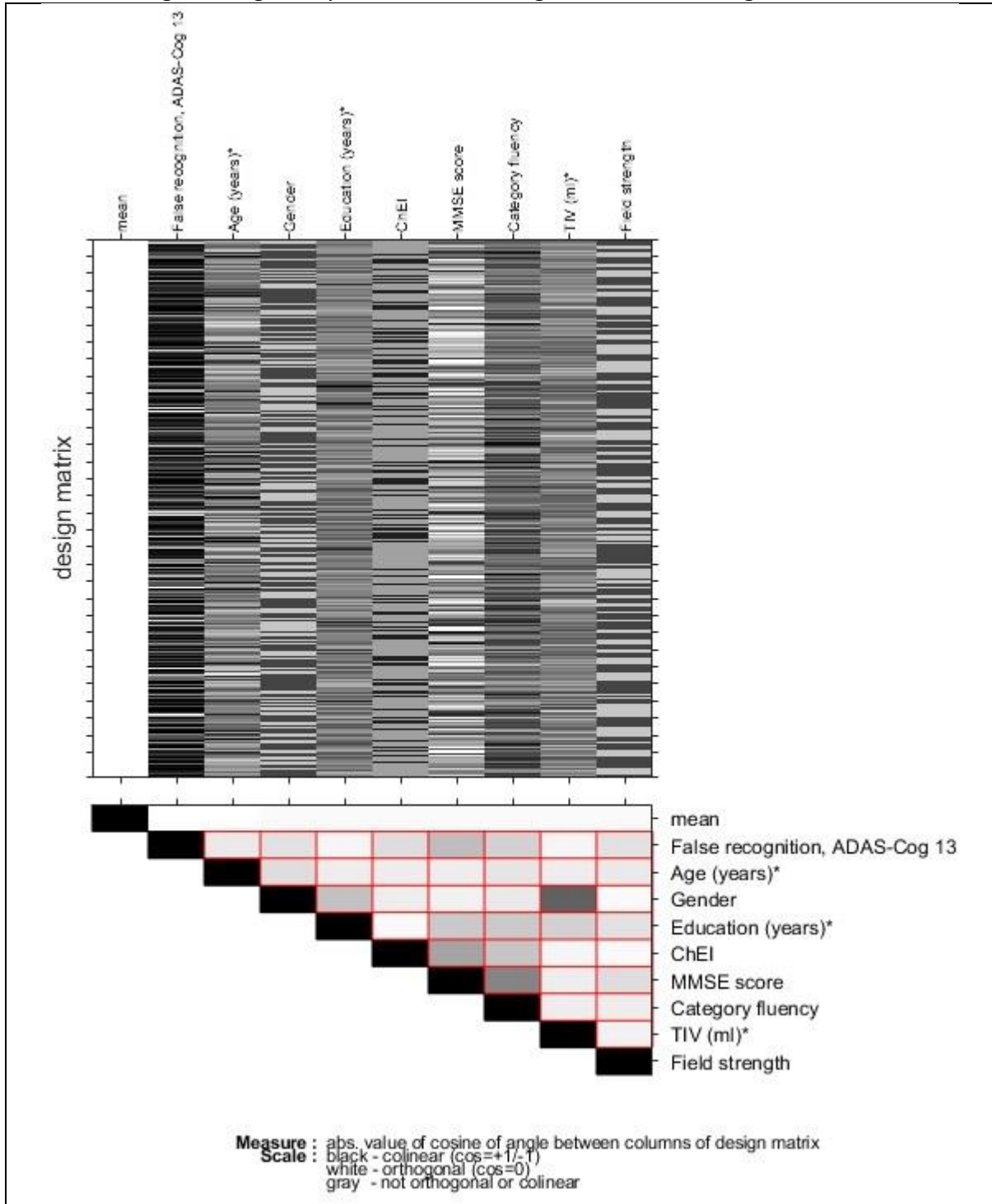
eTable 5. Region of Interest Analysis Model Diagnostics

