# Delusions and False Memory in Alzheimer's Disease

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http://adni.loni.usc.edu/wp-content/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf

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## Key Points

*Question:*

Is there an association between delusions and false memory in Alzheimer's disease on behavioural testing or volumetric neuroimaging?

*Findings:*

In this cross-sectional study, which included 728 participants from the Alzheimer's Disease Neuroimaging Initiative cohort who received an Alzheimer's disease diagnosis during follow up, false recognition was not associated with presence of delusions when accounting for confounding variables. On volumetric neuroimaging there was no overlap in brain regions associated with delusions and those associated with false recognition.

*Meaning*

Findings suggest that delusions in Alzheimer's disease do not arise as a direct consequence of forgetting or misremembering, and support the existence of a transdiagnostic mechanism for psychosis.

## Summary for twitter/tweet:

257 characters: False recognition is not associated with delusions in Alzheimer's disease, on either behavioural testing or volumetric neuroimaging. Findings suggest that delusions in Alzheimer's disease are not a consequence of memory error, and support a transdiagnostic mechanism for psychosis.

## Abstract

*Importance:*

Understanding the mechanisms of delusion formation in Alzheimer's disease (AD) could inform the development of therapeutic interventions. It has been suggested that delusions arise as a consequence of false memories.

*Objective:*

To investigate whether delusions in AD are associated with false recognition, and whether higher rates of false recognition *and* the presence of delusions are associated with lower regional brain volumes in the same brain regions.

*Design:*

Cross-sectional study, using data from Alzheimer's Disease Neuroimaging Initiative (ADNI).

*Setting:*

Over the past 18 years, ADNI has amassed an archive of longitudinal behavioural and biomarker data from 2248 individuals.

*Participants:*

ADNI participants with AD diagnosis at baseline or follow up.

*Main outcomes and measures:*

False recognition, measured by Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog 13) and Rey's Auditory Verbal Learning Test (RAVLT), and volume of brain regions corrected for total intracranial volume.

*Results:*

728 participants included (mean (SD) age: 74.8 (7.4); 317 women, 411 men). Participants with delusions at baseline (n = 42) had higher rates of false recognition on ADAS-Cog 13 (median (IQR) score 3 (1 – 6) compared to 2 (0 – 4) for controls; n = 549, $U$ = 9398.5, $p$ = .042). False recognition was not associated with presence of delusions when confounding variables were included in binary logistic regression models. ADAS-Cog 13 false recognition score was inversely related to volume of left and right hippocampus (Exp(β) .909, 95% CI .882 - .937, $p$ < .001; Exp(β) .940, 95% CI .915 - .965, $p$ < .001), left entorhinal cortex (Exp(β) .939, 95% CI .911 - .969, $p$ < .001), left parahippocampal gyrus (Exp(β) .934, 95% CI .905 - .963, $p$ < .001) and left fusiform gyrus (Exp(β) .974, 95% CI .960 - .989, $p$ < .001). There was no overlap between locations associated with false recognition and those associated with delusions.

*Conclusions and Relevance:*

False memory was not associated with presence of delusions after accounting for confounding variables. Volumetric neuroimaging did not indicate shared neural networks for false memory and delusions. AD delusions do not arise as a direct consequence of misremembering, lending weight to ongoing attempts to delineate specific therapeutic targets for treatment of psychosis.

## Introduction

Dementia is one of the most significant challenges to global health and is the seventh leading cause of death globally.[1-4] Over half of dementia diagnoses are Alzheimer's disease (AD),[5] costing the UK economy over £25 annually. In AD delusions (fixed false beliefs), can be divided into two subtypes: 'persecutory', often involving theft or personal harm, and 'misidentification', including misidentification phenomena and/or hallucinations.[6, 7]These symptoms occur in up to 50% of people with AD and can be highly distressing, reduce quality of life for patients and caregivers and precipitate early institutionalisation.[8-15] Antipsychotic drugs are associated with substantial morbidity and mortality in people with AD[16-18] and it is imperative that safer treatment approaches are identified. Research that enhances our understanding of the cognitive neuroscience of delusion formation in the context of AD would help to more effectively target non-pharmacological and pharmacological treatment strategies.[19]

