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Revisiting Criteria for Psychosis in Alzheimer's Disease and Related Dementias: Toward Better Phenotypic Classification and Biomarker Research

Corinne E. Fischer[a,b,1,*], Zahinoor Ismail[c,1], James M. Youakim[d], Byron Creese[e], Sanjeev Kumar[b,f], Nicolas Nuñez[g], R. Ryan Darby[h], Antonella Di Vita[i,j], Fabrizia D'Antonio[i], Carlo de Lena[i], William J. McGeown[k], Ravona Ramit[l,m], Jill Rasmussen[n], Joanne Bell[o], Huali Wang[p], Marie-Andrée Bruneau[q], Peter K. Panegyres[r], Krista L. Lanctôt[b,s], Luis Agüera-Ortiz[t], Constantine Lyketsos[u], Jeffrey Cummings[v], Dilip V. Jeste[w], Mary Sano[x], D.P. Devanand[y], Robert A. Sweet[z] and Clive Ballard[e]

[a]*Keenan Research Centre for Biomedical Research, St. Michael's Hospital, Toronto, Canada*
[b]*Department of Psychiatry, University of Toronto, Toronto, Canada*
[c]*Departments of Psychiatry, Clinical Neurosciences, and Community Health Sciences; Hotchkiss Brain Institute and O'Brien Institute for Public Health, University of Calgary, Calgary, Canada*
[d]*ACADIA Pharmaceuticals Inc., Princeton, NJ, USA*
[e]*Medical School, College of Medicine and Health, University of Exeter, Exeter, UK*
[f]*Centre for Addiction and Mental Health, Toronto, Canada*
[g]*Department of Psychiatry & Psychology, Mayo Clinic, Rochester, MN, USA*
[h]*Department of Neurology, Vanderbilt University Medical Center, Nashville, TN, USA*
[i]*Department of Human Neuroscience, Sapienza University of Rome, Rome, Italy*
[j]*Department of Psychology, Sapienza University of Rome, Rome, Italy*
[k]*School of Psychological Sciences and Health, University of Strathclyde, Glasgow, UK*
[l]*Memory and Geriatric Psychiatry Clinic, Sheba Medical Center, Tel Hashomer, Israel*
[m]*Sackler School of Medicine, Tel Aviv University, Tel Aviv, Israel*
[n]*Psi-Napse, Surrey, UK*
[o]*Syneos Health, Wilmington, NC, USA*
[p]*Dementia Care and Research Center, Peking University Institute of Mental Health (Sixth Hospital), National Clinical Research Center for Mental Disorders, Beijing, China*
[q]*Department of Psychiatry, University of Montreal, Centre de Recherche de l'Institut Universitaire de gériatrie de Montréal (CRIUGM), Montreal, Canada*
[r]*Director, Neurodegenerative Disorders Research Pty Ltd, West Perth, WA, Australia*
[s]*Hurvitz Brain Sciences Research, Sunnybrook Health Sciences Centre, Toronto, Canada*
[t]*Department of Psychiatry Instituto de Investigación Sanitaria (imas12), Hospital Universitario 12 de Octubre, & Centro de Investigación Biomédica en Red de Salud Mental, CIBERSAM, Madrid, Spain*
[u]*Department of Psychiatry and Behavioral Sciences, Johns Hopkins Bayview, Johns Hopkins Medicine, MD, USA*

[1]Denotes primary co-authors.

*Correspondence to: Dr. Corinne Fischer, Room 17-044 cc Wing, St. Michael's Hospital, 30 Bond St., Toronto, Ontario, M5B 1W8, Canada. Tel.: +1 416 864 5320; E-mail: Corinne.Fischer@unityhealth.to.

[v]*UNLV Department of Brain Health and the Cleveland Clinic Lou Ruvo Center for Brain Health, Las Vegas, NV, USA*
[w]*Departments of Psychiatry and Neurosciences, and Stein Institute for Research on Aging, University of California San Diego, San Diego, CA, USA*
[x]*Mt Sinai School of Medicine, Manhattan, NY, USA*
[y]*Department of Psychiatry, Columbia University, New York City, NY, USA*
[z]*Departments of Psychiatry and Neurology, University of Pittsburgh, PA, USA*

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Abstract.
Background: Psychotic symptoms are common in Alzheimer's disease (AD) and related neurodegenerative disorders and are associated with more rapid disease progression and increased mortality. It is unclear to what degree existing criteria are utilized in clinical research and practice.
Objective: To establish research criteria for the diagnosis of psychosis in AD.
Methods: The International Society to Advance Alzheimer's Research and Treatment (ISTAART) Neuropsychiatric Symptoms (NPS) Professional Interest Area (PIA) psychosis subgroup reviewed existing criteria for psychosis in AD and related dementias. Through a series of in person and on-line meetings, a priority checklist was devised to capture features necessary for current research and clinical needs. PubMed, Medline and other relevant databases were searched for relevant criteria.
Results: Consensus identified three sets of criteria suitable for review including those of Jeste and Finkel, Lyketsos, and the *Diagnostic and Statistical Manual for Mental Disorders*, 5th edition. It was concluded that existing criteria could be augmented by including a more specific differentiation between delusions and hallucinations, address overlap with related conditions (agitation in particular), adding the possibility of symptoms emerging in the preclinical and prodromal phases, and building on developing research in disease biomarkers.
Conclusion: We propose criteria, developed to improve phenotypic classification of psychosis in AD, and advance the research agenda in the field to improve epidemiological, biomarker, and genetics research in the field. These criteria serve as a complement to the International Psychogeriatric Association criteria for psychosis in neurocognitive disorders.

Keywords: Alzheimer's disease, criteria, delusions, hallucinations, mild cognitive impairment, psychosis

INTRODUCTION

Psychotic symptoms occur across a broad range of dementias including Alzheimer's disease (AD), frontotemporal dementia (FTD), and dementia with Lewy bodies (DLB) [1], though they have been most extensively studied in AD. Studies suggest that one third to one half of patients with AD may experience psychotic symptoms during their dementia [2]. In spite of the frequency of these symptoms, it is unclear to what extent the existence of psychotic symptoms impacts clinical decision making. Criteria have been established for the diagnosis of the syndrome of psychosis in AD, and include the Jeste and Finkel [3], Lyketsos [4], and *Diagnostic and Statistical Manual of Mental Disorders*, fifth edition (DSM-5) criteria [5], but these have not been validated extensively and their relative utility remains uncertain. Criteria are important given the impact of psychosis on clinical outcomes. For example, there is compelling literature to suggest that the presence of psychotic symptoms is associated with accelerated cognitive and functional decline through mechanisms that have yet to be delineated [6]. Further, psychotic symptoms are associated with greater distress for the patient and caregiver [7], poor general health [8], increased likelihood of institutionalization [7, 9], and increased mortality [9, 10]. Management of psychotic symptoms could mitigate cognitive and functional decline thereby reducing burden on caregivers [11]. Therefore, identifying and classifying psychotic symptoms has important implications for prognosis, disease management and the testing of new interventions.

Current criteria may benefit from addressing unresolved areas of controversy such as lack of clarity regarding sub categorization of psychotic symptoms (e.g., delusions, hallucinations), their differentiation from related neuropsychiatric symptoms (NPS) such

as agitation, and issues with exclusion of psychosis in the prodromal phase of cognitive disorders. The first major question is whether psychotic symptoms should be considered as one entity or should be broken down into delusions and hallucinations [12]. There is evidence for both approaches; epidemiological and genetic studies support pooling delusions and hallucinations, whereas neuroimaging studies and neuropathology support treating them as distinct categories [12]. Variability in clinical outcomes, symptom onset, and divergent associations with different neurodegenerative pathologies also support separating delusions and hallucinations into separate categories. Moreover, psychotic symptoms also frequently overlap with other NPS such as agitation and depression [13], making it difficult to discern which symptom is driving the observed adverse outcomes.