Region of Interest	ADAS-Cog 13 False Recognition Models [†]				RAVLT False Recognition Models [†]			
	Model likelihood ratio, X^2 ($ps < .001$)	VIF, mean (SD)	Pearson residual, mean (SD)	Cook's distance [‡] , mean (SD)	Model likelihood ratio, X^2 ($ps \leq .002$)	VIF, mean (SD)	Pearson residual, mean (SD)	Cook's distance [‡] , mean (SD)
L Hippocampus	105.0	1.2 (0.1)	0.0 (1.0)	1.4 (2.7)	32.0	1.2 (0.2)	0.0 (1.0)	1.4 (3.4)
R Hippocampus	88.7	1.2 (0.1)	0.0 (1.0)	1.4 (2.7)	26.1	1.2 (0.1)	0.0 (1.0)	1.4 (3.5)
L Entorhinal Cortex	83.0	1.2 (0.1)	0.0 (1.0)	1.4 (2.7)	29.3	1.2 (0.1)	0.0 (1.0)	1.4 (3.6)
R Entorhinal Cortex	78.0	1.2 (0.1)	0.0 (1.0)	1.4 (2.8)	28.6	1.2 (0.1)	0.0 (1.0)	1.4 (3.4)
L Anterior Cingulate Gyrus	69.9	1.2 (0.1)	0.0 (1.0)	1.4 (2.6)	27.0	1.2 (0.1)	0.0 (1.0)	1.5 (4.1)
R Anterior Cingulate Gyrus	71.6	1.2 (0.1)	0.0 (1.0)	1.4 (2.6)	28.0	1.2 (0.1)	0.0 (1.0)	1.5 (3.9)
L Superior Parietal Lobule	68.0	1.2 (0.1)	0.0 (1.0)	1.4 (2.5)	25.6	1.2 (0.1)	0.0 (1.0)	1.4 (3.6)
R Superior Parietal Lobule	66.5	1.2 (0.1)	0.0 (1.0)	1.3 (2.4)	24.6	1.2 (0.1)	0.0 (1.0)	1.4 (3.7)
<i>Ventral Visual Stream</i>								
L Parahippocampal Gyrus	86.3	1.3 (0.2)	0.0 (1.0)	1.4 (2.7)	30.4	1.3 (0.2)	0.0 (1.0)	1.4 (3.5)
R Parahippocampal Gyrus	72.2	1.3 (0.2)	0.0 (1.0)	1.4 (2.7)	29.4	1.3 (0.2)	0.0 (1.0)	1.4 (3.5)
L Fusiform Gyrus	79.1	1.3 (0.2)	0.0 (1.0)	1.4 (2.6)	25.4	1.3 (0.2)	0.0 (1.0)	1.4 (3.6)
R Fusiform Gyrus	72.4	1.2 (0.1)	0.0 (1.0)	1.4 (2.7)	27.5	1.2 (0.1)	0.0 (1.0)	1.4 (3.4)
L Lingual Gyrus	66.2	1.2 (0.1)	0.0 (1.0)	1.4 (2.5)	24.7	1.2 (0.1)	0.0 (1.0)	1.4 (3.7)
R Lingual Gyrus	65.1	1.2 (0.1)	0.0 (1.0)	1.4 (2.5)	25.2	1.2 (0.1)	0.0 (1.0)	1.4 (3.4)
<i>Dorsolateral Prefrontal Cortex</i>								
L Middle Frontal Gyrus	71.4	1.2 (0.1)	0.0 (1.0)	1.4 (2.5)	25.8	1.2 (0.1)	0.0 (1.0)	1.5 (3.8)
R Middle Frontal Gyrus	72.7	1.2 (0.1)	0.0 (1.0)	1.4 (2.6)	26.8	1.2 (0.1)	0.0 (1.0)	1.4 (3.7)

