RESEARCH ARTICLE

Examining the presence and nature of delusions in Alzheimer's disease and frontotemporal dementia syndromes

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Abstract

Objectives: Abnormal beliefs and delusions have been reported in some people with dementia, however, the prevalence of delusions, and their neurocognitive basis has been underexplored. This study aimed to examine the presence, severity, content and neural correlates of delusions in a large, well-characterised cohort of dementia patients using a transdiagnostic, cross-sectional approach.

Methods: Four-hundred and eighty-seven people with dementia were recruited: 102 Alzheimer's disease, 136 behavioural-variant frontotemporal dementia, 154 primary progressive aphasia, 29 motor neurone disease, 46 corticobasal syndrome, 20 progressive supranuclear palsy. All patients underwent neuropsychological assessment and brain magnetic resonance imaging, and the Neuropsychiatric Inventory was conducted with an informant, by an experienced clinician.

Results: In our cohort, 48/487 patients (10.8%) had delusions. A diagnosis of behavioural-variant frontotemporal dementia (18.4%) and Alzheimer's disease (11.8%) were associated with increased risk of delusions. A positive gene mutation was observed in 11/27 people with delusions. Individuals with frequent delusions performed worse on the Addenbrooke's Cognitive Examination ($p = 0.035$), particularly on the orientation/attention ($p = 0.022$) and memory ($p = 0.013$) sub-tests. Voxel-based morphometry analyses found that increased delusional psychopathology was associated with reduced integrity of the right middle frontal gyrus, right planum temporale and left anterior temporal pole.

Conclusion: Our results demonstrate that delusions are relatively common in dementia and uncover a unique cognitive and neural profile associated with the manifestation of delusions. Clinically, delusions may lead to delayed or misdiagnosis. Our results shed light on how to identify individuals at risk of neuropsychiatric features of dementia, a crucial first step to enable targeted symptom management.

Key points

- Delusions showed high prevalence, occurring in 10% of all dementia syndromes.
- Behavioural-variant frontotemporal dementia had an increased risk of delusions.
- Most patients experience polythematic delusions, often and of ranging severity, with delusions being related to more severe attention, orientation and memory deficits.
- Delusions were more common in people with strong family history/genetic mutations.

1 | INTRODUCTION

Delusions – 'fixed beliefs that are not amenable to change in light of conflicting evidence'[1] – are recognised symptoms of many psychiatric disorders, and can also occur in some neurological conditions. The nature of delusions can vary from the bizarre (e.g., the belief that a stranger has removed and replaced one's organs without leaving scars) to the mundane (e.g., that one's spouse is being unfaithful). Delusions have been reported in Dementia with Lewy Bodies and Parkinson's Disease with Dementia, and are associated with later disease stage, worse cognition and reduced insight.[2] However, the extent that delusions occur in other neurodegenerative syndromes is less understood. Indeed, it has been noted that when delusions are reported in people with dementia it can contribute to misdiagnosis.[3] In Alzheimer's disease (AD), estimates vary with studies reporting delusions in 16%–70% of patients throughout the disease course.[4] In frontotemporal dementia (FTD), delusions were reported in only 2 of 86 people with behavioural-variant frontotemporal dementia (bvFTD) over a 2 year period.[5] The prevalence seems to be higher in patients with FTD with comorbid motor neurone disease (FTD-MND).[6] Conversely, in primary progressive aphasia (PPA), delusions appear to be rare.[7] In motor disorders pathologically and clinically associated with FTD, namely corticobasal syndrome (CBS) and progressive supranuclear palsy (PSP), the prevalence of delusions has been rarely studied, however, the existing evidence suggests that delusions are relatively uncommon in these syndromes.[7]