Another potential concern relates to how to differentiate psychotic symptoms as part of a dementia prodrome from psychotic symptoms in established or late onset psychotic disorders. The relationship between psychotic phenomena that appear in the context of neurodegenerative disease and those occurring in the context of idiopathic psychotic disorders has been the subject of recent research [14]. Although intuitively it may seem that psychotic phenomena occurring earlier or later in life may have a similar etiology given that they respond to similar pharmacological agents, this relationship is controversial and far from established. For example, in the CitAD study of citalopram for agitation in AD, the serotonergic antidepressant improved psychotic symptoms, an effect we would not expect in schizophrenia in early life, suggesting different mechanisms for the psychosis in AD in the presence of agitation [15], though further studies are required to confirm this finding. Population studies describe a two- to five-fold risk of developing dementia in patients with early onset schizophrenia, after adjusting for medical comorbidities and general dementia risk factors [16, 17], although there is evidence that this dementia is not AD [18] and findings are far from consistent on this point [19, 20]. Late life schizophrenia has an overlapping but distinct cognitive profile from AD and late life depression [21]. Bipolar disorder is the other major psychiatric illness that can be associated with psychotic phenomena and cognitive deficits, and polygenic overlap with AD has recently been shown [22]. Large population studies have demonstrated between a two- and four-fold increase in the odds of dementia in bipolar disorder patients [23]. The risk seems especially high in patients with onset of bipolar disorder after the age of 70. A number of them may be suffering a prodromal dementia state [24, 25], similar to the profile of those with late onset depression [26]. All of the above data support the association of psychotic phenomena and some form of cognitive impairment in two major psychiatric disorders, schizophrenia and bipolar disorder. However, the absence of clear etiopathological links between these psychiatric disorders and neurodegenerative disorders, such as AD, advise against directly transposing traditional psychosis diagnostic criteria designed for a neurodevelopmental disorder, such as schizophrenia, onto later life emergent disease.

These challenges are further complicated by the fact that late onset psychotic symptoms may be early indicators of an emerging neurodegenerative disorder [14]. With the recent development and validation of constructs such as mild behavioral impairment (MBI) [27], in which psychotic symptomatology is an independent domain, behavioral symptoms can be seen as an early manifestation of a neurodegenerative disorder. Psychosis prior to the onset of cognitive decline and functional impairment (i.e., diagnosis of dementia) is often considered as an exclusion under the current criteria [14]. Further, data suggest that psychosis, when present in AD, may be associated with lower rates of clinical misdiagnosis in pathologically confirmed AD, suggesting psychosis may be a core feature of the disease process [28]. This finding is consistent with the historical accounts of AD, in that Alois Alzheimer's first published case presented with psychotic symptoms in advance of gross cognitive impairment [29].

Finally, the availability of disease biomarkers opens up new possibilities. Biomarkers may enable prediction of who will and will not develop a neurodegenerative disorder, thus allowing for the deployment of disease modifying treatments. The National Institute of Aging has recently developed a new research framework for diagnosing biological AD that takes into account the presence or absence of disease biomarkers [30]. To what extent the presence of psychosis may be associated with specific disease biomarkers is not yet clear, but the association of psychosis with accelerated cognitive decline [6] suggests that a search for disease biomarkers in patients with minimal cognitive decline expressing psychosis may be worthwhile as an avenue for early detection. Diagnostic criteria should have the ability to incorporate newly available biomarkers and should accommodate periodic revisions as new data emerge.

There have been several attempts to establish formalized criteria for psychosis in AD. Moreover, recent developments in the field, including constructs like MBI [31] using neuropsychiatric symptoms to quantify dementia risk, and advances in imaging and biomarkers supporting earlier diagnosis in advance of overt dementia and functional decline, necessitate a review of the criteria. This paper presents a critical review of the existing criteria on psychosis in AD, to determine if these criteria reflect recent advances in the field. These AD-specific criteria are a complement to the provisional clinical criteria for dementia related psychosis developed by the International Psychogeriatric Association (IPA) which are pan-diagnostic from a neurocognitive disorder perspective, and have been developed to assist in detection and clinical trials, both pharmacologic and nonpharmacologic. Specifically, we will review each set of criteria, highlighting their strengths and weaknesses, to inform the discussion on what is required for new criteria, to foster future research and discovery, and address knowledge gaps in the field.

METHODS

The International Society to Advance Alzheimer's Research and Treatment (ISTAART) NPS Professional Interest Area (PIA) psychosis subgroup, a professional organization within the Alzheimer's Association, is a body of experts dedicated to advancing the study of psychosis in AD and related dementias. The NPS PIA held several meetings both on-line and in-person from October 2017 to the present, for the purpose of reviewing existing criteria for psychosis in AD. The group established by consensus an approach to reviewing published criteria for psychosis in AD. Specifically, criteria had to: 1) pertain to AD or mild cognitive impairment (MCI); 2) refer to specific symptoms such as delusions and hallucinations; and 3) have some description of frequency and/or severity. This approach was combined with an exhaustive Medline search including the following key words: psychosis, dementia, criteria, Alzheimer's disease, delusions, and hallucinations, and supplemented by expert consensus. All criteria were reviewed using a predetermined framework (see Fig. 1) which asked questions such as "are delusions distinguished from hallucinations?", "are the criteria limited to AD?", "is there reference to prodromal conditions such as MCI?", "is there a link to biomarkers or cognitive decline?", and "are exclusionary pathologies considered?"

1. How is psychosis defined (are delusions distinguished from hallucinations, are there subtypes of hallucinations/ illusions)?
2. Are the symptoms specific to AD or do they extend to other dementia subtypes?
3. Is there a measure of frequency?
4. Is there a measure of severity?
5. Is there a measure of duration?
6. Is there reference to other neuropsychiatric symptoms?
7. Is there reference to other cognitive symptoms?
8. Does the definition encompass exclusionary criteria?
9. Is there a reference to disease biomarkers?
10. Is there a reference to prodromal states (MCI/MBI)?

Fig. 1. Psychosis criteria checklist.

RESULTS

Three sets of criteria were identified using this method including those described by Jeste and Finkel [3], Lyketsos [4], and the DSM-5 [5] (see below).

Jeste and Finkel criteria

Estimates on the prevalence of psychosis in dementia have been hampered by lack of consensus on definition and limited availability of appropriate assessment methods [2]. Early efforts to address this case ascertainment dilemma included the Jeste and Finkel diagnostic criteria for Psychosis of AD and Related Dementias [3]. Those criteria were developed in DSM-IV [32] style, in order to address the gap between the diagnostic criteria for schizophrenia, as applied to older adults, and those for dementia, which at best offered additional coding if delusions were a prominent part of the illness [3]. Published in 2000, the Jeste and Finkel criteria [3] represented an important advance in the field, as operationalized criteria were essential for appropriately classifying psychosis in dementia, in order to improve prevalence estimates, and for case selection for treatment trials, as several new atypical antipsychotics were being tested in FDA-approved randomized controlled trials for examining efficacy for controlling psychosis and agitation in older people with dementia.

Importantly hallucinations and delusions were both included, the presence of either being adequate to trigger the diagnosis, supported by literature indicating that both hallucinations and delusions are important in understanding psychosis in dementia [33]. Those criteria excluded psychotic symptoms that predated dementia, in order to clearly demarcate psychosis in dementia from schizophrenia, delusional disorders, and psychotic mood disorders in older adults. As is standard with DSM criteria, other exclusions were general medical conditions, or psychotic symptoms in the context of delirium. Clinical trial data were used to validate the Jeste and Finkel criteria [3]. Schneider reanalyzed data from a risperidone clinical trial for agitation in dementia, demonstrating that 75% of participants met the psychosis in dementia criteria [34]. This validation supported psychosis in dementia as a distinct clinical syndrome, with demographic features distinct from dementia without psychosis.

The Jeste and Finkel criteria [3] were immediately helpful, influential in Food and Drug Administration (FDA) deliberations [35], and remain in use today, especially for clinical trial inclusion/exclusion. However, over time, issues have arisen suggesting a need for modification. This is similar to the diagnostic criteria for most psychiatric and medical disorders. As science advances and more research is conducted resulting in new data and insights, it is inevitable that the criteria change with time. Indeed, new versions of the DSM as well as ICD are published every few years. In terms of the Jeste and Finkel criteria, these are somewhat vague with respect to severity and duration. While the criteria are explicit for duration of symptoms (at least intermittently, for 1 month or longer), the severity requirement is simply that of "some disruption in patients' and/or others' functioning." In the context of a clinical diagnosis of dementia, which necessitates functional impairment, attributing a proportion of this to psychosis can be challenging. Even more importantly, however, is the exclusion of pre-existing psychotic symptoms in advance of a formal dementia diagnosis. While intended to separate psychosis in dementia from other psychotic conditions, there are unintended consequences of this demarcation. Clinicians are well aware that there is some imprecision in the cutoff for functional impairment between MCI and dementia, and this imprecision contributes to case ascertainment error in the psychosis of dementia criteria as described by Jeste and Finkel [3]. Evidence suggests that psychosis can precede a formal dementia diagnosis and be manifest during the MCI phase [36–39]. For example, one new study demonstrates that in those with MCI and delusions, the hazard ratio for progression to AD is 13.99 over a 4-year follow up, emphasizing the significance of psychosis in pre-dementia conditions [40]. To exclude those with hallucinations or delusions in the MCI phase restricts the sample, and undermines the ability to link psychosis of the early phases of AD. This dilemma underscores some challenges in the DSM approach, which is mostly silent on natural history and age of onset of illness, features which in this case are salient in distinguishing primary psychotic disorders from psychotic symptoms as part of a neurodegenerative illness [31]. Finally, these criteria were developed before biomarkers became readily available, and were not part of clinical care at the time. Technological advances have raised issues relevant to development of criteria. For example, amyloid positive individuals with MCI and new delusions of theft may have been diagnosed with a delusional disorder under older criteria, but under the new NIA-AA Research Framework criteria for dementia [30], these individuals would be diagnosed as having prodromal AD. Thus, with the field moving toward earlier detection, prevention strategies, and including biomarkers, there is need for the criteria for psychosis in AD to be adjusted to these new circumstances.