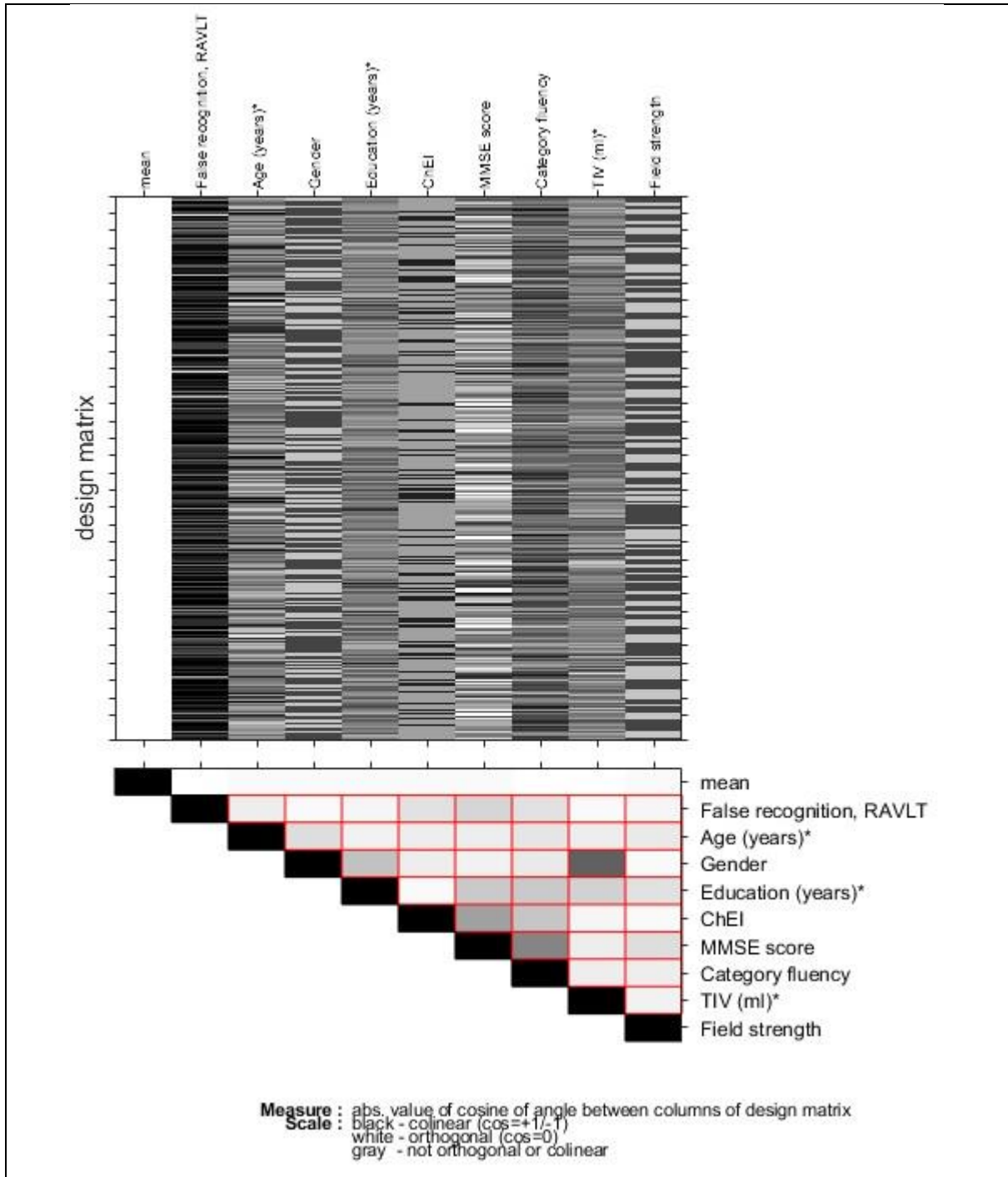
L Superior Frontal Gyrus	66.8	1.2 (0.1)	0.0 (1.0)	1.4 (2.5)	31.5	1.2 (0.1)	0.0 (1.0)	1.5 (4.0)
R Superior Frontal Gyrus	71.2	1.2 (0.1)	0.0 (1.0)	1.4 (2.6)	28.1	1.2 (0.1)	0.0 (1.0)	1.5 (3.8)
<i>Ventrolateral Prefrontal cortex</i>								
L Inferior Frontal Gyrus	73.3	1.2 (0.1)	0.0 (1.0)	1.4 (2.6)	27.9	1.2 (0.1)	0.0 (1.0)	1.4 (3.6)
R Inferior Frontal Gyrus	67.6	1.2 (0.1)	0.0 (1.0)	1.4 (2.6)	26.1	1.2 (0.1)	0.0 (1.0)	1.4 (3.5)
L Inferior Frontal Orbital Gyrus	66.3	1.2 (0.1)	0.0 (1.0)	1.4 (2.7)	24.6	1.2 (0.1)	0.0 (1.0)	1.5 (4.0)
R Inferior Frontal Orbital Gyrus	66.2	1.2 (0.1)	0.0 (1.0)	1.4 (2.7)	24.7	1.2 (0.1)	0.0 (1.0)	1.4 (3.5)
L Inferior Frontal Angular Gyrus	67.7	1.2 (0.1)	0.0 (1.0)	1.4 (2.6)	24.9	1.2 (0.1)	0.0 (1.0)	1.4 (3.5)
R Inferior Frontal Angular Gyrus	66.0	1.2 (0.1)	0.0 (1.0)	1.4 (2.9)	24.6	1.2 (0.1)	0.0 (1.0)	1.4 (3.6)
<i>Medial Prefrontal Cortex</i>								
L Superior Medial Frontal Gyrus	72.0	1.2 (0.1)	0.0 (1.0)	1.4 (2.7)	29.2	1.2 (0.1)	0.0 (1.0)	1.5 (3.9)
R Superior Medial Frontal Gyrus	71.4	1.2 (0.1)	0.0 (1.0)	1.4 (2.6)	30.0	1.2 (0.1)	0.0 (1.0)	1.5 (4.3)
L Medial Frontal Cerebrum	69.1	1.2 (0.1)	0.0 (1.0)	1.4 (2.7)	27.1	1.2 (0.1)	0.0 (1.0)	1.4 (3.7)
R Medial Frontal Cerebrum	70.9	1.2 (0.1)	0.0 (1.0)	1.4 (2.8)	27.2	1.2 (0.1)	0.0 (1.1)	1.4 (3.6)
<i>Orbitofrontal Prefrontal Cortex</i>								
L Lateral Orbital Gyrus	65.7	1.2 (0.1)	0.0 (1.0)	1.4 (2.5)	24.6	1.2 (0.1)	0.0 (1.0)	1.5 (3.8)
R Lateral Orbital Gyrus	65.0	1.2 (0.1)	0.0 (1.0)	1.4 (2.7)	24.8	1.2 (0.1)	0.0 (1.0)	1.5 (4.0)
Notes: [†] n = 725. [‡] x 10 ⁻³ ADAS-Cog 13 = Alzheimer's Disease Assessment Scale–Cognitive Subscale, 13 item; RAVLT = Rey's Auditory Verbal Learning Test; VIF = Variance inflation factor. Poisson regression models include covariates: age, gender, years of education, MMSE score, cholinesterase inhibitor prescription, category fluency for animals and MRI field strength. Pearson residuals additionally visualised on scatter plots and Cook's distance on bar charts.								

