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Neurobiology of Delusions in Alzheimer's Disease

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Abstract Alzheimer's disease (AD) is associated with cognitive and functional impairment as well as neuropsychiatric sequelae, including psychotic symptoms such as delusions and hallucinations. Strong evidence supports the need to study delusions separate from hallucinations. Integrating the epidemiology, clinical correlates, and neuropathological and genetic literature for delusions in AD allows us to speculate on etiology and mechanisms. Plaque and tangle deposition in individuals with susceptible alleles of serotonergic, muscarinic, nicotinic, or *Apoε4* genes appears to result in disruption of cortical circuitry, culminating in delusions. While delusions in AD correspond to a phenotype distinct from AD without delusions, subtypes of delusions may also define further distinct clinical entities. Persecutory delusions may occur earlier in the illness and have a more significant genetic component than misidentification delusions, which are associated with increased cognitive impairment and advanced dementia. Clearly distinguishing between these two syndromes is essential to making progress in the area of delusions in AD.

Keywords Alzheimer's · Dementia · Psychosis · Delusions · Persecutory delusions · Misidentifications · BPSD · Neuropsychiatry · Neuropsychiatric symptoms · NPS · Neuropathology · Genetics · Cognition · Paranoia · Suspiciousness · Confabulation

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Introduction

Despite being considered a disorder of cognition, Alzheimer's disease (AD) is associated with many neuropsychiatric symptoms (NPS) of clinical significance. NPS, also called behavioral and psychological symptoms of dementia (BPSD), are present in up to 97% of people diagnosed with dementia, resulting in suffering, caregiver distress, and extensive resource utilization [1]. These noncognitive manifestations of dementia are the primary reason for transfer of patients with dementia from general hospitals to psychiatric hospitals, and for their institutionalization out of the community [2]. Of these NPS, psychosis is prominent and consists of hallucinations and delusions. Hallucinations are perceptions in the absence of a stimulus, whereas delusions are fixed false beliefs that are neither amenable to reason nor consistent with cultural beliefs. This review focuses on research reports in which delusions in AD (AD+D) can be discussed separately from psychosis in AD (AD+P) in general, or in which the discussion of AD+P is instructive to the understanding of AD+D.

The index patient of Alois Alzheimer [3] suffered from paranoid delusions that were a prominent part of her illness.

Delusions in AD disease may have varying content, including delusions of persecution, theft, infidelity, abandonment, or that the patient's deceased loved ones are still living, as well as misidentification syndromes (MIS) [4]. Misidentification delusions frequently seen in AD often represent true neuropsychiatric manifestations of neurodegeneration and include Capgras type (the feeling that someone known to the patient is replaced by an impostor), phantom boarder syndrome (the feeling that strangers are living in the patient's house), mirror sign (patient misidentification of his or her own image in a mirror), and TV sign (television images misidentified as real) [5]. Despite the longstanding recognition that delusions are part of AD, our understanding of the pathophysiology and pharmacotherapy of delusions is still incomplete. The aim of this review is to reconcile the clinical presentation with the neurobiological underpinnings of AD+D with a focus on neuropathology and genetics in order to better guide future investigation and treatment.

Phenomenology

Strict diagnostic criteria for AD+P, written in the *DSM-IV* format, have been proposed by Jeste and Finkel [6] and include the presence of delusions or hallucinations (auditory or visual) in the context of clinically diagnosed AD. Psychotic symptoms must not predate the onset of the dementia so that a prior history of a primary psychotic disorder such as schizophrenia, schizoaffective disorder, delusional disorder, or mood disorder with psychotic features must be ruled out. Similarly, psychotic symptoms presenting in the context of delirium or resulting from a general medical illness or the use of drugs or other substances are excluded from this proposed diagnostic category. This construct has been validated by Schneider and colleagues [7] in a reanalysis of a risperidone clinical trial in which the Behavioral Pathology in Alzheimer's Disease rating scale was used to capture delusions (mostly persecutory type) and hallucinations (of all types) persisting over 2 to 4 weeks. Of the 625 patients enrolled in the original trial for behavioral issues, 75% met the criteria for AD+P. Thus, while overlapping with agitation or aggression, AD+P was a discrete clinical entity with patient demographics differing from the demographics of nonpsychotic patients with AD (AD-P). However, the breakdown between delusions and hallucinations was not reported.