The limited evidence demonstrates considerable heterogeneity of findings. Previous studies have been limited by a reliance on questionnaire data, relatively small sample sizes and rare simultaneous neuroimaging. Importantly, studies which focus on single diseases alone, are likely to be insufficient to explain the presence of delusional beliefs. In the psychiatric field, a transdiagnostic approach that focuses on symptoms rather than on syndromes—referred to as the Research Domain Criteria (RDoC)[8]—has been gaining traction since the 2010s to explain complex psychiatric phenomena. RDoC offers a new framework for understanding the biological basis of symptoms, while being agnostic regarding diagnostic syndromes.[9] Such an approach is well suited to studying dementia (e.g.,[10]), where diagnostic certainty in life is currently largely unachievable. Furthermore, by focusing on symptoms across diagnoses, this approach has the potential to inform theoretical models and symptoms that span

neurology and psychiatry, such as delusions.[11] In light of these considerations, the current study had two broad aims. First, to conduct a systematic cross-sectional review of all cases who have been seen at a dementia-focused tertiary referral clinic to examine how common delusions are across a range of dementia syndromes, and investigate the nature of delusional content, and their clinical associations. Second, to explore the neural correlates associated with delusions.

2 | MATERIALS AND METHODS

2.1 | Participants

This retrospective, cross-sectional study included all participants who have been seen at the Frontier dementia clinic in Sydney since its inception in 2010 and were diagnosed with a primary neurodegenerative disorder and had completed the Neuropsychiatric Inventory (NPI) at their first clinical assessment. In total, 487 participants were included: 102 AD (94 typical AD, 8 posterior cortical atrophy); 136 bvFTD; 53 semantic dementia (SD) (38 left-predominant, 15 right-predominant); 51 progressive nonfluent aphasia (PNFA); 50 logopenic progressive aphasia (LPA); 46 CBS; 29 MND (27 FTD-MND, 2 MND); 20 PSP; based on current consensus diagnostic criteria[12-17] and diagnosis by a multidisciplinary team. All controls scored above 88/100 on the Addenbrooke's Cognitive Examination (ACE), either the revised (ACE-R) or the third (ACE-III) version, with ACE-III scores converted to ACE-R scores.[18] In addition to a relevant diagnosis, inclusion criteria were: a relatively early stage of the disease (i.e., living in the community and able to manage basic activities of daily living); sufficient level of English proficiency and absence of another major neurological or psychological condition that could explain the presentation. Individuals who were assessed but did not have evidence of a primary neurodegenerative disorder were excluded.

2.2 | Rating of delusions and neuropsychiatric symptoms

Presence of delusions was established with the NPI.[19] Informants were interviewed by a trained clinician to determine the presence or absence of each symptom domain. If the symptom is reported as

present, the frequency and severity of the symptoms were rated and a composite score was calculated by multiplying frequency × severity, with higher scores denoting greater psychopathology. In addition, the clinician recorded the nature of the delusional belief.

2.2.1 | Classification of delusional themes

Case files were reviewed by an experienced clinician to identify the content of delusions, blind to participant diagnosis. Where classification was unclear, discussion with two other experienced clinical researchers (Ramon Landin-Romero, Robyn Langdon) was undertaken until consensus was reached. The case file review included information from the NPI as well as referral and neurology letters following the clinical assessment. The content of delusions was classified according to the Research Version of the Structural Clinical Interview (SCID-RV),[20] which includes 14 types of delusions: reference, persecutory, grandiose, somatic, guilt, jealous, erotomanic, religious, control, thought insertion, thought withdrawal, thought broadcasting, bizarre and other. An additional category—misidentification—was added in light of the high prevalence of this theme in Alzheimer's disease[21] and other dementia syndromes.[7] For each individual the number of types of delusions were determined to enable classification into monothematic (i.e., only one type of delusion reported) and polythematic (i.e., more than one type of delusion reported).

2.3 | Genetic and family history screening

A family history of neurodegenerative disease was obtained, and the Goldman score was calculated.[22] A score of 3.5 or 4 is indicative of sporadic disease whereas scores <3.5 are indicative of familial disease. Genomic DNA was available for screening for the hexanucleotide repeat expansion in *C9orf72* by repeat-primed polymerase chain reaction. Expansion positive *C9orf72* status was determined as previously described.[23] microtubule associated protein tau (MAPT) and granulin precursor (GRN) genes were screened either by Sanger sequencing of all coding exons[24,25] or by whole-exome sequencing (110 bp paired reads at 100X coverage) using the Illumina platform provided by Macrogen, Korea. Processing, mapping and variant calling of raw sequence data were performed using gold-standard Genome Analysis Toolkit pipelines.[26]