Lyketsos criteria

Lyketsos, Breitner and Rabins (2001) [4] suggested that the Jeste criteria [3] were not empirically based and proposed an alternative approach. They did not begin by describing psychosis in dementia or initially establishing diagnostic criteria. Rather, based on their analysis of the participants in the Cache County study of memory and aging who had complete Neuropsychiatric Inventory (NPI) data, they explored the relationships among the various neuropsychiatric symptoms. These investigators observed that AD patients fall into three natural groupings of neuropsychiatric symptoms based on identification of patterns of symptoms that co-occurred in individual patients: 1) those who were unaffected or minimally affected, almost always having only one symptom; 2) those who have a complex polysymptomatic neuropsychiatric disturbance that is predominantly *affective*; and 3) those who have a complex polysymptomatic neuropsychiatric disturbance that is predominantly *psychotic* [41]. Notably, almost half the participants with delusions were assigned to the affective and not the psychotic group. Lyketsos et al. proposed that

the latter two clusters may be thought of as distinct syndromes and proposed criteria to identify patients in those syndromes by emphasizing what symptoms (i.e., affective versus psychotic) were most prominent.

Like the Jeste and Finkel criteria, the criteria for 'Alzheimer-associated psychotic disorder' do not distinguish between delusions and hallucinations and require that the symptoms be associated with disruptions of the patient's life or lives of others. They differ by requiring another neuropsychiatric symptom to be present, such as aberrant motor behavior, although no level of severity for these is indicated. A major strength of these criteria is the distinction between affective and psychotic syndromes, an important feature for incorporation into future criteria, and the recognition that an affective, and *not* psychotic, disturbance can be present even though there are delusions if affective symptoms predominate. While the criteria may represent partial improvement in measurement over the Jeste and Finkel criteria [3], there is no reference to prodromal states or preclinical symptoms, beyond the arbitrarily defined maximum 2 year time frame between the onset of psychosis and the onset of cognitive symptoms. Further, the empirical criteria were informed by psychotic symptoms in patients from the Cache County study, captured via the NPI. However, evidence suggests that instruments such as the NPI, Neurobehavioral Rating Scale, and BEHAVE-AD can capture psychosis in AD differently, thus introducing measurement error into the empirical classification [42]. Furthermore, it is possible that someone could be "minimally symptomatic" but could have a single psychotic feature (9% of their minimally symptomatic subgroup had delusions), but the criteria would not classify that individual as having psychosis (because an additional neuropsychiatric symptom might not be present). Thus, while the criteria were a useful advance, further refinement is needed.

DSM-5

DSM-5 criteria for dementia and related behavioral symptoms were developed after extensive consultation with a task force composed of working groups made up of 160 clinicians and researchers around the world. Final criteria were subsequently approved by a scientific committee appointed by the American Psychiatric Association board of trustees. As such, it was not subject to clinical trial validation as per some of the other criteria. DSM-5 [5] acknowledges that psychotic symptoms (including delusions and hallucinations) may occur in the context of a Major Neurocognitive Disorder such as AD, DLB, and FTD. The complete nomenclature is "Major Neurocognitive Disorder due to AD with behavioral disturbance (psychosis)". DSM-5 does make a distinction between "mild" and "major" neurocognitive disorder so it is possible that psychosis may be present even in patients with mild neurocognitive disorder. When considering other aspects, there is no distinction between delusions and hallucinations—rather, they are considered together as psychosis. There is diagnostic specificity to the degree that the symptoms are framed in the context of a specific neurocognitive disorder (i.e., Major Neurocognitive disorder due to AD with behavioral disturbance (psychosis)). There is no reference to *frequency, severity*, or *duration* of behavioral symptoms, so it is essentially left to the discretion of the clinician to determine whether or not the observed symptoms meet the clinical threshold for psychosis in AD. There may be reference to other NPS if they exist (i.e., Major Neurocognitive Disorder with behavioral disturbance (depression, psychosis)). There is no reference to cognitive symptoms but there is a reference to the standard DSM exclusionary criteria that symptoms are not better explained by another disorder. There is no reference to preclinical disease or disease biomarkers, including cerebrospinal fluid (CSF) measures or positron emission tomography (PET) imaging, though there is a clear reference to prodromal conditions (i.e., Mild Neurocognitive Disorder with behavioral disturbance). In summary, the criteria include reference to specific neurodegenerative diagnoses, account for co-existent NPS, and make reference to prodromal conditions. However, psychotic symptoms are not identified, there is no reference to disease biomarkers, and measures of frequency, duration or severity are absent, which were felt to be important factors for clinical and research applications

DISCUSSION

Prevalence and phenomenology

Discrepancies in prevalence estimates of psychosis in AD and related dementias provide further impetus for establishing agreed upon criteria. In patients with dementia due to AD the prevalence of psychosis is estimated to range between 10%–74%, with a median prevalence of 41% [2]. Delusions are known to be the most common presentation of psychosis in AD

with prevalence estimates ranging from 15–30% in most studies, though some studies report a higher prevalence [2, 36, 43, 44]. The reported prevalence rates of hallucinations range from 5–15%, again with some reports of higher prevalence [2, 36, 43–45]. Importantly, delusions and hallucinations frequently co-occur with other disturbances such as depression and agitation which must be accounted for in future criteria. This broad range of prevalence resulted from the use of a variety of case ascertainment methods in a variety of settings. However, the majority of studies used a combination of semi-structured interviews and formalized rating scales. Nonetheless, the need for psychosis in dementia criteria was highlighted by the broad spectrum of prevalence estimates and frequencies.

Psychosis of AD may be differentiated into mainly two subtypes: the *paranoid subtype*, which includes persecutory delusions, and the *misidentification subtype*, which includes misidentification phenomena and hallucinations [46]. Misidentification delusions may reflect cognitive impairment according to some authorities rather than a delusion per se. Cook and others [46] performed a cross-sectional factor and cluster analysis using the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) behavior rating scale in 188 patients with probable and possible AD. The authors found that patients with a Clinical Dementia Rating Scale (CDR) sum of boxes with severity of dementia >2 had the greatest risk of developing psychosis and 42% of the population had only one psychotic symptom whereas 11% had > 6. Using exploratory factor and cluster analyses, these authors found that there were mainly two principal sub-types of psychosis in AD that were stable according to severity: 1) The *auditory and visual hallucinations (though it is understood that occasionally patients can manifest olfactory and tactile hallucinations)*, combined with misidentification of people; and 2) those with *persecutory delusions*. These groups were independent of each other on both factor and cluster analyses. These analyses supported the need for separate categories of psychosis in AD. There is a high degree of comorbidity between delusions and hallucinations in AD, but evidence from longitudinal studies indicates that around 10–20% of people experience hallucinations without delusions and that the two symptoms are associated with different clinical outcomes [7, 47], suggesting the presence of two distinct clinical phenotypes. Psychotic symptoms are less well characterized in patients with vascular dementia and other dementia etiologies as compared to AD with the possible exception of Parkinson's disease (PD), possibly due to the absence of well-defined patient cohorts.

Trans-diagnostic issues

The appearance of psychotic symptoms with aging may result in a broad differential diagnosis. Establishing unified and agreed upon criteria may assist in distinguishing psychosis resulting from late onset primary psychotic disorders versus psychosis secondary to neurodegeneration. Based on clinical symptoms alone, it might be particularly difficult to distinguish between AD, DLB, and very late onset schizophrenia-like psychoses [48], though some studies have demonstrated phenomenological differences between psychosis in dementia versus primary psychosis suggesting a unique neuropathogenesis [49].