An alternative set of "Alzheimer-associated psychotic disorder" criteria using a syndromic approach to taxonomy has been suggested by Lyketsos and colleagues [8]. In this construct, discrete affective and psychotic syndromes of AD have been delineated [8] and validated [9]. In a consecutive series of 771 patients with probable AD, delusions diagnosed with the Psychosis Dementia Scale within the previous 4 weeks were subclassified into paranoid/misidentification and expansive domains. Although 33% of patients had delusions, only 7% of them had hallucinations, most of whom also had delusions.

A contrasting approach to that of Lyketsos et al. [8] is used by Cook and colleagues [10]. They identified and classified AD+P subtypes based on the presence of individual psychotic symptoms in isolation from other behavioral symptoms. In a cross-sectional study of 188 possible and probable AD patients, factor and cluster analysis of Behavioral Rating Scale items identified 2 separate factors: a misidentification/hallucination factor (including symptoms of simple and delusional misidentifications and hallucinations) and a persecutory delusion factor. Subsequent analysis by the same group has demonstrated that impairment in verbal fluency and visuospatial function is restricted to the misidentification/hallucination subtype, that the paranoid subtype does not differ from nonpsychotic AD patients on cognitive measures, and the ability to detect meaningful biologic associations of AD+P would be enhanced by separate analyses of the misidentification and paranoid delusional phenotypes [11]. These results were consistent with the study of Forstl and colleagues [12] that found that delusions of misidentification were associated with greater cognitive impairment than the absence of delusions in a sample of patients with moderate to severe AD.

Epidemiology and Risk Factors

The results of epidemiologic studies of psychosis in dementia have been variable given the heterogeneity of the study group. A systematic review by Ropacki and Jeste [13] reported that 41% of patients with AD experience psychosis, including 23% with delusions, 5% with hallucinations, and 13% with both. The most common type of delusion is delusion of theft. In this review, AD+P was associated with a more rapid cognitive decline, and its incidence increased progressively over the first 3 years of the illness, with a subsequent plateau. Inadvertent inclusion of patients with Lewy body dementia and poor recollection of family history is considered a confound in these epidemiologic studies (as is the common failure to separate delusions from hallucinations). A more recent study conducted by Weamer and colleagues [14] assessed 361 patients diagnosed with possible or probable AD or mild cognitive impairment without psychosis at baseline. Patients were observed longitudinally until study completion, loss to follow-up, or until the patient became too impaired to return to the clinic for reassessment. Neurological evaluation, cognitive testing with the Mini-Mental State

Examination (MMSE), and diagnostic re-evaluation (including assessment for the presence of psychosis) were conducted on an annual basis. AD+P was observed in 122 (34%) patients during the follow-up period. Global cognitive impairment (ie, the MMSE score) was the only baseline variable consistently associated with a reduced time to onset of psychosis, especially in those with early- to mid-stage disease. Unfortunately, despite a useful longitudinal approach, psychosis was not described in terms of its components, limiting the utility of this study in contributing to the understanding of the neurobiology of delusions. Very recently, in a cross-sectional sample of much older adults with AD (>85 years of age), Ostling and colleagues [15] reported that 22% had delusions and 30% had hallucinations. Although psychosis in general and hallucinations increased with dementia severity, no statistically significant association was found between delusions and dementia severity. This highlights the importance of separating delusions and hallucinations when studying the evolution of these symptoms in AD.

The Cache County Dementia Prevalence study determined prevalence of NPS over a mean and median 5-year follow-up period after diagnosis in a sample with a mean duration of dementia of 2 years at baseline [1]. Point prevalence for delusions was 18% at baseline and 34% to 38% during the past three yearly visits; for hallucinations, it was 10% at baseline and 19% to 24% thereafter. Period prevalence over the 5-year follow-up period was 60% for delusions and 38% for hallucinations. Gauthier and colleagues [16] reviewed the frequency of NPS in samples assessed with the Neuropsychiatric Inventory in three European studies: the Maastricht Study of Behavior in Dementia; the Réseaux Alzheimer Français; and the European Alzheimer Disease Consortium. Delusions occurred in 22% and hallucinations in 9% of these community samples. Sweet and colleagues [17] assessed the types of delusions present in individuals involved in the National Institute of Aging Late Onset AD Family Study. Among 478 unique participants having completed at least 1 behavioral assessment, psychotic symptoms were present in 239 (50%). The most common psychotic symptoms were delusional misidentification of people (23%), paranoia (21%), and believing that dead people were still alive (19%).