As well as being susceptible to delusions, up to 90% of individuals with AD experience memory-related false beliefs (false memories).[20] False memory includes a range of phenomena: confabulation (giving false information without being aware of it), intrusion errors, misremembering word lists, false recognition of novel stimuli and distortions in autobiographical memory.[21] These may be associated with high-risk behaviours, such as missing medication doses due to falsely remembering taking it.[22] False memories in AD also reduce functional ability and increase caregiver distress.[23, 24]

Conceptually, it has been suggested that false memories and delusions are part of a continuum.[25, 26] In healthy individuals, false memories correlate with sub-clinical delusional ideation.[27] Individuals with schizophrenia, particularly those with current psychosis symptoms, are more liable to false recognition on memory testing.[28-33] There is preliminary evidence of a relationship between false memories and delusions in AD, with two previous studies finding individuals with delusions found to score more highly on measures of confabulation.[34, 35] These two studies had small sample sizes (< 25

participants with delusions) and did not control for confounding variables, and further exploration of the relationship between false memories and delusions in AD in a larger sample size is warranted.

Delusions become more common as global cognitive function declines.[8, 36] Sultzer et al. (2014) found an association between delusions and impaired short term memory, measured by the Mattis Dementia Rating Scale (DRS) memory subscale, replicating a similar earlier finding by Jeste et al. (1992). Furthermore, hypometabolism in the right temporal cortex (including the middle, inferior, fusiform, and parahippocampal gyri (PHG)) in AD participants with greater DRS memory impairment overlapped with a region of hypometabolism (including the middle temporal (MTG) and PHG) also associated with delusions.[37] Deficits in visual attention and recognition are also associated with delusions in AD. People with delusions in AD perform more poorly on both the Rapid Visual Processing test and the incomplete letters test of the Visual Object and Space Perception battery[39] and have increased brain atrophy in associated ventral visual stream brain regions.[39, 40] Specifically, those with delusions in AD have been found to have lower left PHG volume.[40] Frontal cortical networks are also linked to delusional symptoms in AD, with primarily right-sided structural and functional changes identified on neuroimaging and evidence of executive dysfunction on behavioural testing.[6, 7, 41] These findings support the hypothesis that delusions in AD may share neurocognitive foundations with impairments in specific domains of cognitive function.

*Objectives*

The aim of the study was to investigate the relationship between false memory and delusions in AD and determine if they have a shared neuropathology, indexed by regional brain volume.

Study hypotheses were that:

1) Individuals with delusions in AD would have more false memories than those without delusions when matched for severity of global cognitive impairment.

2) Both false recognition and the presence of delusions would correlate with reduced volumes of structures in medial temporal lobe (MTL); ventral visual stream; entorhinal cortices; PHG; fusiform gyri (FFG); lingual gyri; PFC; anterior cingulate cortex (ACC) or superior parietal lobules.

## Method

*Sample*

Data were downloaded from the Alzheimer's Disease Neuroimaging Institute (ADNI) database (https://adni.loni.usc.edu/) 26th March 2020. ADNI launched in 2004, with the aim of identifying biomarkers by which to diagnose and track progression of AD and has an extensive archive of behavioural and neuroimaging data for individuals with AD, amnestic mild cognitive impairment (aMCI) and cognitively normal (CN) controls. Each of the 59 participating sites has ethical approval, and all participants provide informed written consent for involvement.

To maximise the number of participants with delusions at baseline, ADNI participants who met study criteria were included from all ADNI phases. Criteria for enrolment in ADNI are described in detail elsewhere, and can be found in Supplement Table 1.[42, 43] Additional study exclusion criteria were: not diagnosed with AD[44] at any timepoint, Neuropsychiatric Inventory (NPI)[45] or NPI-Q[46] not completed at baseline, inconsistent diagnosis of AD through follow-up (if a participant reverted to aMCI), baseline MRI of insufficient quality for analysis, false memory measures not completed. Carer-rated NPI and NPI-Q data from all available timepoints were used to determine if participants developed delusions. Delusions were considered to be present if a participant scored one or more on the delusions item of the NPI-Q or answered 'yes' to the delusions domain of the NPI. The control group was those participants who did not experience delusions at any timepoint. MMSE score was

used as a measure of overall cognitive function, and category fluency for animals as a measure of executive function, as poor performance on measures of executive function is associated with increased false memory.[47]

### *False memory measures*

Two behavioural measures routinely completed at ADNI visits included a measure of false memory – the 13 item Alzheimer's Disease Assessment Scale–Cognitive subscale (ADAS-Cog 13) and the Rey Auditory Verbal Learning Test (RAVLT). The ADAS-Cog 13 includes a word recognition task of 12 target and 12 distractor words. Positive responses to distractors (maximum score 12) were used as an index of false memory. The RAVLT includes a word recognition task of 15 target and 15 distractor words. Total number of intrusions (maximum score 120), and positive responses to distractors (maximum score 15) were used as two further false memory measures. Discrimination (d') and response bias (c) were calculated for false recognition on both tasks as in Macmillan (1993).

