Introduction

Dementia is common in older adults in the United States (US); approximately 7.9 million people are living with dementia, of whom 3.95 million carry a diagnosis of at least 1 dementia type. However, postmortem pathology data from 2 large databases indicate that more than half of individuals with dementia had mixed neuropathologies.

Dementia involves more than cognition

Neuropsychiatric symptoms are common among people with dementia, and their onset can occur at various times in the course of the illness.

Neuropsychiatric symptoms are a common feature across the dementias and include hallucinations, delusions, agitation/aggression, depression, apathy, elation, anxiety, disinhibition, irritability, and aberrant motor behavior (eg, wandering).

Hallucinations and delusions are prevalent across the dementias and burdensome for patients, caregivers, and society

Although the rates of hallucinations and delusions vary based on the dementia type (Figure 1), approximately 2.4 million people in the US have dementia-related hallucinations and delusions.

The presence of hallucinations and delusions in people with Alzheimer’s disease may be associated with a significantly increased risk of cognitive and functional decline; hallucinations, but not delusions, may be associated with a significant increase in the risk of institutionalization and death. Neuropsychiatric symptoms like hallucinations and delusions also have an impact on the caregiver, increasing their...
levels of burden, depression, and distress. These symptoms can also contribute to societal burden by increasing the cost of care for people with dementia. The prevalence and burden of dementia-related hallucinations and delusions combined with the aging US population are significant healthcare challenges for patients, caregivers, and society. Understanding the neurobiology of dementia-related hallucinations and delusions may provide insight into the management of neuropsychiatric symptoms, including hallucinations and delusions.

**Neurobiology of Dementia-Related Hallucinations and Delusions**

The neurobiology of psychosis, particularly its expression in the context of dementia, is complex and unknown. Historically, the neurotransmitter dopamine was implicated in psychosis, but additional research has suggested that 3 interconnected neurotransmitter systems are thought to be involved: dopamine, glutamate, and serotonin. Other factors may play roles in psychosis, but for the purposes of this newsletter, the proposed role of neurotransmitters is the focus.

It is thought that hyperactivity in the dopaminergic mesolimbic pathway, which projects from the midbrain ventral tegmental area to the ventral striatum, leads to hallucinations and delusions. In addition, the dopaminergic neurons in the ventral tegmental area can be projected onto and activated by glutamate neurons that have the ability to modulate the firing of the dopaminergic neurons. These glutamate neurons have serotonin 2A (5-HT2A) receptors, and it is thought that they are themselves modulated by cortical serotonin activity. Therefore, it is believed that 5-HT2A can modulate the activity of both dopamine and glutamate, each of which is hypothesized to contribute to hallucinations and delusions in dementia.

**Hypothetical Mechanism Through Which Serotonin Modulates Glutamate and Dopamine**

The serotonin theory of psychosis in dementia postulates that as serotonergic projections from the Raphe nucleus to the cortex are lost in dementia, 5-HT2A receptors on cortical glutamate neurons are upregulated as a response (Figure 2). It is thought that this, and the loss of inhibition from gamma-aminobutyric acid (GABA)-ergic interneurons due to N-methyl-D-aspartate (NMDA) receptor hypofunction, leads to increased glutamatergic neurotransmission in the occipital cortex, which leads to visual hallucinations. At the same time, the glutamate theory of psychosis posits that increased glutamatergic input to the ventral tegmental area increases the activity of dopaminergic neurons originating there, leading to increased dopamine release in the ventral striatum and resulting in auditory hallucinations and delusions. The dopamine, glutamate, and serotonin pathways are interconnected, and therefore it is possible that neuropsychiatric symptoms in people with dementia are the result of dysfunction in 1 or more of these neurotransmitter pathways.

**Neurobiological Changes Associated With Symptoms of Psychosis in Dementia**

Research on the neuroanatomical and neurochemical changes in the brain has been conducted to better understand the neural correlates of psychosis in people with dementia. The studies highlighted in this newsletter, focusing on dementia in people with Alzheimer’s disease, are intended to provide insight into the complex neurobiological basis for the development of psychosis in this population.

**Increased intraneuronal hyperphosphorylated tau concentrations**

Hyperphosphorylated tau protein is a key biomarker of Alzheimer’s disease pathophysiology and progression. In a study of 45 subjects with Alzheimer’s disease, hyperphosphorylated tau protein levels were measured in terms of the local intraneuronal concentration and the extent of the spread of hyperphosphorylated tau—ie, the fraction of grey matter consisting of hyperphosphorylated tau. Both measures of hyperphosphorylated tau were significantly correlated with Braak staging (local concentration: r=0.491, extent of spread: r=0.758; P<0.001 for both correlations). Researchers also found hyperphosphorylated tau to be elevated in the dorsolateral prefrontal cortex of people with Alzheimer’s disease and psychosis compared to those without psychosis, but the difference between groups was statistically significant only when measuring the local intraneuronal concentrations (P=0.006).