2.4 | Cognitive and behavioural assessment

Global cognitive function was measured with the ACE-R or ACE-III with ACE-III scores converted to ACE-R scores.[18] Attention was assessed via Digit Span Forwards and the Trail Making Test Trails A. Visuospatial-constructional skills and non-verbal episodic memory were measured using the Rey Complex Figure (RCF). Aspects of language, including naming, comprehension, semantic association and word repetition were evaluated via the Sydney Language Battery (SYDBAT).[27] Executive function tasks indexed working memory (Digit Span Backwards), generativity (Letter Fluency), inhibitory control (Hayling Sentence Completion Error Score)[28] and task-switching (Trail Making Test Trails B). Behavioural change was assessed using the Cambridge Behavioural Inventory-Revised informant questionnaire (CBI-R).[29]

2.5 | Neuroimaging acquisition and analyses

Participants underwent whole-brain structural magnetic resonance imaging (MRI) using a 3 T Phillips scanner. High resolution T1-images were obtained using the following protocol: 256 × 256, 200 slices, 1 mm^2 in-plane resolution, 1 mm slice thickness, echo time/repetition time = 2.6/5.8 ms, flip angle = 8°. Brain scans were available for 22 people with Delusions. FMRIB Software Library voxel-based morphometry (VBM), included in the Functional Magnetic Resonance Imaging of the Brain (FMRIB) software library package http://www.fmrib.ox.ac.uk/fsl/fslvbm/index.html was used to analyse the MRI data[30] (See Supplementary Information). A voxel-wise general linear model (GLM)[31] was created to examine voxel-by-voxel negative correlations between NPI delusions composite scores and grey matter (i.e., higher scores, lower voxel integrity), while controlling for confounding variables (diagnosis, sex, age and disease severity) (frontotemporal dementia rating scale, FRS[32]) in the Delusions + participants only. Statistical significance was set at $p < 0.005$ uncorrected for multiple comparisons, with a conservative cluster extent threshold of 100 voxels, to balance the risk of Type I and Type II error.[33]

2.6 | Statistical analyses

Analyses were conducted using IBM SPSS Statistics, Version 25.0. One-way analyses of variance or independent samples *t*-tests were conducted to examine demographic and outcome clinical and cognitive variables. Categorical variables (e.g., sex, Goldman score) were analysed using chi-square tests. For all analyses, statistical significance was set at $p < 0.05$ and Sidak correction for multiple comparisons was applied for *post hoc* analyses. Associations between presence of delusions and diagnosis was assessed using odds ratios that were estimated by means of logistic regressions with weighted observations. To examine predictors of the presence of delusions, we conducted a logistic regression analysis with ACE score, disease duration and diagnostic group included as predictor variables using the stepwise (backwards) approach.

2.7 | Data availability

The data generated during, or analysed as part of the current study, are available from the corresponding author on reasonable request.

2.8 | Reporting guidelines

The Strengthening the Reporting of Observational Studies in Epidemiology [34] cross-sectional reporting guidelines were utilised in the current study.

3 | RESULTS

3.1 | Presence and nature of delusions

Approximately 10% of the patient cohort (48/487) experienced delusions at their first clinical assessment (Table 1). Across clinical groups, 18.4% of bvFTD, 13.8% of FTD-MND and 11.8% of AD patients were reported as experiencing delusions at presentation. When we examined the frequency and severity of delusional symptoms in the 47 of 48 cases who had been reported as having delusions[*], and for whom relevant NPI data were available, we found over 60% experienced delusions at least often ($n = 8$; 17%), frequently ($n = 8$; 17%), or very frequently ($n = 13$; 28%). The delusions were rated as mild in 21 participants (45.7%), moderate in 15 (32.6%), and marked in 10 (21.7%) participants.

The most common delusional theme was persecutory, followed by delusions of reference and then delusions of jealousy. Nine patients showed monothematic delusions, whereas 22 reported polythematic delusions. Of interest, 1 bvFTD patient was reported to have 5 different delusional themes, and 1 AD patient had 6 different delusional themes. For 17/48 cases, insufficient information was available for the delusional theme to be classified.