### *MRI acquisition and image processing*

Baseline MRI scans were used. Scanner hardware differs between ADNI sites and MRI protocol changes between ADNI phases, details available via https://adni.loni.usc.edu/methods/mri-tool/mri-analysis/. Raw T1-weighted sagittal images were downloaded. Image processing was performed using Statistical Parametric Mapping software (SPM12; https://www.fil.ion.ucl.ac.uk/spm/software/spm12/) and the Computational Anatomy Toolbox (CAT12, version 7 (r1725); http://www.neuro.uni-jena.de/cat/) for SPM12.

All scans were individually reviewed for movement artifact and the origin manually reset to the anterior commissure. Images were processed using the CAT12 Geodesic Shooting pipeline, with graph-cut skull stripping and segmentation. Grey matter (GM) volumes were estimated in ml for

regions of interest (ROIs) using the 'Neuromorphometric' atlas.[49] GM image files were smoothed at 8mm full width half maximum prior to whole brain exploratory voxel-based morphometry (VBM) analysis. CAT12 measures of image quality were reviewed.

## *Statistical analyses*

Analyses were carried out in SPSS, with results considered significant at $p < .05$. Confounding variables were determined a priori: age, gender, years of education, MMSE score, cholinesterase inhibitor prescription and category fluency for animals. MRI field strength was included as a covariate for ROI analyses and total intracranial volume (TIV) for VBM analyses.

### Behavioural data

Baseline characteristics and task performance were compared between those with delusions at baseline and the control group, and those with delusions at any time point and the control group. Where there was a significant difference in false memory measure, comparisons were re-run excluding outliers and those who were CN at baseline. This was to confirm that significant results were not an artefact of larger numbers of CN participants in the control group. Binary logistic regression including confounding variables was then used to further explore significant findings.

### Neuroimaging data

ROIs were selected based on a priori hypotheses described above and corrected for global brain volume by calculating each ROI as a proportion of TIV. Correlations between measures of false recognition and ROI volume (as a proportion of TIV) were explored using Poisson regression modelling corrected for overdispersion with the Pearson $X^2$/df value as described by McCullagh and Nelder (1989). For results of regression analyses we express change in ROI volume (as a proportion

of TIV) as a percentage of overall mean ROI volume for ease of interpretation. Covariates were assessed for collinearity using variance inflation factor scores (threshold <2.5),[51] Pearson residuals were plotted and significant models were re-run excluding outliers above a conservative threshold for Cook's distance[52] and those who were CN at baseline.

Prior to VBM analysis continuous variables were mean-centered. Explicit threshold masking was applied using a majority mask as described by Ridgway et al. (2009). T-contrasts were run to explore both positive and negative correlations between performance on false memory measures and brain volume, with a family wise error (FWE) correction applied and an extent threshold of $k = 10$. As positive and negative correlations were run separately, $p$ values were doubled prior to comparing to the significance threshold. Design orthogonality matrices were viewed to assess for collinearity.

TIV-corrected GM volume for ROIs were compared between those with delusions at baseline and the control group, and those with delusions at any time point and the control group, first using independent-samples t-tests and then binary logistic regression models including confounding variables. An exploratory whole brain VBM analysis was carried out to further identify any associations between regional volume and delusion group.

STROBE guidelines for reporting of cross-sectional studies[54] were followed in the preparation of this manuscript.