eFigure 2. Voxel-Based Morphometry (VBM) Design Orthogonality Matrices

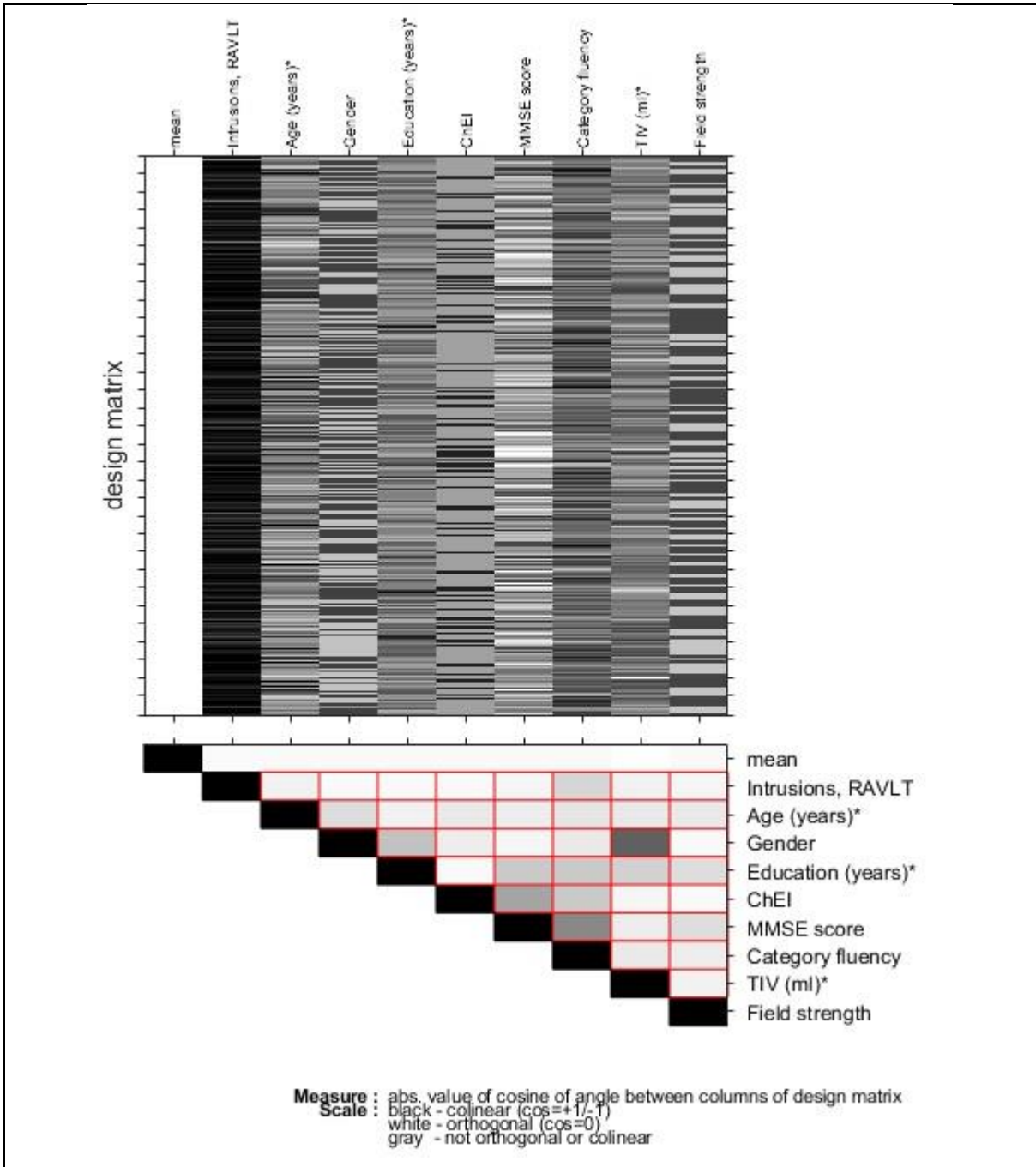
2A. VBM design orthogonality matrix: False recognition on ADAS-Cog 13