The logistic regression model (Table 2) was significant ($x^2 = 37.207$, $p < 0.001$). Significant predictors in the final model were, disease duration ($p = 0.025$) and bvFTD diagnosis ($p = 0.018$) with a trend for cognition (ACE Total Score $p = 0.054$). The final model had specificity of 90.3%, although sensitivity was lower (27.7%), with the model correctly classifying 404/480 participants.

3.2 | Subgroup analyses

To examine potential genetic, neural and cognitive mechanisms contributing to the presence of delusions we compared individuals who experienced delusions 'often', 'frequently' or 'very frequently', referred to as the Delusions+ group. People who reported delusions 'occasionally' were not included in the subgroup analysis. This cut-off was selected in an attempt to identify a relatively homogenous group of patients where delusional symptomatology occurred sufficiently reliably for a potential neurocognitive basis to be identified, and to minimise confounds in reporting of single instances. NPI frequency and severity data for the subgroup are shown in Figure 1.

This group included 16 bvFTD, 6 AD[**], 3 FTD-MND, 3 left-predominant SD, 1 right-predominant SD, 1 LPA. A disease control group (Delusions-) was created by matching each participant with delusions with a patient without delusions from the original cohort,

TABLE 1 Presence and themes of delusions across dementia syndromes

	Delusions+ n (%)	Delusions—n (%)	Reference	Persecutory	Grandiose	Somatic	Guilt	Jealousy	Religious	Control	Thought insertion	Bizarre	Other	Misidentification[a]	Total
AD	12 (11.8)	90 (88.2)	2	4				1							7
bvFTD	25 (18.4)	111 (81.6)	7	11	2	2		6	1	1		3	1	4	38
CBS	0 (0.0)	46 (100.0)		1										1	2
FTD-MND	4 (13.8)	25 (86.2)	1	3	1	1							1	1	8
LPA	2 (4.0)	48 (96.0)	1	2			1				1		1	1	7
PSP	1 (5.0)	19 (95.0)		1											1
SD	4 (7.5)	49 (92.5)	1	2	1			1							5
Grand Total	48 (9.9)	439 (90.1)	12	24	4	3	1	8	1	1	1	3	3	7	68

Note: Sufficient information was available to classify delusional content in 31 cases. Each count represents the number of times that delusional theme was reported (i.e., each participant can contribute to more than one category of delusion).

[a]The misidentification category was added to the SCID-RV classification of delusional themes.

TABLE 2 Logistic regression results

	β (SE)	Lower	Odds ratio	Upper	p
ACE Total score	0.01 (0.01)	1.00	1.00	1.00	0.054
Disease duration	0.12 (0.05)	1.01	1.12	1.24	**0.025**
bvFTD diagnosis	0.76 (0.32)	1.14	2.13	3.99	**0.018**
PNFA diagnosis	−18.71 (5576.27)	0.00	0.00	-	0.997
CBS diagnosis	−18.75 (5951.70)	0.00	0.00	-	0.998
Constant	−2.31 (0.40)				

Note: $R^2 = 0.08$ (Cox & Snell), 0.16 (Nagelkerke). Final model $x^2 = 41.505$, $p < 0.001$.
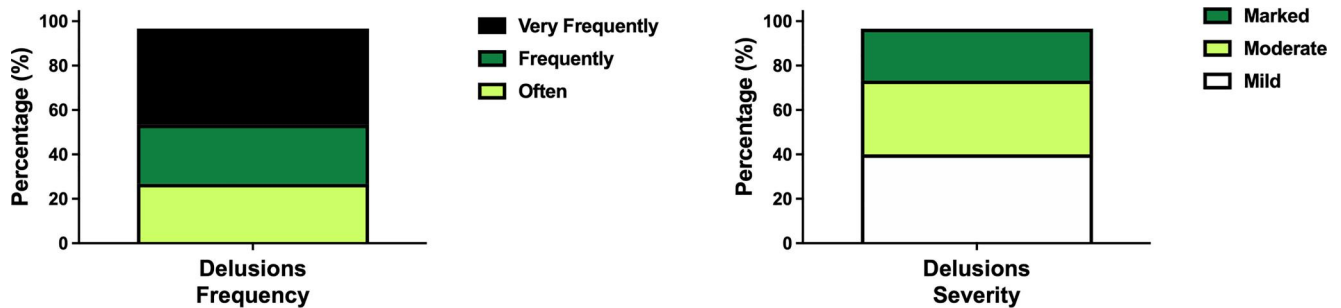
FIGURE 1 Frequency and severity of delusions as determined by the Neuropsychiatric Inventory (NPI)