## Results

*Sample Characteristics*

Of 728 participants included in the study, 317 (43.5%) were female and 411 (56.5%) were male. The mean (SD) age was 74.8 (7.4) years. 386 (53.0%) had an AD diagnosis at baseline and 585 (80.4%)

had received an AD diagnosis by the end of the second year of follow-up. The mean (SD) baseline MMSE score for the group was 25.1 (2.9). Delusions were present at baseline in 42 participants and at a later time point in a further 137 participants. Those with delusions at baseline (n = 42) and those with delusions at baseline *or* any other time point (n = 179) were compared to the remaining 549 participants who formed the control group. Breakdown of psychosis symptoms by subtype was only available for the 32 participants with delusions at baseline for whom a full NPI was completed, see Supplement Table 2. The participant selection flow chart is Figure 1 in the Supplement.

Between-group differences in demographic details and baseline assessments are reported in Table 1. Those with delusions at baseline differed significantly from the control group in race, diagnosis at baseline, years since diagnosis, antipsychotic prescribing, NPI-Q score, presence of hallucinations, MMSE score and category fluency for animals.

One scan was removed due to motion artefact. Comparison between this individual and remaining sample is presented in Supplement Table 3.

*False Memory Measures in Participants with Delusions vs Control Participants*

Those with delusions at baseline had higher rates of false recognition on ADAS-Cog 13 and worse discrimination performance on RAVLT, with no significant difference between the groups on any other false memory measure, see Table 2. All results remained statistically significant after excluding outliers and those who were CN at baseline. There were no significant differences between those with delusions at any time point and the control group for any false memory measure, discrimination or response bias.

False recognition on ADAS-Cog 13 or RAVLT were not associated with presence of delusions when confounding factors were included in binary logistic regression models. Only MMSE score was significantly associated with delusions in the models, presented in Supplement Table 4.

*Brain Regions Associated with False Memory*

All of the models that assessed the relationship between pre-specified ROIs and false recognition on both ADAS-Cog 13 and RAVLT were significant ($p$s < .005), with an inverse relationship between volume of several ROIs and number of words falsely recognised, see Table 3. Following Bonferroni correction, the relationship between false recognition on ADAS-Cog 13 and volume of MTL ROIs (hippocampus and entorhinal cortex bilaterally) and ventral visual stream ROIs (left PHG and FFG) remained significant, see Table 3 and Figure 1. All models assessing the relationship between intrusions on RAVLT were significant, however no ROI reached individual significance within any model.

Model diagnostics are presented in Table 5 in the Supplement, and indicated good model fit by the parameters described. ROIs which survived Bonferroni correction remained significant when outliers and those who were CN at baseline were excluded.

On VBM analysis, the model for false recognition on ADAS-Cog 13 revealed an inverse relationship between false recognition and GM volume in right hippocampus (MNI space coordinates of peak voxel x = 17, y = -11, z = -14, $k$ = 76, $Z$ = 5.01, $p_{FWE}$ = .020 and x = 29, y = -29, z = -9, $k$ = 40, $Z$ = 4.53, $p_{FWE}$ = .036), left FFG (x = -27, y = -29, z = -15, $k$ = 3220, $Z$ = 3220, $p_{FWE}$ = < .001) and left MTG (x = -35, y = 9, z = -33, $k$ = 100, $Z$ = 4.02, $p_{FWE}$ = .014), significant at the cluster-level, see Figure 2a. The

unthresholded effect size map for the model is displayed in Figure 2b. Design orthogonality matrices are presented in Supplement Figure 2.

*Brain Regions Associated with Delusions*

In those with delusions at baseline, the right ACC was significantly smaller as a proportion of TIV than in the control group ($1.87 \pm 0.39 \times 10^{-3}$ and $1.99 \pm 0.35 \times 10^{-3}$ respectively; $t_{589} = 2.147$, $p = .032$). However, this finding was no longer significant when Bonferroni correction was applied or when confounding factors were included in the regression model ($p = .054$). All of the regression models for presence of delusions at baseline were statistically significant but right PHG was the only ROI that achieved individual significance within the models (Supplement Table 6). Delusions at baseline were more likely as the volume of the right PHG (as a proportion of TIV) increased (Exp(β) 1.146, 95% CI 1.002 – 1.311, $p = .047$). This finding did not survive Bonferroni correction. None of the regression models for those with delusions at any timepoint reached significance. On VBM analysis, no clusters reached significance.