Differential diagnosis in dementia

The criteria currently applied for psychosis of AD as described above include a diagnosis of AD according to established criteria. These criteria do not, however, with the possible exception of DSM-5, consider the possibility that psychosis symptoms may manifest in the phase of MCI due to AD, and none consider symptoms that are in the pre-clinical phase preceding cognitive impairment as established for MBI [27]. The AD neuropathological process is known to start many years before the appearance of cognitive symptoms and it has recently been demonstrated that the presence of neuritic plaques is associated with a higher risk of psychosis in subjects without cognitive impairment [50]. Detecting specific phenomenological characteristics of psychosis of AD, even before the onset of cognitive decline, may help to define criteria specific to the AD psychotic phenotype.

Visual hallucinations have not specifically been described in the criteria yet have distinct phenomenological characteristics across different types of dementia. Visual hallucinations in AD usually consist of familiar or unfamiliar people and objects [51]. In PD dementia and DLB, psychotic symptoms are distinct and well characterized: illusions and pareidolia (misinterpreting a stimulus), passage hallucinations, sensation of presence, and vivid stereotyped visual hallucinations [52, 53]. They appear in premorbid stages, even prior to cognitive impairment and are associated with neuroimaging and neuropathological changes in regions associ-

ated with the integration of visual stimuli [54]. In FTD, psychotic symptoms are less frequent (10%) except in some genetic variants like C9Orf72 where 21–56% of patients present with bizarre somatic delusions and multimodal hallucinations [55]. In this disease, there is a psychosis phenotype since probands of C9ORF72 FTD are more at risk for schizophrenia or late-onset schizophrenia [56]. Late onset psychotic disorders have also been associated with other tauopathies like argyrophilic grain disease [57].

Differential diagnosis in psychotic disorders

Persecutory delusions importantly are also common in psychiatric disorders such as schizophrenia or delusional disorder, making the distinction from late onset psychotic disorders challenging. However, in such disorders, delusions may be more bizarre and the cognitive decline, if present, is not progressive. In AD, persecutory delusions when present tend to have a less bizarre quality [12]. When present in MCI and early phase AD, misidentification delusions are associated with more rapid cognitive decline [12]. Misidentifications in AD, however, generally occur later in the disease course compared to persecutory ones [33], are more common in AD than primary psychiatric disorders, are associated with greater hippocampal pathology [58] and might reflect abnormalities of memory or other cognitive functions. While these subtle distinctions are generally known to clinicians, in particular the distinction between misidentification delusions and delusions of theft with dementia, they have not to date been incorporated into any formalized criteria.

In other psychiatric disorders, although visual hallucinations are less frequent than auditory hallucinations, visual hallucinations are reported to bear the perceptual properties of externally-originating stimuli, to be vivid, and often to be associated with auditory hallucinations and delusions related to the content of the hallucinations. The content, which is frightening, can consist of visions of angels, the devil, and saints [59]. In late onset schizophrenia, or very late onset schizophrenia, paranoid or partition delusions with visual, olfactory, and tactile hallucinations are more often present, and have not been associated with AD biomarkers [60, 61]. While the paranoid subtype of delusion in AD includes only delusions with persecutory contents, the misidentification subtype of delusion in AD includes delusions of misidentification and hallucinations. It might be important to distinguish disorders of thought (delusion) from disorders of perception (hallucination), both of which are traditionally included under the rubric of the work "psychosis".

Trajectory of psychotic symptoms in dementia

The natural history of psychotic symptoms in dementia is an important dimension of an emerging definition. Typically, symptoms of psychosis vary in people with AD. Psychotic symptoms once present commonly persist for at least a year in two thirds of people [46, 62]. A follow-up study reported a 2-year persistence of delusions and hallucinations in 43% and 73% of people, respectively [63]. However, this apparent persistence may conceal an underlying pattern of remission and recurrence. For example, in 125 people with AD followed monthly for 12 months, 30 (54%) had resolution of symptoms over 3 months without specific treatment, but among these, eight (27%) had a subsequent relapse in the first year [64]. In a related study, Devanand and colleagues followed 235 patients with early AD using the Columbia University Scale for Psychopathology in AD for 5 years and discovered that psychotic symptoms were moderately persistent relative to agitation which was very persistent and mood symptoms which were mildly persistent [65]. By comparison, in DLB, visual hallucinations are more persistent, with 80% of individuals who have these symptoms continuing to experience them after 12 months [66]. Similarly, in late onset psychosis without dementia, the delusional beliefs are very persistent, with periods of resolution unlikely without antipsychotic therapy; treatment response is more likely to reduce severity rather than to achieve resolution.

The temporal onset of psychosis during the disease course should be considered in a definition. Persecutory delusions may manifest themselves early in the disease course whereas misidentifications generally emerge later as a part of a continuum [67]. Psychotic symptoms have been found to be less well documented in the later stages of dementia, as patients may become unable to express their delusions or hallucinations [3]. At the other end of the spectrum, psychotic symptoms of lesser severity may also occur in the absence of cognitive deficits in elderly people and may represent a prodromal phase of AD or other neurodegenerative dementia. It would be at least theoretically relevant to include differences in temporal onset of psychotic symptoms related to disease phase in the criteria for psychosis in AD.

Neurobiological studies

Imaging markers

None of the criteria discussed above make reference to disease-specific or psychosis-specific biomarkers. However, several studies have found abnormalities of neuroimaging biomarkers for dementia-related psychosis, including reduced gray matter volume on T1 weighted structural magnetic resonance imaging (MRI) [68–71], decreased cerebral blood flow on single photon emission computed tomography (SPECT) [72–74], and decreased metabolism on FDG-PET [75]. Several qualitative reviews have summarized these findings, noting significant heterogeneity, although in general findings have implicated the right frontal cortex [76–78]. A recent study has suggested that delusional AD patients may undergo more rapid grey matter volume loss in the temporal lobes prior to manifesting delusions and this may be preceded by an increase in grey matter in these same brain regions, raising the possibility of neuroplastic mechanisms [79]. The assumption that neuropsychiatric symptoms in dementia should reproducibly localize to a specific brain location has been challenging, and it has been proposed that lesions associated with delusions are distributed in different parts of the same functionally connected brain network [80]. Neurodegeneration in several different parts of the same functionally connected brain network, including the right frontal cortex, can lead to psychosis. Network localization may offer a method for accounting for the heterogeneity in neuroimaging biomarkers of psychosis among different patients.

Molecular imaging studies

Molecular imaging has been used to investigate changes to neurotransmitter systems in patients with dementia-related psychosis. A new medication targeting the serotonin 5HT-2A receptor, pimavanserin, has recently been approved for the treatment of psychosis in PD [81]. PD patients with hallucinations have increased serotonin 5HT-2A receptor binding in the ventral visual stream compared with PD patients without psychosis using the PET radioligand [F^{18}] setoperone [82]. Studies have shown decreased serotonin 5HT-2A receptors in AD but have not assessed the relationship of this to neuropsychiatric symptoms [83]. PD patients who go on to develop hallucinations have decreased dopamine transport activity in the ventral striatum at baseline [84]. One prior study found that dopamine D2/3 receptor binding relates to anti-psychotic efficacy in AD [85]. These preliminary studies suggest that neurotransmitter receptor imaging may be a useful approach to individualizing treatment approaches to psychosis in AD and to understanding the relationship of these symptoms with underlying dementia etiologies.

Genetic studies

Genetic studies suggest some overlap between AD with psychosis and schizophrenia [86, 87] and recent evidence has shown that the association between AD with psychosis and genetic liability for schizophrenia is strongest when analysis is restricted to individuals with delusions [88] suggesting common mechanisms of delusions as a central feature of psychosis across the lifespan. However, while potentially informative for refining clinical classifications, given the small amount of variance explained, this approach will not be useful for clinical prediction. Genetic studies suggest that psychosis in AD may be a partially heritable condition, with an estimated odds ratio of 3.2 among siblings presenting with dementia-related psychosis [89], a finding that has been replicated in multiple cohort studies [90]. It does not appear that *APOE4* mediates psychotic symptoms in AD patients [91], though more recent studies focused on analyses of post-mortem suggests a possible association [51].