**Increased density of neocortical neurofibrillary tangles**

Neurofibrillary tangles are aggregates of hyperphosphorylated tau protein and are a major neuropathological hallmark of Alzheimer’s disease. Farber and colleagues hypothesized that people with Alzheimer’s disease and psychosis have greater neurofibrillary tangles than those without psychosis. In a study of 109 subjects with autopsy-confirmed Alzheimer’s disease, neurofibrillary tangles were statistically more dense in the middle frontal gyrus, superior temporal cortex,
and inferior parietal lobe in the group of subjects with Alzheimer’s disease and psychosis compared to the group without psychosis (P<0.05). Furthermore, the association between elevated neurofibrillary tangles and psychosis was not influenced by the severity of the subject’s dementia. 29

**Decreased grey matter in right frontal areas**

Ting and colleagues hypothesized that delusions in people with dementia may be the result of a decrease in function in the right frontal lobes, resulting in the inhibition of intrusive thoughts. In a cross-sectional analysis of brain tissue in 58 people with mild cognitive impairment/early Alzheimer’s disease, decreased grey matter in right frontal areas was observed in the group with psychosis compared to the group without psychosis, with the largest cluster of grey matter reduction in the insula. 30

**5-HT_{2A} receptor genotype is associated with delusions on the Neuropsychiatric Inventory delusion subscale**

Assal and colleagues conducted a study of 96 patients with Alzheimer’s disease from the Alzheimer’s Disease Research Center at the University of California at Los Angeles to examine the relationship between genetic polymorphisms related to neurotransmission and neuropsychiatric symptoms in Alzheimer’s disease. In this study, the TT 5-HT_{2A} receptor genotype was associated with the delusions Neuropsychiatric Inventory, or NPI, subscale, whereas the CC genotype was associated with protection from delusions. 31

**Decreased 5-HT concentrations**

The finding of a relationship between delusions and the TT 5-HT_{2A} receptor genotype is particularly relevant, given the established relationship between psychosis in dementia and reduced serotonergic neurotransmission. In a study by Zubenko and colleagues, brain tissue from 27 patients with Alzheimer’s disease was examined. Psychosis was associated with a statistically significant reduction in serotonin levels in the prosubiculum (P<0.05), and trends in that direction were found for all other areas examined (Figure 3). Psychosis was not associated with significant changes in dopamine levels. 32

**The Potential Role of Cerebral Cortex Changes in Dementia-Related Hallucinations and Delusions**

In addition to receptor-level alterations, structural and functional neuroimaging studies have identified changes in brain networks that may contribute to the pathophysiology of hallucinations and delusions in dementia.

**Hypoperfusion in frontal areas**

Symptoms of psychosis in people with Alzheimer’s disease have been correlated with abnormalities in perfusion (the flow of blood) in certain regions of the brain. 33 Mega and colleagues examined the functional neuroimaging correlates of hallucinations and delusions in 20 people with Alzheimer’s disease. The study showed that the group with hallucinations and delusions (n=10) showed significantly lower perfusion in left and right prefrontal areas, left striatum, and left parietal cortex (P<0.0001) than the group without hallucinations and delusions (n=10). 33

**More extensive grey-matter loss in Parkinson’s disease with visual hallucinations**

In a study by Ibarretxe-Bilbao and colleagues, progressive loss of grey matter was compared in people with Parkinson’s disease with (n=12) or without (n=14) visual hallucinations to healthy controls (n=12). Compared to healthy controls who did not show any significant grey-matter loss, individuals with Parkinson’s disease and visual hallucinations showed extensive grey-matter loss involving the limbic, paralimbic, and neocortical areas (P<0.05). Those with Parkinson’s disease and no visual hallucinations showed deterioration only in small clusters of frontal areas and the cerebellum compared to healthy controls (P<0.05; Figure 4). 34

**Hypoperfusion in bilateral parietal and occipital areas in dementia with Lewy bodies**

Similar to the Mega et al study, Nagahama and colleagues evaluated the neuroimaging correlates of hallucinations and delusions in individuals with dementia with Lewy bodies. Controlling for other cognitive, behavioral, and psychiatric symptoms, the researchers used single-photon emission computed tomography, or SPECT, to compare regional cerebral blood flow in 100 subjects with and without hallucinations and delusions. People with dementia with Lewy bodies and hallucinations showed significant hypoperfusion in the left angular gyrus, left occipital gyrus, right supramarginal gyrus, and right angular gyrus compared to those without hallucinations (P<0.001). 35

**Figure 3. Mean 5-HT concentrations in people with Alzheimer’s disease, with and without psychosis.**

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**Figure 4. Hypoperfusion in bilateral parietal and occipital areas in dementia with Lewy bodies.**

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Dementia involves more than a deterioration in cognitive function, and neuropsychiatric symptoms—such as hallucinations and delusions—are prevalent across the dementias. Hallucinations and delusions may increase the risk of disease progression and increase the cost of care, stress on caregivers, and risk of institutionalization.

While the neurobiology of dementia-related hallucinations and delusions is complex and not fully understood, research suggests that hallucinations and delusions in dementia are not solely triggered by increases in brain dopamine. It is proposed that glutamate and serotonin also play important roles, in particular to decrease in serotonergic neurotransmission. There is also growing evidence that neuroanatomic changes and even genetic polymorphisms can differentiate between patients who have dementia with and without psychosis. An improved understanding of the role that the serotonergic system plays in the neurochemical underpinnings of hallucinations and delusions in dementia opens new avenues for further research and drug development.

**References:**

![Figure 4. More extensive grey-matter loss in Parkinson’s disease with visual hallucinations.](Image)