## Discussion

In line with our hypothesis, participants with delusions at baseline had higher rates of false recognition on ADAS-Cog 13. However, the relationship did not survive the inclusion of multiple confounding variables in regression models. On ROI analysis there was an inverse relationship between false recognition on ADAS-Cog 13 and volumes of ROIs within the MTL (hippocampus and entorhinal cortex bilaterally) and ventral visual stream (left PHG and FFG). None of the associations between ROI volume and delusions survived Bonferroni correction, nor was there overlap with areas associated with false recognition. This lack of association between delusions and false recognition is in contrast with two previous studies that reported greater confabulation in AD subjects with

delusions. However, as discussed, these studies had small sample sizes and did not control for confounding variables.[34, 35]

Our results confirm a role for MTL and ventral visual stream in false memory in AD.[55] Both hippocampus[56-59] and entorhinal cortex[60-62] are known to be crucial for recognition memory.[63] Individuals with hippocampal lesions demonstrate a combination of impaired recollection with preserved familiarity thought to predispose to false recognition.[64, 65] Reduced left hippocampal (and PHG) volume has also previously been associated with increased false recognition on RAVLT in a smaller group (n = 77) of individuals with AD.[66] PHG and FFG are part of the hippocampal-PFC network of context encoding and retrieval.[67-69] PHG and left FFG activity are observed during correct recognition on recognition memory testing[70-72] and have thus been implicated in distinguishing true from false memory.[71, 72] Our data confirm these findings, as lower volumes of PHG and left FFG were associated with increased false memories.

While we found no overlap between the neural networks involved in false memory and delusions, the brain regions in which reduced volume was associated with increased false recognition have been associated with psychosis symptoms in AD in other cohorts. Lower right hippocampal volume has been consistently linked to psychosis symptoms in AD,[73-75] with left entorhinal atrophy in AD recently reported to increase risk of psychosis.[73] The MTL is part of a network involved in encoding and retrieval of memory for spatial and temporal context, mediated via functional connections to the PFC.[76, 77] It has been hypothesised that MTL volume loss, and subsequent dysfunction within this network, leads to psychosis as a result of impaired ability to attribute context to sensory input, causing increased prediction errors and delusion formation.[78] Lower PHG volume has been found in those with current delusions in AD, and prospectively in those who go on to develop delusions,[40, 79] and right FFG atrophy has also been associated with AD psychosis.[80]

Delusions at baseline were more likely as the volume of the right PHG increased. While this did not survive Bonferroni correction, it may indicate a potential role of asymmetry in delusion formation in

AD. Rightward asymmetry of PHG volume has also been found when comparing individuals with AD to those with MCI and healthy older adults,[81] and it is therefore possible that this is a marker of disease severity rather than being a causal factor in delusion formation. However, a limited existing literature suggests a possible role for right PHG overactivity in delusion formation in schizophrenia; Surguladze et al. (2006) found that individuals with schizophrenia had reduced right PHG activity in response to fearful faces and increased activity in response to neutral faces compared to controls, with increased activity correlating with degree of reality distortion and Kirino et al. (2019) observed that right PHG activity on fMRI correlated with severity of positive symptoms.

*Limitations*

This study has several limitations. Firstly, the number of participants with delusions at baseline is relatively small. This is perhaps unsurprising given the relatively mild severity of AD in the sample. It is therefore reassuring that including participants with delusions at any time point also did not show any association between delusions and regional brain volume. Of note, we were not able to explore results by psychosis subtype. Given that the subtypes are associated with distinct neural correlates, this may have obfuscated results, and may go some way to explain why no frontal lobe involvement was identified.

Overlap in cognitive function between those with MCI and early AD is acknowledged, making correctly diagnosing these individuals challenging.[84] As the ADNI cut-off for 'cognitively normal' is an MMSE score of 24, in order to maximise sample size we included individuals who received an AD diagnosis at any timepoint. This introduced further diagnostic heterogeneity. However, cognitive function (measured by MMSE) was included as a covariate in analyses, which may go some way to controlling for this. It cannot be completely ruled out that a proportion of participants had undiagnosed Lewy body dementia or posterior cortical atrophy, although a previous analysis of atrophy in posterior cortex and visuospatial deficits in ADNI participants did not reveal the deterioration over time that would be expected with a posterior cortical atrophy diagnosis.[85] Relying

on the carer-rated NPI to determine the presence of delusions has limitations, as carers may have been unaware of infrequently experienced unusual beliefs. In addition, the nature of longitudinal research with set follow-up time points means that some occurrences of delusions could have been missed. We chose variables to include in regression models a priori, and in balancing potential contributing confounding factors with risk of multicollinearity and overfitting of models did not include antipsychotic use, presence of hallucinations or biomarkers.