on a one-to-one basis. The matching was conducted hierarchically for the following variables: (i) diagnosis and certainty, (ii) clinical disease stage (FRS), (iii) sex, (iv) age and (v) education. All cases were matched on at least the first two variables and were selected blind to genetic mutation status.

3.2.1 | Genetic and family history screening

Because this is not a formal genetic study, genetic screening is conducted based on several factors (e.g., family history, clinical diagnosis). The number of individuals in the subgroup analysis with available genetic data is shown in Table 3. In the Delusions+ group, 11/27 individuals had a positive gene mutation compared to only 1/26 in the Delusions− group (8%). In the Delusions+ groups, the most common gene mutation was *C9orf72* (8/27 screened), whereas none of the 26 Delusions-patients which were screened for *C9orf72* had a positive result. The distribution of Goldman scores indicated a significantly higher number of people with a strong family history in the Delusions+ group[†] ($x^2 = 5.994$, $p = 0.014$), with 13 people in the Delusions+ group and 5 people in Delusions− group reporting a strong family history (Goldman score <3.5).

3.2.2 | Behavioural and cognitive profile

The Delusions+ group had more abnormal beliefs reported on the CBI than the Delusions− group (Table 4, $p < 0.001$). Notably, the Delusions+ group also had greater impairments in everyday skills ($p = 0.004$), stereotypical behaviours ($p = 0.031$), sleep disturbances ($p = 0.003$), memory problems ($p = 0.012$) and mood disturbances ($p = 0.017$). On the NPI, the Delusions+ group also had more hallucinations than the Delusions− group ($p = 0.006$) and a trend for greater disinhibition ($p = 0.078$) and anxiety ($p = 0.076$) (Table 4).

Examination of the cognitive profile of the Delusions+ and Delusions− groups revealed more severe cognitive deficits in the Delusions+ group (Supplementary Table 2). Specifically, the Delusions + group performed worse than the Delusions− group on the ACE ($p = 0.035$), in particular, the attention/orientation ($p = 0.022$) and memory ($p = 0.013$) subtests. In addition, the Delusions+ group had worse visuospatial memory than the Delusions− group (Rey Complex Figure copy; $p = 0.006$) and slightly reduced capacity to repeat words on the SYDBAT (Delusions+ vs. controls, $p = 0.001$; Delusions+ vs. Delusions−, $p = 0.040$) (See Supplementary Table 2).

3.2.3 | Neuroimaging analyses

In the Delusions+ group, more severe delusional psychopathology was correlated with decreased grey matter integrity in the right middle frontal gyrus and right temporoparietal junction, encroaching into the planum temporale and the supramarginal gyrus, as well as the left anterior temporal lobe, left temporal pole and left middle and inferior temporal gyrus (see Figure 2 and Supplementary Table 1).

% With genetic screening	Delusions+ n = 27/30 (90%)	Delusions− n = 26/30 (87%)
C9orf72	8/27 (30%)	0/26 (0%)
GRN	2/13 (15%)	1/14 (7%)
MAPT	1/14 (7%)	0/15 (0%)

TABLE 3 Findings from genetic screening in the Delusions+ and Delusions− groups

Note: Numbers refer to: number of individuals tested positive/number of individuals tested for the gene abnormality.

Abbreviations: GRN, granulin precursor; MAPT, microtubule associated protein tau.

