# Neuropsychiatric symptoms in Alzheimer's disease: Past progress and anticipation of the future

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**Abstract**        Neuropsychiatric symptoms (NPS) in Alzheimer's disease (AD) are widespread and disabling. This has been known since Dr. Alois Alzheimer's first case, Frau Auguste D., presented with emotional distress and delusions of infidelity/excessive jealousy, followed by cognitive symptoms. Being cognizant of this, in 2010 the Alzheimer's Association convened a research roundtable on the topic of NPS in AD. A major outcome of the roundtable was the founding of a Professional Interest Area (PIA) within the International Society to Advance Alzheimer's Research and Treatment (ISTAART). The NPS-PIA has prepared a series of documents that are intended to summarize the literature and provide more detailed specific recommendations for NPS research. This overview paper is the first of these living documents that will be updated periodically as the science advances. The overview is followed by syndrome-specific synthetic reviews and recommendations prepared by NPS-PIA workgroups on depression, apathy, sleep, agitation, and psychosis.
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## 1. Introduction

At the advent of the 21st century, *Neurology* and *American Journal of Psychiatry*, the official journals of the American Academy of Neurology and the American Psychiatric Association, respectively, reviewed the past and anticipated the future of neurology and psychiatry [1,2]. Both journals eloquently indicated that the history of Alzheimer's disease (AD) is a history of neuropsychiatry. Alois Alzheimer, Emil Kraepelin, and other prominent neuropsychiatrists were keen to understand brain changes underlying mental illness [2].

It was at that historical moment that Alzheimer described the clinical manifestations and subsequent classic neuropathological features of what was later known as AD. Alzheimer's first case, Frau Auguste D., presented with emotional distress and delusions of infidelity/excessive jealousy. She developed subsequently developed memory, visuospatial, and language problems [3]. Autopsy revealed what later became known as "the classic AD pathology" (neuritic plaques, neurofibrillary tangles, and neuronal loss). Thus, the search for the physical basis of mental illness led to the discovery of AD pathology, and the other byproduct of this effort was the genesis of the field of neuropathology [1,2].

Over the last 100 years, mankind has acquired substantial scientific knowledge about AD. Part of this success is attributable to having reliable criteria to define dementia, including dementia of Alzheimer's type (DAT). The American Psychiatric Association's *Diagnostic and Statistical Manual IV* (DSM-IV) diagnostic criteria for dementia [4] and the National Institute of Neurological and Communicative Disorders and Stroke and Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria for AD [5] are widely used in research and clinical settings. Although these criteria have excellent correlation with neuropathological changes on postmortem examination [6], investigators, particularly clinical trialists in the field of AD, later advocated for biomarker-based diagnostic criteria for AD and related disorders [7]. A recent initiative of the National Institute on Aging along with the Alzheimer's Association (NIA-AA) developed new diagnostic criteria. The NIA-AA task force classified AD into three phases: preclinical phase (research category) [8], mild cognitive impairment (MCI) due to AD [9], and dementia due to AD [10]. The preclinical criteria are based on brain imaging and biomarkers [8], although the validity of AD biomarkers has yet to be established [6]. The clinical phases (i.e., MCI due to AD [9] and dementia due to AD [10]) are primarily defined by using cognitive signs and symptoms in combination with biomarkers.

Although AD is well known to cause cognitive symptoms, advances in neuroscience have established that there are extensive and reciprocal neuronal connections between the epicenters of emotions and cognitions [11]. Thus, it should be no surprise that the manifestations of AD are not limited to cognitive symptoms; rather, they include a range of neuropsychiatric symptoms (NPS) of AD. The near universal prevalence of NPS in AD, combined with the serious and disabling effects they have on patients and caregivers [12], has focused significant recent attention on the fact that few effective and safe treatments exist [12].

In an effort to address this major gap, the Alzheimer's Association convened a 2010 research roundtable on the topic of NPS in AD [12]. A major outcome of the roundtable was the founding of the Neuropsychiatric Syndromes of AD Professional Interest Area (NPS-PIA) of the International Society to Advance Alzheimer's Research and Treatment (ISTAART), composed of a large international group of scientists, clinicians, and educators. NPS-PIA has as its mission to educate the broader AD field on this area and to stimulate

treatment development for NPS. The NPS-PIA has provided summary recommendations as part of the effort to develop a national strategic plan as called upon by the National Alzheimer's Project Act (NAPA) for AD [12]. The NPS-PIA is now creating a series of documents that are intended to summarize the literature and provide more detailed, specific recommendations for NPS research. This overview paper is the first of these living documents that will be updated periodically as the science advances.