A large study by Harciarek and Kertesz [18] investigated the prevalence of MIS in 392 individuals with probable AD determined by a semistructured interview of patients and reliable caregivers. MIS were identified in 16% of participants. The most frequent form of MIS were Capgras delusions, often accompanied by reduplication of place, phantom boarder phenomenon, or both. As part of the Medical Research Council Cognitive Function and Aging study, Savva and colleagues [19•] determined the prevalence and correlates of NPS in a cohort of 587 participants with dementia, and assessed subtypes of AD+D. At baseline, persecutory beliefs were held by 25% of individuals and misidentifications by 20%. At 2-year follow-up, the incidence of new misidentifications was higher than that of new persecutory delusions. A factor analysis revealed a four-factor solution, with persecutory delusions and misidentifications best fit on separate factors, again supporting the idea that these two types of delusions are separate phenomena with separate trajectories and possibly separate neurobiological underpinnings.

It can be difficult to differentiate between a true delusion and a belief that is secondary to other cognitive difficulties (eg, misplacing personal belongings and concluding that the items were stolen, or confabulating a story to make sense of one's confusing experience). This is particularly the case given that severity of cognitive dysfunction has been shown to be a strong predictor of AD+P [14, 20]. However, in the descriptive analysis of the randomized VISTA (Video-Imaging Synthesis of Treating Alzheimer's Disease) trial [21], misplacements were distinguished from delusions, with 51% of patients with AD and misplacements not having delusions. In the 49% of patients with AD and misplacements who had delusions, 36% were delusions of theft. A recent Japanese study assessed the prevalence and risk factors for delusions of theft in a sample of 56 AD patients: 25% of patients had delusions of theft, and these were associated with female gender, absence of cohabiting family members, neurotic personality, and retained social cognitive function [22].

Frontal impairment as measured by the Frontal Assessment Battery (FAB) has been associated with AD+D in general and persecutory delusions in particular. Nagata and colleagues [23••] examined the relationship between persecutory delusions and frontal lobe function using the Japanese version of the FAB. A total of 48 probable AD patients (MMSE≥18 and Clinical Dementia Rating of 0.5 or 1.0) were divided into two groups: AD+D and AD without delusions (AD-D). The groups did not differ significantly with regard to sex, age, duration of illness, education, or MMSE scores. However, mean (+SD) FAB scores were significantly different between the two groups (AD+D, 11.6+2.8; AD-D, 13.9+2.5). Logistic regression showed that the FAB scores, but not the MMSE scores, were associated with persecutory delusions. In contrast, frontal executive functioning was not associated with confabulations in a sample of 22 probable AD patients with confabulation compared with 22 matched controls [24]. These findings implicate frontal lobe impairment specifically, and separately from global cognitive impairment in the presence of persecutory AD+D (and not confabulation), and emphasize the need to evaluate cognition more closely in determining the association between cognition and delusional subtypes.

Delusions also have been shown to have an impact on real world functioning in AD. A recent review by Fischer and colleagues [25] showed that delusions are associated with reduced functional performance in patients with AD. The authors commented that studies conducted to date likely have underestimated the impact of delusions on daily functioning. This is due to an overreliance on functional assessment scales of basic versus instrumental activities of daily living, the use of crude assessments of cognition, and the lack of longitudinal assessments.

Neuropathology

Several postmortem and imaging studies have attempted to elucidate the neuropathology and neurochemistry of delusions in dementia. Using 27 autopsy-confirmed AD cases, Zubenko and colleagues [26] found that psychosis was associated with a significantly increased density of senile plaques and neurofibrillary tangles in the prosubiculum and middle frontal cortex, and found trends toward increases in the superior temporal and entorhinal cortices. Psychosis was also associated with the relative preservation of norepinephrine in the substantia nigra and a significant reduction in serotonin in the prosubiculum, with trends toward serotonin reduction in the middle frontal gyrus, superior temporal cortex, entorhinal cortex, substantia nigra, thalamus, amygdala, and caudate nucleus. Psychosis was not divided into delusions and hallucinations, limiting the interpretation of these data specifically for delusions.