	Delusions+	Delusions−	*t* statistic	*p*
CBI				
Memory	62.89 ± 19.31	49.14 ± 21.91	2.58	0.012
Everyday skills	56.54 ± 31.57	33.88 ± 26.00	3.04	0.004
Self-care	25.76 ± 27.44	15.42 ± 21.51	1.63	0.110
Mood	43.13 ± 20.98	29.58 ± 21.71	2.46	0.017
Beliefs	33.89 ± 25.89	3.89 ± 7.17	6.12	<0.001
Abnormal behaviour	40.14 ± 23.25	31.69 ± 22.25	1.44	0.155
Eating habits	44.17 ± 30.26	32.43 ± 25.33	1.63	0.109
Sleep	57.92 ± 34.35	32.92 ± 26.97	3.14	0.003
Stereotypical behaviour	56.25 ± 33.72	39.10 ± 25.85	2.21	0.031
Motivation	67.17 ± 31.91	61.17 ± 32.18	0.73	0.471
NPI				
Agitation	3.03 ± 2.99	2.13 ± 2.69	1.23	0.225
Anxiety	2.93 ± 3.70	1.43 ± 2.62	1.81	0.076
Apathy	5.33 ± 3.55	4.30 ± 3.86	1.08	0.285
Appetite	4.37 ± 4.17	4.70 ± 3.90	0.32	0.750
Depression	2.00 ± 3.30	1.07 ± 2.4	1.24	0.222
Disinhibition	3.97 ± 4.71	2.23 ± 2.36	1.80	0.078
Elation	1.00 ± 2.59	0.70 ± 1.75	0.53	0.600
Hallucinations	1.20 ± 2.22	0.00 ± 0.00	2.96	0.006
Irritability	3.00 ± 3.95	1.67 ± 2.60	1.54	0.129
Sleep	2.37 ± 3.39	1.70 ± 3.63	0.74	0.465
Aberrant motor behaviour	4.27 ± 4.18	2.60 ± 3.57	1.66	0.102

TABLE 4 Ratings of behaviour and neuropsychiatric features in patients with and without delusions

Note: Values are mean ± standard deviation.

Abbreviations: CBI, Cambridge Behavioural Inventory; NPI, neuropsychiatric inventory composite score (i.e., frequency × severity).

4 | DISCUSSION

Here, we examined the presence, nature and neural correlates of delusions in a consecutive cohort of patients presenting to the Frontier dementia clinic in Sydney. Approximately 10% of the >450 patients experienced delusions at presentation, with delusions more common in patients diagnosed with frontotemporal dementia (bvFTD and FTD-MND) and Alzheimer's disease (AD). Patients with delusions were more disoriented and had greater memory impairment than patients without delusions. In the following sections, we consider how this large and comprehensive study can inform our understanding of the neurocognitive mechanisms underpinning delusions in neurodegenerative disorders.

Diagnosis of bvFTD was associated with a 3-fold increase of the presence of delusions. A higher prevalence of delusions was also observed with a diagnosis of FTD-MND and AD. In contrast, patients
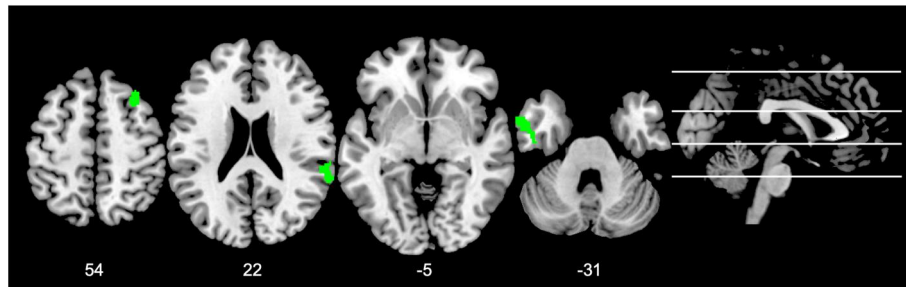
FIGURE 2 Regions that correlated with increased delusional psychopathology (NPI composite score) within the Delusions+ group. Left side of the brain is shown on the left side of the figure. Diagnosis group, age at scan, sex and disease severity (FRS Rasch Score) were included as covariates. Analyses are reported at $p < 0.005$ voxelwise, uncorrected for multiple comparisons with a minimum cluster size of 100 voxels