2B. VBM design orthogonality matrix: False recognition on RAVLT



2C. VBM design orthogonality matrix: Intrusions on RAVLT



Notes:

* mean centered variables.

ADAS-Cog 13 = Alzheimer's Disease Assessment Scale-Cognitive Subscale, 13 item; ChEI = cholinesterase inhibitor prescription; MMSE = Mini Mental State Examination; RAVLT = Rey's Auditory Verbal Learning Test; TIV = total intracranial volume.

eTable 6. Comparison of Volume in Identified Regions of Interest Between Those With Delusions at Baseline and the Control Group

Region of Interest	Control‡ (n = 549)	Delusions at baseline‡ (n = 42)	Control vs Delusions at baseline, <i>P</i> Value	Binary logistic regression models (<i>ps</i> < .05)†			
				One unit = % Mean ROI Volume	Odds ratio (95% CI)	<i>P</i> Value	% change baseline delusions per unit
L Hippocampus	1.40 (0.27)	1.36 (0.24)	$t_{589} = .869, p = .385$	7.4	1.026 (.829, 1.180)	.717	-
R Hippocampus	1.60 (0.32)	1.56 (0.29)	$t_{589} = .853, p = .394$	6.6	1.002 (.891, 1.126)	.979	-
L Entorhinal Cortex	1.29 (0.28)	1.32 (0.29)	$t_{589} = -.486, p = .627$	8.1	1.122 (.984, 1.278)	.085	-
R Entorhinal Cortex	1.34 (0.28)	1.35 (0.28)	$t_{589} = -.332, p = .740$	7.8	1.094 (.959, 1.247)	.182	-
L Anterior Cingulate Gyrus	2.63 (0.38)	2.55 (0.43)	$t_{589} = 1.302, p = .193$	3.9	.976 (.890, 1.071)	.612	-
R Anterior Cingulate Gyrus	1.99 (0.35)	1.87 (0.39)	$t_{589} = 2.147, p = .032$	5.2	.912 (.830, 1.002)	.054	-
L Superior Parietal Lobule	5.41 (0.72)	5.56 (0.83)	$t_{589} = -1.325, p = .186$	1.9	1.045 (.999, 1.093)	.054	-
R Superior Parietal Lobule	5.30 (0.69)	5.35 (0.79)	$t_{589} = -.429, p = .668$	1.9	1.019 (.971, 1.070)	.442	-
<i>Ventral Visual Stream</i>							
L Parahippocampal Gyrus	1.71 (0.29)	1.72 (0.31)	$t_{589} = -.206, p = .837$	6.0	1.083 (.945, 1.241)	.254	-
R Parahippocampal Gyrus	1.70 (0.30)	1.75 (0.34)	$t_{589} = .259, p = .259$	6.1	1.146 (1.002, 1.311)	.047	14.6
L Fusiform Gyrus	4.38 (0.60)	4.39 (0.66)	$t_{589} = -.186, p = .853$	2.3	§	-	-
R Fusiform Gyrus	4.28 (0.58)	4.25 (0.62)	$t_{589} = .343, p = .732$	2.4	1.038 (.971, 1.109)	.278	-
L Lingual Gyrus	4.43 (0.60)	4.45 (0.65)	$t_{589} = -.189, p = .850$	2.3	1.028 (.968, 1.092)	.365	-
R Lingual Gyrus	4.66 (0.61)	4.60 (0.64)	$t_{589} = .622, p = .534$	2.2	.989 (.931, 1.050)	.722	-
<i>Dorsolateral Prefrontal Cortex</i>							
L Middle Frontal Gyrus	9.78 (1.08)	9.58 (1.29)	$t_{589} = 1.084, p = .279$	1.0	.991 (.961, 1.021)	.554	-
R Middle Frontal Gyrus	9.72 (1.09)	9.53 (1.07)	$t_{589} = 1.092, p = .275$	1.0	.990 (.960, 1.021)	.526	-