The NPS-PIA made the choice to organize itself around five syndromic areas. NPS-PIA workgroups in each have prepared syndrome-specific reviews and recommendations presented as online appendices (in decreasing order of crude prevalence rates): depression (Appendix A), apathy (Appendix B), sleep (Appendix C), agitation (Appendix D), and psychosis (Appendix E). This approach is intended to reflect the evidence that NPS tend to cluster into distinct groups [13] and that treatment development through neurobiological understanding might be more effective using this approach. However, it is well recognized that these syndromes overlap with one another; therefore, this approach is only a starting point that may evolve over time. This paper will review key background theories and research pertaining to the neuropsychiatry of AD.

## 2. Measurement of NPS

Treatment development is anchored upon accurate measurement of NPS in AD. In the past few decades, several approaches have been used to measure NPS in the context of AD. These measurements are primarily performed by using scales that target individual symptoms/syndromes such as depression [14], apathy [15], agitation [16], or psychosis [17] as well as scales that measure multiple symptoms. The latter include the following: Behavior Rating Scale for Dementia of the Consortium to Establish a Registry for Alzheimer's Disease [18,19], Brief Psychiatric Rating Scale [20], the Psychogeriatric Dependency Rating Scale [21], Multidimensional Observation Scale for Elderly Subjects [22], the Revised Memory and Behavior Problems Checklist [23], and the Neuropsychiatric Inventory (NPI) [24]. The NPI, the most commonly used scale [25], measures 12 emotional behaviors, and data are collected from an informant, typically a close family member. In addition to measuring the psychopathology of AD, the NPI has also been widely used in clinical trials [26–30].

The NPI catalyzed neuropsychiatric research in AD. Its initial use mainly focused on clinical samples [31]. However, one limitation of clinical samples is the potential for referral bias leading to exaggerated frequency estimates [32,33]. Therefore, population-based studies were needed to investigate NPS in AD and related disorders. In the United States, the first population-based effort that examined NPS in AD by using NPI was the Cache County study [13]. In subsequent population-based studies, the investigation of NPS was further extended to persons with MCI and com-

pared to cognitively normal persons [34,35]. These studies showed that depression, apathy, irritability, and other NPS are common in normal cognitive aging and MCI [34,35]. Investigators abroad similarly reported that NPS is common in AD and related disorders [36].

Although the development and wide application of the NPI and the briefer version, the Neuropsychiatric Inventory Questionnaire (NPI-Q) [37], have proven to be useful in the field of aging and AD [38], investigators continue to be concerned about the limitation of collecting data only from the informant. This concern was made explicit by a consensus paper published by an expert panel convened by the Alzheimer's Association in collaboration with the leaders in academia and industry [25]. The panel indicated that NPI is the most widely used scale to measure NPS in AD and further raised a crucial question, "Why have drugs for neuropsychiatric symptoms not fared so well?" and suggested a possible explanation, "Perhaps the wrong symptoms are being targeted" [25]. The expert panel called for the development of a clinician-rated comprehensive evaluation of NPS in AD [25]. Indeed, a year later, an international team of investigators published a validated scale known as the Neuropsychiatric Inventory-Clinician rating scale (NPI-C) [39]. The NPI-C uses the LEAD standard (longitudinal evaluation performed by an expert, using all data available) [40] and thus collects data from the patient and the informant. In the NPI-C, the clinician examines the patient in addition to interviewing the caregiver and makes clinical judgments about the occurrence and severity of a range of individual NPS. The NPI-C capitalized on the strength of NPI/NPI-Q and at the same time rectified one of the weaknesses [39], which was over-reliance on proxy report. If we assume that we are able to accurately measure NPS in AD, then the next key step is identifying a coherent and plausible neurobiological model as we strive to develop new treatment modalities for NPS in AD.