Biomarker studies

There are limited studies investigating the relationship between *in vivo* neuropathological biomarkers and psychosis symptoms in dementia. Elevated total CSF tau levels have been reported in AD patients with psychosis versus AD patients without psychosis, although there were no differences in amyloid beta protein levels or phosphorylated tau levels [92]. Neuropathological studies additionally seem to support a role for phosphorylated tau in AD patients with psychosis, thus suggesting it may serve as a useful biomarker in future studies [93]. CSF biomarkers of amyloid and tau may also be useful in differentiating psychosis related to AD versus psychosis related to a psychiatric condition in older adults [94]. No prior studies have used amyloid or tau PET tracers to investigate regionally specific neuropathological markers of psychosis in dementia, though evidence linking psychosis in AD to phosphorylated tau suggests this may be a useful approach [61, 92, 93]. There is a suggested link of psychosis with vascular and Lewy body pathology based on postmortem data though replication with *in vivo* samples is required [95]. In summary, preliminary data suggest that biomarkers

of psychosis in AD may exist, and that pTau is a promising target for study. Future studies examining psychosis in AD should incorporate measures of tau as well as other biomarkers. To date there is no definitive biomarker based on existing evidence, thus limiting the utility of a biomarker-based approach. What may be more helpful would be an approach where biomarkers are evaluated in patients who present with psychotic symptoms in late life, to further ascertain whether symptoms are secondary to a neurodegenerative disorder versus a primary psychiatric illness.

Future directions

Neurobiological studies to date suggest that psychosis in AD and related dementias may be associated with distinct imaging, genetic, neuropathological, and CSF biomarkers. Notably, most of the neurobiological studies to date have focused on patients with established dementia given psychotic symptoms are much more rare in prodromal states and may be confused with primary psychiatric pathology. Further study of psychosis associated biomarkers in patients with prodromal conditions is clearly required.

Summary and next steps

We have reviewed the existing criteria for dementia related psychosis, including those published by Jeste and Finkel [3], Lyketsos [4], and the DSM-5 working group [5]. While all of these criteria have specific strengths and have substantially furthered our understanding of the relationship between psychosis and neurodegeneration, there are several issues that limit their utility. These limitations include: 1) the lack of symptom specificity, particularly in relation to psychotic symptoms observed in other primary psychiatric illnesses; 2) the inconsistent separation of hallucinations and delusions and differentiation of persecutory from misidentification delusions; 3) not framing psychotic symptoms in a natural history timeline thus underappreciating age of illness onset/phase of life, dementia stage, or symptom persistence and fluctuations; 4) not accounting for co-occurrent depression or agitation which might be the primary symptoms of the disturbance (with psychotic symptoms being secondary); 5) not incorporating prodromal or preclinical states; 6) and the absence of disease biomarkers in the criteria themselves (i.e., for patients with AD/MCI, are they biomarker positive). Moreover, with the exception of the Jeste and Finkel criteria [3], it is not clear to what extent these criteria have been employed in clinical drug trials. Future criteria should incorporate specific symptoms that are indicative of dementia related psychosis and allow for the possibility that psychosis may be an early symptom of an emerging neurocognitive disorder. These changes will result in more specific prevalence estimates for AD related psychosis, assist

Table 1
Dementia-related psychosis framework

1. Neurocognitive Disorder or Neurodegenerative Disease
Diagnosed by established criteria (e.g., National Institute on Aging (NIA)-Alzheimer's Association (AA) Research Diagnostic Framework for AD; NIA-AA diagnosis of Alzheimer's Dementia or MCI due to AD, DSM, International Working Group criteria for prodromal AD, etc.) Neurodegenerative disease may manifest with *either* clinical, neuroimaging, or biomarker findings.
a. Clinical: progressive deterioration of behavior or cognition by observation or history (as provided by a knowledgeable informant)
b. Neuroimaging findings suggesting neurodegeneration (e.g., MRI, PET)
c. Fluid biomarker positivity for relevant markers (e.g., amyloid, tau)
2. Stage of Neurodegenerative Disease
a. Preclinical disease (e.g., normal cognition, subjective cognitive decline, MBI-preclinical)
b. Prodromal disease (MCI, MBI-prodromal)
c. Dementia: i) mild, ii) moderate, or iii) severe
3. Psychotic Symptoms – Persisting, at Least Intermittently, for 4 Weeks Either i) Fluctuating or ii) Persistent
a. Delusions
i. persecutory or
ii. misidentification
iii other
b. Hallucinations
i. Code sensory modality (auditory, visual, etc.)
4. Exclusion Criteria
a. Psychotic symptoms better accounted for by non-neurodegenerative nervous system disease or medical conditions or Delirium
b. Psychotic symptoms better accounted for by a present primary psychiatric disorder
c. Psychotic symptoms better accounted for by an affective or agitation neuropsychiatric syndrome
d. Past history of psychotic symptoms

with research into the underlying disease mechanisms and provide a means of measuring the effectiveness of novel drug treatments where appropriate. We propose new research criteria that define a *psychotic phenotype of AD*, distinct from affective or agitation phenotypes of AD, which recognizes symptoms may precede the onset of clinical dementia and which address the gaps identified above. These criteria improve phenotypic classification of psychosis in AD, and advance the research agenda in the field to improve epidemiological, biomarker and genetics research in the field. These criteria serve as a complement to the provisional clinical criteria psychosis related to neurocognitive disorders recently developed by the IPA, which are pan-diagnostic from a neurocognitive disorder perspective, and have been developed with input from clinicians and caregivers to assist in detection, treatment and for use in clinical trials of both nonpharmacological and pharmacological interventions to assist in the development of drugs and other interventions to reduce symptoms and distress.

We propose our criteria in Table 1. The recommended framework incorporates the strengths of current criteria, addresses the weaknesses identified in this review, and incorporates recent advances in our understanding of psychosis in AD and related dementias. These criteria complement the IPA criteria, in that they formally include preclinical and prodromal AD. In addition, these criteria focus on biomarkers and foster genetic research via clear exclusion criteria for case definitions. This foundational work can inform future research and further exploration of psychosis in AD and related dementias by capturing salient illness features that can be missed in current nosological approaches.

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REFERENCES

[1] Murray PS, Kumar S, Demichele-Sweet MA, Sweet RA (2014) Psychosis in Alzheimer's disease. *Biol Psychiatry* **75**, 542-552.

[2] Ropacki SA, Jeste DV (2005) Epidemiology of and risk factors for psychosis of Alzheimer's disease: A review of 55 studies published from 1990 to 2003. *Am J Psychiatry* **162**, 2022-2030.

[3] Jeste DV, Finkel SI (2000) Psychosis of Alzheimer's disease and related dementias. Diagnostic criteria for a distinct syndrome. *Am J Geriatr Psychiatry* **8**, 29-34.

[4] Lyketsos CG, Breitner JC, Rabins PV (2001) An evidence-based proposal for the classification of neuropsychiatric disturbance in Alzheimer's disease. *Int J Geriatr Psychiatry* **16**, 1037-1042.

[5] American Psychiatric Association (3013) *Diagnostic and statistical manual of mental disorders: DSM-5*. American Psychiatric Association, Washington, DC.

[6] Emanuel JE, Lopez OL, Houck PR, Becker JT, Weamer EA, Demichele-Sweet MA, Kuller L, Sweet RA (2011) Trajectory of cognitive decline as a predictor of psychosis in early Alzheimer disease in the cardiovascular health study. *Am J Geriatr Psychiatry* **19**, 160-168.

[7] Connors MH, Ames D, Woodward M, Brodaty H (2018) Psychosis and clinical outcomes in Alzheimer disease: A longitudinal study. *Am J Geriatr Psychiatry* **26**, 304-313.

[8] Bassiony MM, Steinberg MS, Warren A, Rosenblatt A, Baker AS, Lyketsos CG (2000) Delusions and hallucinations in Alzheimer's disease: Prevalence and clinical correlates. *Int J Geriatr Psychiatry* **15**, 99-107.

[9] Scarmeas N, Brandt J, Albert M, Hadjigeorgiou G, Papadimitriou A, Dubois B, Sarazin M, Devanand D, Honig L, Marder K, Bell K, Wegesin D, Blacker D, Stern Y (2005) Delusions and hallucinations are associated with worse outcome in Alzheimer disease. *Arch Neurol* **62**, 1601-1608.

[10] Wilson RSTY, Aggarwal NT, Gilley DW, Mccann JJ, Bienias JL, Evans DA (2006) Hallucinations, cognitive decline, and death in Alzheimer's disease. *Neuroepidemiology* **26**, 68-75.