Subsequently, Förstl and colleagues [27] investigated 56 patients with definite AD and focused on delusional subtypes. Misidentifications were associated with lower neuron counts in the area CA1 of the hippocampus, while paranoid delusions were observed in patients with less severe cell loss in the parahippocampal gyrus but with lower cell counts in the serotonergic dorsal raphe nucleus. Mukaetova-Ladinska and colleagues [28] reported that a positive history of misidentification delusions is related to an increased density of neuritic plaques in fronto-parieto-occipital lobes. Farber and colleagues [29] observed 109 patients with AD and after their death compared the pathology in those with and without psychosis. Delusions occurred in almost all patients with psychosis (94%), and hallucinations in the absence of delusions were very rare (6%). Suspiciousness was the most common delusion, present in 62%, with misidentifications present in 43%. Although there were no differences in total senile plaques or cored senile plaques, a greater density of neocortical neurofibrillary tangles was found in AD+D as compared with AD-D. This increase was independent of dementia severity.

Lai and colleagues [30] used postmortem radioligand binding assays to quantify muscarinic receptors in AD patients. Overall, there was a decrease in M_2 density in the frontal lobes of patients with AD compared with controls. Within the group of AD patients, M_2 receptor density was higher in Brodmann area 11 (orbitofrontal cortex) of the patients with delusions than in those without delusions. A postmortem magnetic resonance spectroscopy study identified markers suggesting greater neuropil disruption in the dorsolateral prefrontal cortex, superior temporal gyrus, and inferior parietal cortex in AD+P compared with AD-P patients [31]. One can speculate that this greater disruption represents an acceleration of AD-related neurodegeneration. Proton magnetic resonance spectroscopy also allows the indirect measurement of AD pathology in living patients and has been used to implicate the anterior cingulate cortex (ACC) in patients with mild AD and delusions compared with those without delusions [32]. Delusional thinking was assessed in 30 AD patients using the BEHAVE-AD (Behavioral Pathology in Alzheimer's Disease) scale, and compared with AD-D patients (n=22), AD+D patients (n=8) had significantly decreased N-acetylaspartate/creatine ratio (a marker of neuronal density, decreased in AD) and increased myo-inositol/creatine ratio (an early marker of AD) in the ACC. Of importance in this study was the finding that these markers were unrelated to cognition, thus implicating early and distinct neuropathology in the ACC in the development of psychosis. The distribution of persecutory and misidentification delusions was not reported.

Genetics

Although there is clear evidence for the heritability of AD+P [17], there is also evidence that AD+D specifically is a heritable trait. Familial aggregation studies of probands and siblings with AD have shown a higher chance of concordance for AD+D in siblings and probands than by chance alone [33]. Using genome scans of 148 AD pedigrees, Avramopoulos and colleagues [34] identified a locus on chromosome 2p that is linked with AD+D and a locus on 14q that predisposes individuals to a form of dementia without comorbid psychotic features.

The role of ApolipoproteinE ε4 (*Apoε4*) in AD+P is unclear due to conflicting studies using varying methodologies [35]. When addressing delusions specifically, there is evidence supporting the role of *Apoε4* in predicting AD+D. In a study of 158 patients with AD, delusions correlated with number of *Apoε4* alleles [36]. In a prospective study of 87 patients with AD, the number of *Apoε4* alleles was predictive of delusions, with 1 allele carrying a 2.5-fold risk and 2 alleles a 5.6-fold risk [37]. In another longitudinal study of 151 AD patients of all severities observed in a memory clinic, the presence of at least one *Apoε4* allele conferred increased hazard ratios for the development of

delusions (3.4-fold) and hallucinations (19.0-fold) [38]. In a sample of 171 patients with late-onset AD consecutively admitted to a memory clinic, the presence of at least one *Apoε4* allele significantly increased the risk of developing delusions in the early stage of the illness compared with the absence of this allele. This association did not hold for hallucinations or psychosis in general [39]. In a study looking at 110 AD patients, the number of *Apoε4* alleles has been associated with prevalence and severity of delusions in AD, with homozygosity conferring the greatest delusional burden [40]. In a large independent cohort of 388 patients with longitudinal measures of NPS, the ε3/ε3 genotype of the ApolipoproteinE gene was negatively associated with hallucinations but not significant for delusions, suggesting different genetic determinants for these separate phenomena [41]. In future studies of AD+D, *Apoε4* status, age at onset of illness, and subtype of delusions will be important factors in characterizing the sample group.