The retrospective nature of this study meant that we didn't use a validated false memory test and had to repurpose components of available test data. In terms of neuroimaging methodology, while including participants from the entire database allowed a larger sample size, the inclusion of data acquired from different imaging protocols was a significant source of heterogeneity. However, previous VBM analyses using structural MRI data from AD participants across multiple sites and scanners have reported minimal confounding of results[86, 87] and magnetic field strength was included as a confounding variable in our analyses. As is the case for all research using structural MRI, limitations include the inability to infer causality from patterns of atrophy and poor reproducibility of MRI findings across studies.[88, 89]

## Conclusions

Results from this study indicate that, despite the superficial resemblances, delusions in AD are more than simply an extension of memory errors or confabulation. This confirms psychosis in AD as a valid target for pharmacological and non-pharmacological treatment approaches and supports the existence of a transdiagnostic mechanism for psychosis.

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the manuscript for publication. Dr Emma M[c]Lachlan had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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***Table 1*** *Demographic details and baseline screening assessment results*

| | Control (n = 549)‡ | Delusions at baseline (n = 42) | Delusions at any time point (n = 179) | Control vs Delusions at baseline, *P* Value | Control vs Delusions at any time point, *P* Value |
|---|---|---|---|---|---|
| Age, mean (SD), years | 74.8 (7.5) | 76.0 (6.4) | 75.0 (7.2) | $t_{589}$ = 1.007, $p$ = .314 | $t_{726}$ = -.306, $p$ = .760 |
| No. (%) female | 224 (40.8) | 18 (43) | 93 (52) | $X^2$ = .068, $p$ = .794 | $X^2$ = 6.831, **$p$ = .009** |
| No. (%) right handed | 504 (92) | 38 (91) | 169 (94) | †$p$ = .767 | $X^2$ = 1.171, $p$ = .327 |
| Education, mean (SD), years | 15.6 (2.8) | 15.6 (2.8) | 15.4 (2.9) | $t_{589}$ = .115, $p$ = .908 | $t_{726}$ = .892, $p$ = .372 |
| No. (%) hallucinations at baseline | 8 (2) | 7 (17) | 16 (9) | †**$p$ < .001** | $X^2$ = 23.699, **$p$ < .001** |
| *Race* | | | | | |
| No. (%) White | 519 (94.5) | 36 (86) | 162 (90.5) | †**$p$ = .037** | †$p$ = .058 |
| No (%) Black | 13 (2) | 4 (9.5) | 12 (7) | | |
| No (%) Asian | 12 (2) | 2 (5) | 4 (2) | | |
| No. (%) Mixed race | 5 (1) | 0 (0) | 1 (1) | | |
| *Diagnosis* | | | | | |
| No. (%) cognitively normal | 21 (38) | 0 (0.0) | 6 (3) | †**$p$ = .003** | $X^2$ = 2.751, $p$ = .253 |
| No. (%) amnestic MCI | 228 (41.5) | 8 (19) | 87 (49) | | |
| No. (%) Alzheimer's disease | 300 (54.6) | 34 (81) | 86 (48) | | |
| *Medication* | | | | | |
| No. (%) ChEI/Memantine | 400 (73.0) | 34 (81) | 123 (69) | $X^2$ = 1.271, $p$ = .283 | $X^2$ = 1.223, $p$ = .269 |
| No. (%) antidepressant | 179 (33) | 17 (41) | 72 (40) | $X^2$ = 1.073, $p$ = .311 | $X^2$ = 3.411, $p$ = .065 |
| No. (%) antipsychotic | 4 (0) | 4 (10) | 6 (3) | †**$p$ = .001** | †**$p$ = .017** |
| *Screening Assessments* | | | | | |
| NPI-Q, median (IQR), score | 1 (0 – 3) | 7 (5 – 9) | 3 (1 – 6) | $U$ = 3032.0, **$p$ < .001** | $U$ = 35917.0, **$p$ < .001** |