[11] Poirier A, Voyer P, Légaré F, Morin M, Witteman HO, Kröger E, Martineau B, Rodríguez C, Giguere AM (2017) Caring for seniors living with dementia means caring for their caregivers too. *Can J Public Health* **108**, e639-e642.

[12] Fischer CE, Sweet RA (2016) Psychosis in Alzheimer's disease: A review of recent research findings. *Curr Behav Neurosci Rep* **3**, 308-317.

[13] Peters ME, Schwartz S, Han D, Rabins PV, Steinberg M, Tschanz JT, Lyketsos CG (2015) Neuropsychiatric symptoms as predictors of progression to severe Alzheimer's dementia and death: The Cache County Dementia Progression Study. *Am J Psychiatry* **172**, 460-465.

[14] Fischer CE, Aguera-Ortiz L (2018) Psychosis and dementia: Risk factor, prodrome, or cause? *Int Psychogeriatr* **30**, 209-219.

[15] Porsteinsson AP, Drye LT, Pollock BG, Devanand DP, Frangakis C, Ismail Z, Marano C, Meinert CL, Mintzer JE, Munro CA, Pelton G, Rabins PV, Rosenberg PB, Schneider LS, Shade DM, Weintraub D, Yesavage J, Lyketsos CG, CitAD Research Group (2014) Effect of citalopram on agitation in Alzheimer disease: The CitAD randomized clinical trial. *JAMA* **311**, 682-691.

[16] Ribe AR, Laursen TM, Charles M, Katon W, Fenger-Gron M, Davydow D, Chwastiak L, Cerimele JM, Vestergaard M (2015) Long-term risk of dementia in persons with

schizophrenia: A Danish population-based cohort study. *JAMA Psychiatry* **72**, 1095-1101.

[17] Ku H, Lee EK, Lee KU, Lee MY, Kwon JW (2016) Higher prevalence of dementia in patients with schizophrenia: A nationwide population-based study. *Asia Pac Psychiatry* **8**, 145-153.

[18] Purohit DP, Perl DP, Haroutunian V, Powchik P, Davidson M, Davis KL (1998) Alzheimer disease and related neurodegenerative diseases in elderly patients with schizophrenia: A postmortem neuropathologic study of 100 cases. *Arch Gen Psychiatry* **55**, 205-211.

[19] Heaton RK, Gladsjo JA, Palmer BW, Kuck J, Marcotte TD, Jeste DV (2001) Stability and course of neuropsychological deficits in schizophrenia. *Arch Gen Psychiatry* **58**, 24-32.

[20] Jeste DV, Wolkowitz OM, Palmer BW (2011) Divergent trajectories of physical, cognitive, and psychosocial aging in schizophrenia. *Schizophr Bull* **37**, 451-455.

[21] Ting C, Rajji TK, Ismail Z, Tang-Wai DF, Apanasiewicz N, Miranda D, Mamo D, Mulsant BH (2010) Differentiating the cognitive profile of schizophrenia from that of Alzheimer disease and depression in late life. *PLoS One* **5**, e10151.

[22] Drange OK, Smeland OB, Shadrin AA, Finseth PI, Witoelar A, Frei O, Psychiatric Genomics Consortium Bipolar Disorder Working Group, Wang Y, Hassani S, Djurovic S, Dale AM, Andreassen OA (2019) Genetic overlap between Alzheimer's disease and bipolar disorder implicates the MARK2 and VAC14 genes. *Front Neurosci* **13**, 220.

[23] Wu KY, Chang CM, Liang HY, Wu CS, Chia-Hsuan Wu E, Chen CH, Chau YL, Tsai HJ (2013) Increased risk of developing dementia in patients with bipolar disorder: A nested matched case-control study. *Bipolar Disord* **15**, 787-794.

[24] Almeida OP, McCaul K, Hankey GJ, Yeap BB, Golledge J, Flicker L (2016) Risk of dementia and death in community-dwelling older men with bipolar disorder. *Br J Psychiatry* **209**, 121-126.

[25] Diniz BS, Teixeira AL, Cao F, Gildengers A, Soares JC, Butters MA, Reynolds CF, 3rd (2017) History of bipolar disorder and the risk of dementia: A systematic review and meta-analysis. *Am J Geriatr Psychiatry* **25**, 357-362.

[26] Ismail Z, Gatchel J, Bateman DR, Barcelos-Ferreira R, Chantillon M, Jaeger J, Donovan NJ, Mortby ME (2018) Affective and emotional dysregulation as pre-dementia risk markers: Exploring the mild behavioral impairment symptoms of depression, anxiety, irritability, and euphoria. *Int Psychogeriatr* **30**, 185-196.

[27] Fischer CE, Ting WK, Millikin CP, Ismail Z, Schweizer TA, Alzheimer Disease Neuroimaging Initiative (2016) Gray matter atrophy in patients with mild cognitive impairment/Alzheimer's disease over the course of developing delusions. *Int J Geriatr Psychiatry* **31**, 76-82.

[28] Fischer CE, Qian W, Schweizer TA, Ismail Z, Smith EE, Millikin CP, Munoz DG (2017) Determining the impact of psychosis on rates of false-positive and false-negative diagnosis in Alzheimer's disease. *Alzheimers Dement (N Y)* **3**, 385-392.

[29] Geda YE, Schneider LS, Gitlin LN, Miller DS, Smith GS, Bell J, Evans J, Lee M, Porsteinsson A, Lanctôt KL (2013) Neuropsychiatric symptoms in Alzheimer's disease: Past progress and anticipation of the future. *Alzheimers Dement* **9**, 602-608.

[30] Jack CR Jr, Bennett DA, Blennow K, Carrillo MC, Dunn B, Haeberlein SB, Holtzman DM, Jagust W, Jessen F, Karlawish J, Liu E, Molinuevo JL, Montine T, Phelps C, Rankin KP, Rowe CC, Scheltens P, Siemers E, Snyder HM, Sperling R, Contributors (2018) NIA-AA Research Framework: Toward a biological definition of Alzheimer's disease. *Alzheimers Dement* **14**, 535-562.

[31] Ismail Z, Smith EE, Geda Y, Sultzer D, Brodaty H, Smith G, Aguera-Ortiz L, Sweet R, Miller D, Lyketsos CG, ISTAART Neuropsychiatric Symptoms Professional Interest Area (2016) Neuropsychiatric symptoms as early manifestations of emergent dementia: Provisional diagnostic criteria for mild behavioral impairment. *Alzheimers Dement* **12**, 195-202.

[32] American Psychiatric Association (1994) *Diagnostic Criteria From DSM-IV*, American Psychiatric Association, Washington, DC.

[33] Ismail Z, Nguyen MQ, Fischer CE, Schweizer TA, Mulsant BH, Mamo D (2011) Neurobiology of delusions in Alzheimer's disease. *Curr Psychiatry Rep* **13**, 211-218.

[34] Schneider LS, Katz IR, Park S, Napolitano J, Martinez RA, Azen SP (2003) Psychosis of Alzheimer disease: Validity of the construct and response to risperidone. *Am J Geriatr Psychiatry* **11**, 414-425.

[35] Laughren T, Gordon M (2000) *FDA background on Zeldox (ziprasidone hydrochloride capsules)*. Pfizer, Inc. Psychopharmacological Drugs Advisory Committee. July 19, 2000.

[36] Lyketsos CG, Lopez O, Jones B, Fitzpatrick AL, Breitner J, DeKosky S (2002) Prevalence of neuropsychiatric symptoms in dementia and mild cognitive impairment: Results from the cardiovascular health study. *JAMA* **288**, 1475-1483.

[37] Van der Mussele S, Mariën P, Saerens J, Somers N, Goeman J, De Deyn PP, Engelborghs S (2015) Psychosis associated behavioral and psychological signs and symptoms in mild cognitive impairment and Alzheimer's dementia. *Aging Ment Health* **19**, 818-828.

[38] Chan DC, Kasper JD, Black BS, Rabins PV (2003) Prevalence and correlates of behavioral and psychiatric symptoms in community-dwelling elders with dementia or mild cognitive impairment: The Memory and Medical Care Study. *Int J Geriatr Psychiatr* **18**, 174-182.

[39] Gallagher D, Fischer CE, Iaboni A (2017) Neuropsychiatric symptoms in mild cognitive impairment: An update on prevalence, mechanisms, and clinical significance. *Can J Psychiatry* **62**, 161-169.