Genes involved in neurotransmitter systems have been identified as important in the pathogenesis of AD+D. There is mixed evidence for the serotonin 2A (*5HT-2A*) receptor single nucleotide polymorphism 102 T/C. Association studies have identified the T allele as the risk allele for AD+D [42]. The T allele also has been associated with a higher prevalence of delusions and treatment resistance to second-generation antipsychotics [43]. The C allele has been found to be protective for delusions [44] but to be the risk allele for hallucinations in the absence of delusions [45]. Similarly, with the *5HT-2C* single nucleotide polymorphism Cys23Ser, Ser 23 was found to be the risk allele for hallucinations in the absence of delusions, and this effect was additive to *5HT-2A* C102 [45]. The serotonin transporter promoter region (*5HT-TPR*) also has been implicated in AD+D. Homozygosity for the long arm leads to an increase in *5HTT* mRNA transcription and *5HT* uptake compared with genes containing at least one short arm and is protective for AD+D [46]. The dopaminergic system also has been investigated, with dopamine receptor *DRD3* 1/1 allele implicated in delusions compared with the *DRD3* 2/2 allele [47]. However, much more work is required to help us better understand the role of neurotransmitter genetics in AD+D.

The idea that so-called psychosis-modifier genes may act similarly during neurodevelopment to produce schizophrenia, or throughout neurodegeneration to produce AD+P was supported by an investigation of the interleukin *(IL)-1β* gene [48]. Functional *IL-1β* promoter polymorphisms have been associated with AD+D, leading to speculation that diminished *IL-1β* output may promote the psychotic phenotype through altered neurotransmitter interaction (via *DA* or *5HT*) or reduced neuronal repair after amyloid-mediated neurotoxicity. Carson and colleagues [49•] have investigated genetic variations in the α7 nicotinic receptor and psychotic symptoms in AD. Sampling 409 individuals from the Northern Ireland BPSD cohort, an association was found between the rs6494223 T allele and delusional symptoms in AD. The frequency of delusional symptoms was higher in patients homozygous for the T allele compared with the CC or CT genotypes. This result was not confounded by MMSE scores. Also of interest was the location of the single nucleotide polymorphism close to D15S1360, the dinucleotide repeat polymorphism associated with schizophrenia. Table 1 summarizes the neuropathological and genetics findings associated with AD+D. Table 2 reviews the differences between misidentification and persecutory delusions in AD.

Discussion

The study of AD+D is an evolving field that is becoming more refined with time. Historically, AD+D was almost exclusively discussed within the context of AD+P, but more literature assessing delusions as separate from hallucinations and assessing subtypes of delusions is emerging. Understanding the presentation, epidemiology, association with cognitive impairment in specific domains, and rate of cognitive decline of persecutory versus misidentification delusions is essential in understanding the neurobiological underpinnings of these syndromes. The absence of controlling for the confounding factors limits the interpretation of much of the existing literature.

Neuropathological studies emphasize the important roles of plaque and tangle density in AD+D, suggesting that frontal plaques and tangles are associated with delusions. The effect of these plaques and tangles on neurotransmitter systems may underscore their role in manifestation of the illness. Serotonergic systems are disrupted in psychosis both cortically and subcortically and are associated with persecutory delusions rather than misidentifications. Muscarinic density in the orbitofrontal cortex also has been linked to AD+D. Furthermore, cortical cell loss is associated with persecutory delusions, whereas hippocampal cell loss (and thus cognitive impairment) is associated with misidentifications. The triaxial inclusion of plaque and tangle density, plaque and tangle location, and effect on neurotransmitter systems results in a complicated neuropathological model of AD+D. Difficulty in controlling for the various permutations and combinations of these three variables underscores the heterogeneity of data in this area. Further neuropathological studies with clearly described clinical samples are warranted.