| | | | | | |
|---|---|---|---|---|---|
| MMSE, mean (SD), score | 25.0 (2.9) | 23.4 (2.7) | 25.1 (2.9) | $t_{589}$ = -3.537, ***p* < .001** | $t_{726}$ = -.102, $p$ = .919 |
| GDS-15, median (IQR), score | 1 (1 – 2) | 1 (0 – 3) | 1 (1 – 2) | $U$ = 10948.0, $p$ = .576 | $U$ = 48397.0, $p$ = .755 |
| Category fluency, mean (SD), score | 14.0 (5.4) | 11.5 (4.5) | 13.8 (4.9) | $t_{588}$ = 2.919, ***p* = .004** | $t_{725}$ = .409, $p$ = .683 |
| Notes:<br>MCI = mild cognitive impairment; ChEI = cholinesterase inhibitor; GDS-15 = short form Geriatric Depression Scale; MMSE = Mini Mental State Examination; NPI-Q = Neuropsychiatric Inventory Questionnaire.<br>† $p$ value from Fisher's exact test. ‡ Control group n = 548 for Medication and Category fluency. | | | | | |

***Table 2*** *Performance on measures of false memory for those with delusions at baseline vs the control group*

| False Memory Measure | Control (n = 549)† | Delusions at baseline (n = 42)‡ | Control vs Delusions at baseline, *P* Value |
|---|---|---|---|
| *ADAS-Cog 13* | | | |
| False recognition, median (IQR) (Maximum total score 12) | 2 (0 – 4) | 3 (1 – 6) | $U$ = 9398.5, ***p* = .042** |
| Discrimination (d'), median (IQR) | 1.5 (0.9 - 2.1) | 1.3 (0.8 - 1.6) | $U$ = 9451.0, $p$ = .051 |
| Response bias (c), mean (SD) | -0.1 (0.6) | -0.0 (0.7) | $t_{594}$ = -1.287, $p$ = .199 |
| *RAVLT* | | | |
| False recognition, median (IQR) (Maximum total score 15) | 2 (1 – 4) | 2.5 (1 – 4) | $U$ = 9806.0, $p$ = .105 |
| Discrimination (d'), median (IQR) | 1.1 (0.5 - 1.7) | 0.7 (0.4 - 1.1) | $U$ = 8738.5, ***p* = .009** |
| Response bias (c), median (IQR) | -0.4 (-0.8 - -0.1) | -0.5 (-0.8 - -0.1) | $U$ = 11078.5, $p$ = .688 |
| Intrusions, median (IQR) (Maximum total score 120) | 4 (2 – 9) | 6 (2 – 8) | $U$ = 10245.0, $p$ = .550 |

Notes:
ADAS-Cog 13 = Alzheimer's Disease Assessment Scale–Cognitive Subscale, 13 item; RAVLT = Rey's Auditory Verbal Learning Test.
† Control group n = 548 for RAVLT false recognition and n = 543 RAVLT intrusions; ‡ Delusion group n = 40 for RAVLT intrusions.