diagnosed with primary progressive aphasia (SD, PNFA, LPA) or a motor disorder (CBS, PSP), rarely experienced delusions. A recent meta-analysis reported delusions in ~30% of drug-naïve AD patients.[35] This higher prevalence may reflect differences in disease stage, whereby delusions may increase with disease severity.[35] Here, we focused on AD patients at first presentation, which concurs with previous findings of a prevalence of 8%–16% in the very mild-mild stages of AD.[35] In bvFTD, previously reported rates of delusions are highly variable, ranging from 2.3%[5] to as high as 17%–20%.[36,37] Our results indicate that the upper end of this scale is more likely to be accurate, with 18.4% of bvFTD patients experiencing delusions at first presentation. The high presence of delusions likely contributes to the ~50% of bvFTD patients who are initially diagnosed with a primary psychiatric disorder.[3,38] Interestingly some evidence suggests that patients clinically diagnosed with FTD are more likely to have Alzheimer's pathology if their clinical profile included delusions.[37] While pathological data are not currently available in this cohort, it will be important to follow these bvFTD patients to determine the proportion of these clinically diagnosed patients who are actually harbouring Alzheimer's pathology.

A second important variable, which may account for the relatively high proportion of patients diagnosed with both bvFTD and FTD-MND with delusions, are genetic abnormalities and/or a strong family history of disease.[39] Psychotic symptoms, including delusions, have been reported to be substantially more common in patients carrying the *C9orf72* gene expansion, than those without.[40] Here, we found evidence that abnormalities in the three major FTD genes, *C9orf72*, *MAPT* and *GRN*, were present in people with delusions. Indeed, patients with delusions were more likely to have a *C9orf72* expansion, which aligns with previous findings in the field.[36] Our results highlight that in individuals who are presenting with novel neuropsychiatric symptoms, later in life, differential diagnosis should include neurodegenerative as well as psychiatric aetiologies.[16] Future studies are essential to elucidate biomarkers that can more effectively differentiate between psychiatric and neurodegenerative disorders.[38]

A number of cognitive neuropsychiatric theories of delusions have been proposed to account for the emergence of monothematic delusions.[41,42] The two-factor model of delusions, suggests that delusions arise from: (i) a neuropsychological impairment which invokes

an abnormal experience and explains the specific content of the individual's delusion and (ii) impaired belief reasoning, such that the delusional belief is irrationally adopted and maintained in the face of abundant counter-evidence.[42] Delusional content in this cohort was variable but notably most individuals with delusions reported more than one delusional theme. The predominant theme was persecutory, followed by delusions of reference and delusions of jealousy. In schizophrenia, persecutory delusions often co-occur with delusions of reference.[43] Previous studies have reported that persecutory delusions are especially common in dementia,[4] which accords with our findings.

Our regression model as well as comprehensive neuropsychological assessment confirmed that disease severity is an important predictor of delusions, which aligns with previous studies in Alzheimer's disease.[44] In addition, the regression model found that cognitive impairment was also an important contributor to delusions. Between groups, the Delusions+ patients were more disoriented and had worse episodic memory. They also experienced more hallucinations, which may have triggered delusions in some cases, as is seen in psychosis. The presence of memory impairment may accord with predominantly persecutory delusions (e.g., belief that people are stealing things, people taking their money) or even polythematic delusions when different episodes of memory failure prompt different delusional explanations (e.g., delusional jealousy of a spouse). According to the two-factor model, the second factor, also required for the development and persistence of delusions, is deficient belief evaluation or reasoning capacity,[45] purported to be associated with frontal dysfunction.[46] Somewhat surprisingly, the Delusions+ group were not disproportionately impaired on any measure of executive functioning, although our neuropsychological battery was not specifically designed to comprehensively target executive functioning and reasoning. It was beyond the scope of this study to examine the specific profiles of cognitive impairment and determine how they relate to individual delusional content, or to compare the cognitive profiles of those with monothematic versus polythematic delusions; however, this warrants future investigation.