[40] Dietlin S, Soto M, Kiyasova V, Pueyo M, de Mauleon A, Delrieu J, Ousset PJ, Vellas B (2019) Neuropsychiatric symptoms and risk of progression to Alzheimer's disease among mild cognitive impairment subjects. *J Alzheimers Dis* **70**, 25-34.

[41] Lyketsos CG, Sheppard JM, Steinberg M, Tschanz JA, Norton MC, Steffens DC, Breitner JC (2001) Neuropsychiatric disturbance in Alzheimer's disease clusters into three groups: The Cache County study. *Int J Geriatr Psychiatry* **16**, 1043-1053.

[42] Ismail Z, Emeremni CA, Houck PR, Mazumdar S, Rosen J, Rajji TK, Pollock BG, Mulsant BH (2013) A comparison of the E-BEHAVE-AD, NBRS, and NPI in quantifying clinical improvement in treatment of agitation and psychosis associated with dementia. *Am J Geriatr Psychiatry* **21**, 78-87.

[43] Lopez OL, Becker JT, Sweet RA (2005) Non-cognitive symptoms in mild cognitive impairment subjects. *Neurocase* **11**, 65-71.

[44] Geda YE, Smith GE, Knopman DS, Boeve BF, Tangalos EG, Ivnik RJ, Mrazek DA, Edland SD, Petersen RC (2004)

De novo genesis of neuropsychiatric symptoms in mild cognitive impairment (MCI). *Int Psychogeriatr* **16**, 51-60.

[45] Kotrla KJ, Chacko RC, Harper RG, Doody R (1995) Clinical variables associated with psychosis in Alzheimer's disease. *Am J Psychiatry* **152**, 1377-1379.

[46] Cook SE, Miyahara S, Bacanu S-A, Perez-Madriñan G, Lopez OL, Kaufer DI, Nimgaonkar VL, Wisniewski SR, DeKosky ST, Sweet RA (2003) Psychotic symptoms in Alzheimer disease: Evidence for subtypes. *Am J Geriatr Psychiatry* **11**, 406-413.

[47] Qian W, Fischer CE, Schweizer TA, Munoz DG (2018) Association between psychosis phenotype and APOE genotype on the clinical profiles of Alzheimer's disease. *Curr Alzheimer Res* **15**, 187-194.

[48] Howard R, Rabins PV, Seeman MV, Jeste DV (2000) Late-onset schizophrenia and very-late-onset schizophrenia-like psychosis: An international consensus. The International Late-Onset Schizophrenia Group. *Am J Psychiatry* **157**, 172-178.

[49] Leroi I, Voulgari A, Breitner JC, Lyketsos CG (2003) The epidemiology of psychosis in dementia. *Am J Geriatr Psychiatry* **11**, 83-91.

[50] Kim J, Schweizer TA, Fischer CE, Munoz DG (2018) Psychosis in "cognitively asymptomatic" elderly subjects is associated with neuritic plaque load, not neurofibrillary tangles. *Alzheimer Dis Assoc Disord* **32**, 185-189.

[51] Ballard C, McKeith I, Harrison R, Obrien J, Thompson P, Lowery K, Perry R, Ince P (1997) A detailed phenomenological comparison of complex visual hallucinations in dementia with Lewy bodies and Alzheimer's disease. *Int Psychogeriatr* **9**, 381-388.

[52] Ffytche DH, Pereira JB, Ballard C, Chaudhuri KR, Weintraub D, Aarsland D (2017) Risk factors for early psychosis in PD: Insights from the Parkinson's progression markers initiative. *J Neurol Neurosurg Psychiatry* **88**, 325-331.

[53] Erskine D, Taylor JP, Thomas A, Collerton D, McKeith I, Khundakar A, Attems J, Morris C (2019) Pathological changes to the subcortical visual system and its relationship to visual hallucinations in dementia with Lewy bodies. *Neurosci Bull* **35**, 295-300.

[54] McKeith IG, Boeve BF, Dickson DW, Halliday G, Taylor JP, Weintraub D, Aarsland D, Galvin J, Attems J, Ballard CG, Bayston A, Beach TG, Blanc F, Bohnen N, Bonanni L, Bras J, Brundin P, Burn D, Chen-Plotkin A, Duda JE, El-Agnaf O, Feldman H, Ferman TJ, Ffytche D, Fujishiro H, Galasko D, Goldman JG, Gomperts SN, Graff-Radford NR, Honig LS, Iranzo A, Kantarci K, Kaufer D, Kukull W, Lee VMY, Leverenz JB, Lewis S, Lippa C, Lunde A, Masellis M, Masliah E, McLean P, Mollenhauer B, Montine TJ, Moreno E, Mori E, Murray M, O'Brien JT, Orimo S, Postuma RB, Ramaswamy S, Ross OA, Salmon DP, Singleton A, Taylor A, Thomas A, Tiraboschi P, Toledo JB, Trojanowski JQ, Tsuang D, Walker Z, Yamada M, Kosaka K (2017) Diagnosis and management of dementia with Lewy bodies: Fourth consensus report of the DLB Consortium. *Neurology* **89**, 88-100.

[55] Ducharme S, Bajestan S, Dickerson BC, Voon V (2017) Psychiatric presentations of C9orf72 mutation: What are the diagnostic implications for clinicians? *J Neuropsychiatry Clin Neurosci* **29**, 195-205.

[56] Devenney EM, Ahmed RM, Halliday G, Piguet O, Kiernan MC, Hodges JR (2018) Psychiatric disorders in C9orf72 kindreds: Study of 1,414 family members. *Neurology* **91**, e1498-e1507.

[57] Togo T, Isojima D, Akatsu H, Suzuki K, Uchikado H, Katsuse O, Iseki E, Kosaka K, Hirayasu Y (2005) Clinical features of argyrophilic grain disease: A retrospective survey of cases with neuropsychiatric symptoms. *Am J Geriatr Psychiatry* **13**, 1083-1091.

[58] Förstl H, Burns A, Levy R, Cairns N (1994) Neuropathological correlates of psychotic phenomena in confirmed Alzheimer's disease. *Br J Psychiatry* **165**, 53-59.

[59] Waters F, Collerton D, Ffytche DH, Jardri R, Pins D, Dudley R, Blom JD, Mosimann UP, Eperjesi F, Ford S, Laroi F (2014) Visual hallucinations in the psychosis spectrum and comparative information from neurodegenerative disorders and eye disease. *Schizophr Bull* **40 Suppl 4**, S233-245.

[60] Cohen CI, Meesters PD, Zhao J (2015) New perspectives on schizophrenia in later life: Implications for treatment, policy, and research. *Lancet Psychiatry* **2**, 340-350.

[61] Seppälä TT, Louhija UM, Appelberg B, Herukka SK, Juva K (2014) Comparison between clinical diagnosis and CSF biomarkers of Alzheimer disease in elderly patients with late onset psychosis: Helsinki old age psychosis study (HOPS). *Am J Geriatr Psychiatry* **22**, 908-916.

[62] Vilalta-Franch J, Lopez-Pousa S, Calvo-Perxas L, Garre-Olmo J (2013) Psychosis of Alzheimer disease: Prevalence, incidence, persistence, risk factors, and mortality. *Am J Geriatr Psychiatry* **21**, 1135-1143.

[63] Haupt M, Kurz A, Jänner M (2000) A 2-year follow-up of behavioural and psychological symptoms in Alzheimer's disease. *Dement Geriatr Cogn Disord* **11**, 147-152.

[64] Ballard CGSK, Patel A, Gahir M, Solis M, Coope B, Wilcock G (1995) The prevalence and phenomenology of psychotic symptoms in dementia sufferers. *Int J Geriatr Psychiatr* **10**, 477-485.

[65] Devanand DP, Jacobs DM, Tang MX, Del Castillo-Castaneda C, Sano M, Marder K, Bell K, Bylsma FW, Brandt J, Albert M, Stern Y (1997) The course of psychopathologic features in mild to moderate Alzheimer disease. *Arch Gen Psychiatry* **54**, 257-263.

[66] Ballard CG, O'Brien JT, Swann AG, Thompson P, Neill D, McKeith IG (2001) The natural history of psychosis and depression in dementia with Lewy bodies and Alzheimer's disease: Persistence and new cases over 1 year of follow-up. *J Clin Psychiatry* **62**, 46-49.

[67] Reeves SJ, Gould RL, Powell JF, Howard RJ (2012) Origins of delusions in Alzheimer's disease. *Neurosci Biobehav Rev* **36**, 2274-2287.