***Table 3*** *Relationship between the volume of regions of interest and false recognition tests*

| Region of Interest | One unit = % Mean ROI Volume | ADAS-Cog 13 False Recognition Models† | | | RAVLT False Recognition Models† | | |
|---|---|---|---|---|---|---|---|
| | | Exp(β) (95% CI) | *P* Value | % change in score per unit | Exp(β) (95% CI) | *P* Value | % change in score per unit |
| L Hippocampus | 7.4 | .909 (.882, .937) | < **.001*** | 9.1 | .960 (.932, .989) | **.008** | 4.0 |
| R Hippocampus | 6.6 | .940 (.915, .965) | < **.001*** | 6.0 | .984 (.959, 1.010) | .227 | - |
| L Entorhinal Cortex | 8.1 | .939 (.911, .969) | < **.001*** | 6.1 | .968 (.940, .997) | **.030** | 3.2 |
| R Entorhinal Cortex | 7.8 | .948 (.920, .978) | **.001** | 5.2 | .971 (.943, 1.000) | .050 | - |
| L Anterior Cingulate Gyrus | 3.9 | .977 (.957, .998) | .034 | 2.3 | .985 (.966, 1.005) | .135 | - |
| R Anterior Cingulate Gyrus | 5.2 | .974 (.953, .995) | .014 | 2.6 | .982 (.963, 1.002) | .082 | - |
| L Superior Parietal Lobule | 1.9 | .991 (.980, 1.002) | .108 | - | .995 (.984, 1.005) | .330 | - |
| R Superior Parietal Lobule | 1.9 | .994 (.982, 1.005) | .270 | - | 1.000 (.989, 1.011) | .989 | - |
| *Ventral Visual Stream* | | | | | | | |
| L Parahippocampal Gyrus | 6.0 | .934 (.905, .963) | < **.001*** | 6.6 | .964 (.936, .993) | **.016** | 3.6 |
| R Parahippocampal Gyrus | 6.1 | .963 (.935, .992) | **.012** | 3.7 | .969 (.943, .997) | **.031** | 3.1 |
| L Fusiform Gyrus | 2.3 | .974 (.960, .989) | < **.001*** | 2.6 | .994 (.980, 1.007) | .358 | - |
| R Fusiform Gyrus | 2.4 | .981 (.967, .996) | **.011** | 1.9 | .988 (.975, 1.002) | .096 | - |
| L Lingual Gyrus | 2.3 | .993 (.979, 1.007) | .306 | - | .998 (.985, 1.011) | .756 | - |
| R Lingual Gyrus | 2.2 | .998 (.984, 1.011) | .740 | - | .995 (.982, 1.008) | .430 | - |
| *Dorsolateral Prefrontal Cortex* | | | | | | | |
| L Middle Frontal Gyrus | 1.0 | .991 (.984, .998) | **.014** | 0.9 | .996 (.990, 1.003) | .277 | - |
| R Middle Frontal Gyrus | 1.0 | .991 (.984, .997) | **.008** | 0.9 | .995 (.989, 1.002) | .147 | - |
| L Superior Frontal Gyrus | 1.3 | .994 (.985, 1.003) | .201 | - | .988 (.980, .997) | **.010** | 1.2 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| R Superior Frontal Gyrus | 1.3 | .989 (.980, .998) | **.020** | 1.1 | .992 (.984, 1.000) | .065 | - |
| *Ventrolateral Prefrontal cortex* | | | | | | | |
| L Inferior Frontal Gyrus | 5.7 | .960 (.932, .989) | **.007** | 4.0 | .975 (.948, 1.003) | .076 | - |
| R Inferior Frontal Gyrus | 5.6 | .976 (.948, 1.006) | .113 | - | .983 (.956, 1.011) | .231 | - |
| L Inferior Frontal Orbital Gyrus | 11.7 | .968 (.912, 1.028) | .292 | - | .998 (.943, 1.055) | .933 | - |
| R Inferior Frontal Orbital Gyrus | 12.1 | .967 (.909, 1.029) | .286 | - | 1.006 (.950, 1.065) | .834 | - |
| L Inferior Frontal Angular Gyrus | 5.7 | .976 (.947, 1.006) | .121 | - | 1.008 (.979, 1.037) | .594 | - |
| R Inferior Frontal Angular Gyrus | 5.6 | .983 (.953, 1.015) | .295 | - | .998 (.968, 1.027) | .869 | - |
| *Medial Prefrontal Cortex* | | | | | | | |
| L Superior Medial Frontal Gyrus | 3.0 | .973 (.955, .993) | **.009** | 2.7 | .980 (.962, .999) | **.036** | 2.0 |
| R Superior Medial Frontal Gyrus | 2.5 | .982 (.968, .996) | **.015** | 1.8 | .984 (.971, .998) | **.023** | 1.6 |
| L Medial Frontal Cerebrum | 11.3 | .954 (.908, 1.001) | .057 | - | .964 (.922, 1.010) | .123 | - |
| R Medial Frontal Cerebrum | 10.6 | .946 (.901, .992) | **.023** | 5.4 | .964 (.921, 1.009) | .113 | - |
| *Orbitofrontal Prefrontal Cortex* | | | | | | | |
| L Lateral Orbital Gyrus | 8.2 | .979 (.931, 1.030) | .411 | - | 1.004 (.957, 1.053) | .874 | - |
| R Lateral Orbital Gyrus | 7.7 | .997 (.951, 1.046) | .916 | - | .990 (.946, 1.035) | .656 | - |

Notes:
† n = 725.
ADAS-Cog 13 = Alzheimer's Disease Assessment Scale–Cognitive Subscale, 13 item; RAVLT = Rey's Auditory Verbal Learning Test
Poisson regression models include covariates: age, gender, years of education, MMSE score, cholinesterase inhibitor prescription, category fluency for animals and MRI field strength.
* Survived Bonferroni correction ($p < .001$)