## 3. The neurobiology of NPS in AD

One of the crucial challenges to the field is elucidating the neurobiological underpinnings of NPS in AD. There are historical examples from related disciplines. The time-honored lesion method demonstrated that left-sided stroke is associated with depression [41]. Additionally, investigations in late-life depression have proposed that white matter lesions may disrupt the frontal-subcortical pathways involved in the regulation of mood [42,43]. The investigation of the neurobiological substrates of NPS in AD has pursued a similar path of correlating symptoms with postmortem lesions [44] and using neuroimaging technologies.

## 4. A sound theoretical model is crucial to understand the neurobiology of NPS in AD

The preamble to neurobiological research is having a coherent model informed by years of empirical research. The advances made in neuroscience over the last 2 decades

have paved the way to develop more sound theoretical models that inform the neurobiological underpinnings of NPS in AD. The three major neurobiological models relevant to NPS in AD are the frontal-subcortical circuits [45,46], cortico-cortical networks [11], and the monoaminergic system [47].

### 4.1. Frontal-subcortical circuits

Geschwind's pioneering work on disconnection syndrome inspired models that were based on networks and circuits [48]. NPS such as disinhibition or apathy can be observed based on lesions far from the frontal cortex via involvement of a crucial structure in a circuit mediating a particular behavior [45]. The circuit model posits that there at least three frontal-subcortical circuits that mediate human behavior: (1) a circuit that mediates planning, organization, and executive function (dorsolateral circuit); (2) a model mediating motivated behavior (apathy circuit); and (3) a circuit mediating inhibitory control and conformity with social norms (orbitofrontal circuit). Each circuit has a frontal component, a basal ganglia substrate, and a thalamic component; the circuit is completed by linking back to its frontal origins. For example, the inhibitory control circuit loops between the orbitofrontal cortex, the ventral caudate, the mediodorsal thalamus, and back to the orbitofrontal cortex [46].

### 4.2. Cortico-cortical network

The cortico-cortical network model posits that the human brain consists of five large-scale neurocognitive networks [11,49]. These networks are partially segregated and overlapping. The memory-emotion network is one of the five networks, and the epicenters of the memory-emotion network are the hippocampus and amygdala, respectively [50]. These epicenters have extensive reciprocal connections [51]. Thus, emotion and cognition are closely related.

### 4.3. The monoaminergic system: Cell bodies in the "south" diffusely project "north" via long axons

In addition to circuits and networks, the field has been interested in the role of the ascending monoaminergic system in the pathophysiology of NPS in AD. The general organization of this system is such that cell bodies of neurons producing serotonin, norepinephrine, or dopamine are primarily located in the brain stem (midbrain, pons, and medulla) and diffusely project via long axons to virtually all parts of the brain [47] to mediate human behavior. The neurobiological models of NPS in AD, as discussed above, are the foundations of neuroimaging and biomarker research of NPS in AD.

### 4.4. Neuroimaging and biomarker research

Structural and functional imaging work has implicated circuits, networks, and the monoaminergic systems [52–54]. Investigators have examined the neurobiological

underpinnings of delusions [54,55], apathy [56], and depression [57]. In addition to neuroimaging and biomarker investigations, genetic studies have contributed to the understanding of NPS in AD. Over the last 10 years, increasing evidence suggests that AD with psychosis may represent a distinct phenotype with a genetic basis [58,59].

Amyloid imaging studies using the Pittsburgh compound B ($^{11}$C-PiB)-positron emission tomography (PET) have primarily targeted cognitive symptoms [60,61]. At the NPS research roundtable, Geda et al presented some of the first studies of NPS in AD using amyloid imaging [12]. Their exploratory analyses, derived from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database, examined the correlation between NPI-Q scores and PiB retention in cognitively normal persons or those with prodromal AD. After adjusting for age, sex, and education, there were weak correlations between global $^{11}$C-PiB-PET as well as regional (prefrontal, temporal, and parietal) retention and total NPI-Q scores; significance was lost after adjusting for Mini-Mental State Examination scores [12]. The relationship between the primary AD pathology (plaques, tangles, and regional neuronal loss) and NPS remains to be elucidated.