[68] Bruen PD, McGeown WJ, Shanks MF, Venneri A (2008) Neuroanatomical correlates of neuropsychiatric symptoms in Alzheimer's disease. *Brain* **131**, 2455-2463.

[69] Lee YM, Chung YI, Park JM, Lee BD, Moon E, Jeong HJ, Kim JH, Kim HJ, Mun CW, Kim TH, Kim YH, Kim EJ (2016) Decreased gray matter volume is associated with the subtypes of psychotic symptoms in patients with antipsychotic-naive mild or moderate Alzheimer's disease: A voxel-based morphometry study. *Psychiatry Res Neuroimaging* **249**, 45-51.

[70] Nakaaki S, Sato J, Torii K, Oka M, Negi A, Nakamae T, Narumoto J, Miyata J, Furukawa TA, Mimura M (2013) Neuroanatomical abnormalities before onset of delusions in patients with Alzheimer's disease: A voxel-based morphometry study. *Neuropsychiatr Dis Treat* **9**, 1-8.

[71] Serra L, Perri R, Cercignani M, Spano B, Fadda L, Marra C, Carlesimo GA, Caltagirone C, Bozzali M (2010) Are the behavioral symptoms of Alzheimer's disease directly associated with neurodegeneration? *J Alzheimers Dis* **21**, 627-639.

[72] Matsuoka T, Narumoto J, Shibata K, Okamura A, Nakamura K, Okuyama C, Nishimura T, Fukui K (2010) Insular hypoperfusion correlates with the severity of delusions in individuals with Alzheimer's disease. *Dement Geriatr Cogn Disord* **29**, 287-293.

[73] Moran EK, Becker JA, Satlin A, Lyoo IK, Fischman AJ, Johnson KA (2008) Psychosis of Alzheimer's disease: Gender differences in regional perfusion. *Neurobiol Aging* **29**, 1218-1225.

[74] Nakatsuka M, Meguro K, Tsuboi H, Nakamura K, Akanuma K, Yamaguchi S (2013) Content of delusional thoughts in Alzheimer's disease and assessment of content-specific brain dysfunctions with BEHAVE-AD-FW and SPECT. *Int Psychogeriatr* **25**, 939-948.

[75] Sultzer DL, Leskin LP, Melrose RJ, Harwood DG, Narvaez TA, Ando TK, Mandelkern MA (2014) Neurobiology of delusions, memory, and insight in Alzheimer disease. *Am J Geriatr Psychiatry* **22**, 1346-1355.

[76] Ismail Z, Nguyen MQ, Fischer CE, Schweizer TA, Mulsant BH (2012) Neuroimaging of delusions in Alzheimer's disease. *Psychiatry Res* **202**, 89-95.

[77] Jellinger KA (2012) Cerebral correlates of psychotic syndromes in neurodegenerative diseases. *J Cell Mol Med* **16**, 995-1012.

[78] Rosenberg PB, Nowrangi MA, Lyketsos CG (2015) Neuropsychiatric symptoms in Alzheimer's disease: What might be associated brain circuits? *Mol Aspects Med* **43-44**, 25-37.

[79] Qian W, Schweizer TA, Churchill NW, Millikin C, Ismail Z, Smith EE5 Lix LM, Munoz DG, Barfett JJ, Rajji TK, Fischer CE (2018) Grey matter changes associated with the development of delusions in Alzheimer's disease. *Am J Geriatr Psychiatry* **27**, 490-498.

[80] Darby RR, Joutsa J, Fox MD (2019) Network localization of heterogeneous neuroimaging findings. *Brain* **142**, 70-79.

[81] Cummings J, Isaacson S, Mills R, Williams H, Chi-Burris K, Corbett A, Dhall R, Ballard C (2014) Pimavanserin for patients with Parkinson's disease psychosis: A randomised, placebo-controlled phase 3 trial. *Lancet* **383**, 533-540.

[82] Ballanger B, Strafella AP, van Eimeren T, Zurowski M, Rusjan PM, Houle S, Fox SH (2010) Serotonin 2A receptors and visual hallucinations in Parkinson disease. *Arch Neurol* **67**, 416-421.

[83] Blin J, Baron JC, Dubois B, Crouzel C, Fiorelli M, Attar-Lévy D, Pillon B, Fournier D, Vidailhet M, Agid Y (1993) Loss of brain 5-HT2 receptors in Alzheimer's disease In vivo assessment with positron emission tomography and [18F]setoperone. *Brain* **116**, 497-510.

[84] Jaakkola E, Joutsa J, Makinen E, Johansson J, Kaasinen V (2017) Ventral striatal dopaminergic defect is associated with hallucinations in Parkinson's disease. *Eur J Neurol* **24**, 1341-1347.

[85] Reeves S, McLachlan E, Bertrand J, Antonio FD, Brownings S, Nair A, Greaves S, Smith A, Taylor D, Dunn J, Marsden P, Kessler R, Howard R (2017) Therapeutic window of dopamine D2/3 receptor occupancy to treat psychosis in Alzheimer's disease. *Brain* **140**, 1117-1127.

[86] Zheng XDF, Barmada MM, Richardson GA, Lopez OL, Sweet RA (2014) A rare duplication on chromosome 16p11.2 is identified in patients with psychosis in Alzheimer's disease. *PLoS One* **9**, e111462.

[87] Hollingworth P, Hamshere ML, Holmans PA, O'Donovan MC, Sims R, Powell J, Lovestone S, Myers A, DeVrieze FW, Hardy J, Goate A, Owen M, Williams J (2007) Increased familial risk and genomewide significant linkage for Alzheimer's disease with psychosis. *Am J Med Genet B Neuropsychiatr Genet* **144B**, 841-848.

[88] Creese B, Vassos E, Bergh S, Athanasiu L, Johar I, Rongve A, Medbøen IT, Vasconcelos Da Silva M, Aakhus E, Andersen F, Bettella F, Braekhus A, Djurovic S, Paroni G, Proitsi P, Saltvedt I, Seripa D, Stordal E, Fladby T, Aarsland D, Andreassen OA, Ballard C, Selbaek G AddNeuroMed consortium and the Alzheimer's Disease Neuroimaging Initiative (2019) Examining the association between genetic liability for schizophrenia and psychotic symptoms in Alzheimer's disease. *Transl Psychiatry* **9**, 273.

[89] Sweet RA, Nimgaonkar VL, Devlin B, Lopez OL, DeKosky ST (2002) Increased familial risk of the psychotic phenotype of Alzheimer disease. *Neurology* **58**, 907-911.

[90] Sweet RA, Bennett DA, Graff-Radford NR, Mayeux R, National institute on aging late-onset Alzheimer's disease family study group (2010) Assessment and familial aggregation of psychosis in Alzheimer's disease from the National Institute on Aging Late Onset Alzheimer's Disease Family Study. *Brain* **133**, 1155-1162.

[91] DeMichele-Sweet MA, Sweet RA (2010) Genetics of psychosis in Alzheimer's disease: A review. *J Alzheimers Dis* **19**, 761-780.

[92] Koppel J, Sunday S, Buthorn J, Goldberg T, Davies P, Greenwald B, Alzheimer's Disease Neuroimaging Initiative (2013) Elevated CSF Tau is associated with psychosis in Alzheimer's disease. *Am J Psychiatry* **170**, 1212-1213.

[93] Krivinko JM, Erickson SL, Ding Y, Sun Z, Penzes P, MacDonald ML, Yates NA, Ikonomovic MD, Lopez OL, Sweet RA, Kofler J (2019) Synaptic proteome compensation and resilience to psychosis in Alzheimer's disease. *Am J Psychiatry* **175**, 999-1009.

[94] Paquet C, Magnin E, Wallon D, Troussiere AC, Dumurgier J, Jager A, Bellivier F, Bouaziz-Amar E, Blanc F, Beaufils E, Miguet-Alfonsi C, Quillard M, Schraen S, Pasquier F, Hannequin D, Robert P, Hugon J, Mouton-Liger F, For ePLM network and collaborators (2016) Utility of CSF biomarkers in psychiatric disorders: A national multicentre prospective study. *Alzheimers Res Ther* **8**, 27.

[95] Fischer CE, Qian W, Schweizer TA, Millikin CP, Ismail Z, Smith EE, Lix LM, Shelton P, Munoz DG (2016) Lewy bodies, vascular risk factors, and subcortical arteriosclerotic leukoencephalopathy, but not Alzheimer pathology, are associated with development of psychosis in Alzheimer's disease. *J Alzheimers Dis* **50**, 283-295.