From a neurobiological perspective, our results extend previous research providing new insights into the emergence of delusions in brain disorders. Delusional psychopathology was associated with reduced integrity in the right middle frontal gyrus, left anterior

temporal lobe and right supramarginal gyrus, which concords with recent lesion mapping studies of monothematic delusions and functional imaging studies of psychosis[47] and may reflect its role in prediction error processing.[48] A common neurobiological basis for delusions across neurodegenerative and psychiatric syndromes has been previously hypothesised,[11] and is supported by the current results. The involvement of the right frontal cortex in the pathogenesis of delusions has been suggested by Coltheart[46] and demonstrated by recent lesion mapping studies of monothematic delusions and functional imaging studies of psychosis.[47,49] This brain region is also important in aspects of prediction error processing.[48] While our neuroimaging analyses controlled for diagnosis, they cannot rule out the possibility that disease-specific neurocognitive mechanisms also contribute to the emergence of delusions. In Alzheimer's disease, impaired visuoperceptual function appears to be particularly important in the manifestation of misidentification type delusions, which may reflect atrophy in temporo-occipital brain regions,[50] while persecutory delusions in Alzheimer's disease have been linked with frontostriatal dysfunction. Future studies with larger numbers of people with varying delusional subtype and dementia subtype, combined with neuroimaging data will be invaluable in examining these relationships further.

In the context of neurodegenerative disorders, delusions and hallucinations are increasingly recognised as important clinical phenomena in Dementia with Lewy Bodies and Parkinson's Disease Dementia.[2] In these syndromes, a spectrum of psychosis has been proposed, with symptoms ranging from minor illusions, passage hallucinations and presence hallucinations, through to delusions and multimodal hallucinations at the more severe end of the spectrum. Importantly, these symptoms have been linked to distinct neurobiological mechanisms. Delusions and loss of insight have been linked with widespread cortical Lewy Body pathology. Our results converge and suggest that atrophy across multiple brain regions underpin the manifestation of delusions, which is associated with greater cognitive impairment and disease stage. While individuals with Parkinson's disease Dementia and Dementia with Lewy Bodies were not available for testing as part of this cohort, comparison of these syndromes is an interesting avenue for future work. Moreover, investigation of clinicopathological relationships will be important for future studies, to understand the relationship between the nature of delusions and the location and type of pathological features.

Clinically, delusions can be very distressing. From a management perspective, recent evidence has shown that the presence of delusions is a predictor of institutionalisation.[51] Furthermore, worryingly, the use of antipsychotic medication is a predictor of mortality.[51] How can our results inform improved clinical management? First, our results demonstrate that routine screening of delusions is an important aspect of clinical assessment, particularly in bvFTD, FTD-MND and AD, and individuals with genetic abnormalities and/or a strong family history of disease. Second, our results suggest that delusions are more likely to be present in individuals with greater cognitive impairment. The need for treatment of delusions may depend on the delusional content. Where delusions are relatively benign, it may be more appropriate to educate carers about the cognitive basis of delusions and advise them that rationalisation of delusional beliefs is unlikely to be effective. Thus, environmental modification, informed by the delusional belief and nature of cognitive impairment may be an appropriate management strategy.

CONFLICT OF INTEREST

The authors have no Conflicts of Interest to declare.

ETHICS APPROVAL

This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the South Eastern Sydney Local Health District Human Research Ethics Committee (HREC ref no. 10/126 & 13/177).

CONSENT TO PARTICIPATE

Informed consent was obtained from all individual participants included in the study.

CONSENT FOR PUBLICATION

Patients provided informed consent regarding publishing their data.

AUTHOR CONTRIBUTIONS

Conceptualisation: Fiona Kumfor, Emma Devenney, Emily Connaughton, Robyn Langdon, Ramon Landin-Romero; Methodology: Fiona Kumfor, Cheng Tao Liang, Jessica L. Hazelton, Cristian E.

DATA AVAILABILITY STATEMENT

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ENDNOTES

[*] Data were missing for the frequency and severity of symptoms in one Delusions+ participant whose informant had answered 'yes' to the delusions screening question. To take a conservative approach for our analyses, this person was nevertheless included in the Delusions+ group.

[**] Includes 1 patient diagnosed with posterior cortical atrophy.

[†] Goldman scores not available for 2 people in the Delusions+ group.

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SUPPORTING INFORMATION

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