Genetic studies to date have established strong heritability for psychosis in AD, suggesting a role for *Apoε4* load in delusional thinking, providing potential links to genes associated with primary psychotic disorders, and starting to identify potential neurotransmitter targets for pharmacologic

Table 1 Summary of neuropathology, genetics, and cognition for Alzheimer's disease with delusions

	Neuropathology	Genetics	Cognition and function
Alzheimer's disease with delusions	Greater density of neocortical neurofibrillary tangles in AD+D compared with AD-D	Higher chance of concordance for AD+D in siblings and probands	Delusions may be associated with worse functional performance in AD patients
	Higher muscarinic receptor (M_2) density in the orbitofrontal cortex (Brodmann area 11) in AD+D compared with AD-D	Locus on chromosome 2p linked to AD+D	
	Significantly decreased N-acetylaspartate/creatine ratio and increased myo-inositol/creatine ratio in the anterior cingulate cortex in AD+D compared with AD-D	Number of *Apoε4* alleles predictive of AD+D (1 allele carrying a 2.5-fold risk and 2 alleles a 5.6-fold risk); also associated with the prevalence and severity of delusions in AD	
		Presence of *Apoε4* increased hazard ratio for development of delusions 3.4-fold	
		For late-onset AD, presence of *Apoε4* allele increased risk of developing delusions in earlier stage of AD than in patients not carrying this allele	
		Homozygosity of *Apoε4* alleles associated with greater delusional burden	
		Evidence of serotonin 2A receptor single nucleotide polymorphism 102 T/C; T allele associated with increased presence of delusions, while C allele is protective for delusions	
		5HT-TPR homozygosity in the long arm is protective for AD+D as compared with genes containing at least 1 short arm	
		α7 nicotinic receptor association between rs6494223 T allele and delusions in AD; frequency of delusional symptoms higher in patients homozygous for the T allele compared with the CC or CT genotypes	

5HT-TPR serotonin transporter promoter region, *AD* Alzheimer's disease, *AD+D* Alzheimer's disease with delusions, *AD-D* Alzheimer's disease without delusions

intervention. A recent clinical trial demonstrated the efficacy of citalopram in treating the psychosis of dementia, further implicating serotonergic mechanisms [50].

Relating the neuropathological and genetic findings using structural and functional imaging studies holds promise for the identification of endophenotypes that can then be used in future mechanistic and pharmacologic studies. Ideally, these future studies will control for the many variables in the clinical sample. Practically, however, this is difficult. To further investigate delusions in dementia, several steps must be taken. This starts with uniformity in diagnosis. A uniform standard of qualifying and quantifying AD+D is essential.

Table 2 Differences between misidentification and persecutory delusions in Alzheimer's disease

	Neuropathology	Cognition and function
Misidentification delusions	Lower neuron counts in the area CA1 of the hippocampus	Greater cognitive impairment at baseline vs AD-D
	Increased density of neuritic plaques in the fronto-parieto-occipital lobes	AD+D patients with hallucinations show greater impairment in verbal fluency and visuospatial function compared with AD-D patients
Persecutory delusions	Associated with cortical and subcortical serotonergic system disruption	Greater frontal impairment measured by the Frontal Assessment Battery (AD +D, 11.6±2.8; AD-D, 13.9±2.5)
	Less severe cell loss in the parahippocampal gyrus	Frontal Assessment Battery scores significantly influenced by the manifestation of persecutory delusions
	Lower cell counts in the serotonergic dorsal raphe nucleus	

AD+D Alzheimer's disease with delusions, *AD-D* Alzheimer's disease without delusions

This standard should be valid and reliable and should specifically characterize the dementia and the delusional subtypes. Stage and age at onset of dementia are crucial, as is the duration of delusional thinking. Future studies should accurately report as much demographic and clinical data as possible in order to make comparisons of the literature more valid and further elucidate the etiopathology of AD+D.

Conclusions

Integrating the epidemiology, clinical correlates, and the neuropathological and genetic literature in AD+D allows us to speculate on the etiology and mechanisms of AD+D. Plaque and tangle deposition in genetically predisposed individuals with susceptible alleles of serotonergic, muscarinic, nicotinic, or *Apoε4* genes appears to result in disruption of cortical circuitry, culminating in delusions in the context of AD. Although delusions in AD seem to correspond to a phenotype distinct from AD-D, subtypes of delusions may also define further distinct clinical entities. Persecutory delusions may occur earlier in the illness and have a more significant genetic component than misidentification delusions, which are associated with increased cognitive impairment and advanced dementia. Clearly distinguishing between these two syndromes is essential for making progress in the area of AD+D.

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- •• Of major importance

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