L Superior Frontal Gyrus	7.85 (0.85)	7.68 (0.76)	$t_{589} = 1.274, p = .203$	1.3	.979 (.940, 1.020)	.320	-
R Superior Frontal Gyrus	7.88 (0.85)	7.79 (0.83)	$t_{589} = 0.615, p = .539$	1.3	.994 (.956, 1.034)	.758	-
<i>Ventrolateral Prefrontal cortex</i>							
L Inferior Frontal Gyrus	1.80 (0.26)	1.78 (0.27)	$t_{589} = .362, p = .717$	5.7	.999 (.876, 1.141)	.994	-
R Inferior Frontal Gyrus	1.82 (0.26)	1.76 (0.24)	$t_{589} = 1.371, p = .171$	5.6	.926 (.814, 1.054)	.245	-
L Inferior Frontal Orbital Gyrus	0.87 (0.13)	0.88 (0.14)	$t_{589} = -.078, p = .938$	11.7	1.072 (.825, 1.393)	.601	-
R Inferior Frontal Orbital Gyrus	0.84 (0.12)	0.84 (0.15)	$t_{589} = .043, p = .966$	12.1	1.103 (.847, 1.436)	.469	-
L Inferior Frontal Angular Gyrus	1.79 (0.26)	1.74 (0.28)	$t_{589} = 1.217, p = .224$	5.7	.926 (.810, 1.058)	.259	-
R Inferior Frontal Angular Gyrus	1.83 (0.26)	1.78 (0.21)	$t_{589} = 1.116, p = .265$	5.6	.938 (.819, 1.074)	.355	-
<i>Medial Prefrontal Cortex</i>							
L Superior Medial Frontal Gyrus	3.38 (0.39)	3.30 (0.39)	$t_{589} = 1.319, p = .188$	3.0	.966 (.884, 1.056)	.450	-
R Superior Medial Frontal Gyrus	4.11 (0.53)	4.02 (0.56)	$t_{589} = .990, p = .323$	2.5	.990 (.929, 1.055)	.763	-
L Medial Frontal Cerebrum	0.92 (0.16)	0.88 (0.15)	$t_{589} = 1.395, p = .164$	11.3	.938 (.760, 1.158)	.551	-
R Medial Frontal Cerebrum	0.97 (0.16)	0.93 (0.17)	$t_{589} = 1.568, p = .117$	10.6	.928 (.750, 1.148)	.490	-
<i>Orbitofrontal Prefrontal Cortex</i>							
L Lateral Orbital Gyrus	1.24 (0.15)	1.22 (0.16)	$t_{589} = .697, p = .486$	8.2	.966 (.776, 1.203)	.756	-
R Lateral Orbital Gyrus	1.32 (0.16)	1.29 (0.16)	$t_{589} = 1.288, p = .198$	7.7	.921 (.742, 1.143)	.455	-
<p>Notes: [†] n = 589. [‡] All measures are mean brain volume for specified region of interest, as proportion of total intracranial volume, at baseline x 10⁻³. Expressed as mean (SD). Models included covariates: age, gender, years of education, cholinesterase inhibitor prescription, MMSE score, category fluency for animals and MRI field strength. Model fit assessed by Hosmer and Lemeshow test, all <i>ps</i> > .05 indicating acceptable model fit except where indicated. [§] Hosmer and Lemeshow test <i>p</i> < .05, did not proceed to model interpretation. No <i>p</i> values remained significant after Bonferroni correction.</p>							