## 5. Mechanisms linking NPS with AD

If we assume that NPS is accurately measured in AD, the next key question is to postulate mechanisms connecting NPS to AD [62]. On the basis of previous research [63], we propose four possible mechanisms that link NPS with MCI or DAT: (1) Etiologic pathway: According to this model, a neuropsychiatric symptom is in the chain of causality leading to symptomatic AD by virtue of its effect on the brain, such as activations of the neuroendocrine axis [64]. In this context, the symptom reflects an underlying pathology or brain state that is causally linked to the development of AD pathology and its associated cognitive symptoms. An important corollary of this hypothesis is that an intervention targeting NPS may delay the onset of MCI or DAT. (2) Shared risk factor or confounding: A NPS is noncausally associated with AD/MCI because there is a third factor that leads to the genesis of AD/MCI and NPS. The third factor (confounder) could be genetic, environmental, or both. Brain vascular disease or white matter change is an example [43]. (3) NPS caused by AD through reverse causality or psychological reaction: A person experiencing cognitive decline may develop depression, anxiety, or a similar NPS as a psychological reaction. In this model, insight into the cognitive decline is a key antecedent of the psychological reaction. Alternatively, NPS may be a direct noncognitive manifestation of the AD neurodegenerative disease because it affects key brain areas underlying behavior, emotion, or perception. (4) Interaction: A synergistic interaction between NPS and a biological factor leads to DAT/MCI. This model is supported in one study in which the hazard ratio of developing incident MCI given
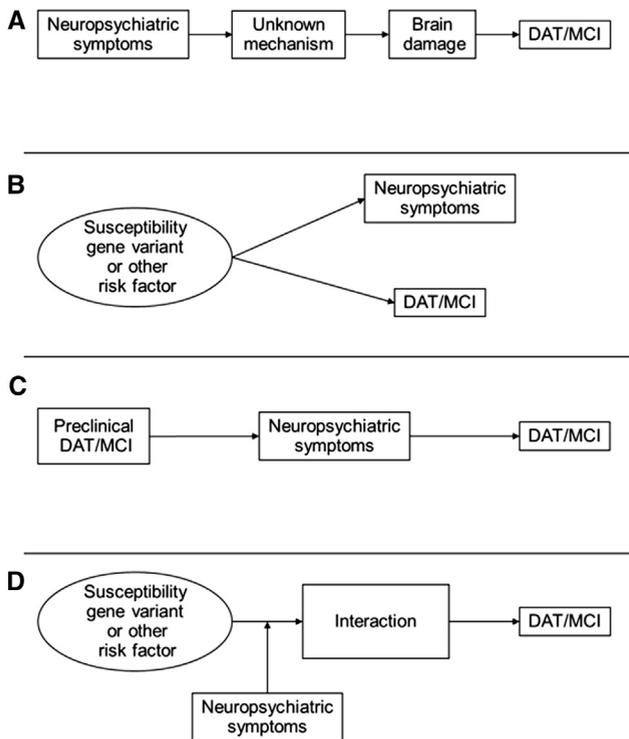
Fig. 1. Possible mechanisms linking NPS to DAT/MCI: (A) etiologic pathway, (B) confounding, (C) reverse causality, and (D) interaction. Modified from Geda et al., Archives of Neurology, 2006.

depression (vs no depression) was 2.0 but increased to 5.0 in the presence of depression and apolipoprotein E $\varepsilon$4 carrier status [63]. These four mechanisms (and other possible mechanisms) are not mutually exclusive; thus, they may act in some sort of combinations (Fig. 1).

## 6. Treatment development

Development of novel treatments targeting NPS in AD is dependent on three major factors: (1) reliable and valid measurement of NPS in AD, (2) a cohesive and plausible neurobiological model that takes into consideration emotional behavior and cognition, and (3) advances in neuroimaging and biomarkers that enable investigators to monitor response to treatment. Additionally, treatment development should not be limited to pharmacological interventions [65]. The clinical phenotype of NPS in AD is expressed in the context of environmental factors; therefore, treatment developments must take into consideration neurobiological and psychosocial contexts of the development and manifestations of NPS in AD [66–68].

In summary, NPS in AD are a key component of the disease, and over the disease course they affect almost all patients with serious consequences. NPS are a major focus of treatment development efforts on the basis of a growing understanding of their causes and biologic basis. The papers that follow provide greater detail on individual NPS along with detailed research recommendations.

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