Neurobiology of Delusions, Memory, and Insight in Alzheimer Disease

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Objective: *Delusional thoughts are common among patients with Alzheimer disease (AD) and may be conceptually linked to memory deficits (cannot recall accurate information, which leads to inaccurate beliefs) and poor insight (unable to appreciate the illogic of beliefs). This study's goals were to examine the clinical associations among delusions, memory deficits, and poor insight; explore neurobiologic correlates for these symptoms; and identify shared mechanisms.* **Methods:** *In a cross-sectional analysis, 88 outpatients with AD (mean Mini-Mental State Exam score: 19.3) were studied. Delusional thoughts were assessed with the Neuropsychiatric Inventory, level of inaccurate insight was assessed with the Neurobehavioral Rating Scale, and memory was assessed with the Mattis Dementia Rating Scale memory subscale.* ^{18}*F-fluorodeoxyglucose positron emission tomography was used to measure regional cortical metabolism. Relationships between clinical ratings and regional cortical metabolic activity (voxel-based) were assessed using SPM2.* **Results:** *Patients with delusions had lower Dementia Rating Scale memory subscale scores. Neurobehavioral Rating Scale inaccurate insight scores were no different in those with and without delusions. Cortical metabolic activity was lower in the right lateral frontal cortex, orbitofrontal cortex, and bilateral temporal cortex in patients with delusions. Low cortical metabolic activity in the right lateral, inferior, and medial temporal cortex was associated with poorer memory. This region partially overlapped the region of hypometabolism associated with delusions. In contrast, low cortical metabolic activity in bilateral medial frontal cortex was associated with poor insight.* **Conclusion:** *Delusions in AD are associated with dysfunction in specific frontal and temporal cortical regions. Delusions are partially clinically and neurobiologically linked to memory deficits but not to poor insight.* (Am J Geriatr Psychiatry 2013; ■:■−■)

Key Words: Alzheimer disease, delusions, insight, memory, FDG-PET, cerebral metabolism

Received November 26, 2012; revised June 14, 2013; accepted June 18, 2013. From the Brain, Behavior, and Aging Research Center (DLS, LPL, RJM, DGH, TAN, TKA) and Nuclear Medicine Service (MAM), VA Greater Los Angeles Healthcare System, Los Angeles, CA; Department of Psychiatry & Biobehavioral Sciences (DLS, RJM, DGH), David Geffen School of Medicine at UCLA, Los Angeles, CA; and Department of Physics (MAM), University of California, Irvine, Irvine, CA. Presented in part at the 25th annual meeting of the American Association for Geriatric Psychiatry, Washington, DC, March 16–19, 2012. Send correspondence and reprint requests to David L. Sultzer, M.D., Brain, Behavior, and Aging Research Center, VA Greater Los Angeles Healthcare System, 11301 Wilshire Boulevard, 116AE, Los Angeles, CA 90073. e-mail: dsultzer@ucla.edu

http://dx.doi.org/10.1016/j.jagp.2013.06.005

INTRODUCTION

Delusional thoughts are common among patients with Alzheimer disease (AD).[1] These noncognitive symptoms have important clinical implications because they contribute prominently to behavioral disturbances, institutionalization, and caregiver burden.[2,3] However, the etiologic factors underlying delusions in AD remain unclear. Conceptually, delusional thoughts may be associated with memory deficits and poor insight. For example, the inability to recall accurate information may foster inaccurate beliefs. Poor insight, defined as reduced awareness of cognitive or functional deficits and impaired intuitive understanding, may undermine the patient's appreciation of the illogical nature of these beliefs. Although impaired memory and insight may be linked to delusional thoughts, the relationships are not necessarily causal and the extent of relationships and the neuropathologic processes that mediate them are not known.

Studies of the clinical correlates of delusional thoughts have typically evaluated relationships with global cognition. Most studies find that delusions are more common among those AD patients with advanced cognitive deficits.[1,4,5] Few studies have examined the relationship between delusional thoughts and memory deficits specifically[6] or the relationship between delusional thoughts and impaired insight. Two studies found a correlation between delusional thoughts and a lack of awareness of cognitive deficits in AD.[7,8] In addition, Kazui et al.[9] found that both memory impairment and delusions were significantly associated with lack of insight, suggesting that these three symptoms are clinically related.

Although the exact pathophysiologic mechanisms are unclear, neuroimaging studies indicate that delusional thoughts may be associated with dysfunction in frontal and temporal cortex in patients with AD.[10–15] Previous research has also shown an association between lack of insight in AD and right hemisphere and frontal lobe dysfunction that incompletely overlaps with regions of cortical dysfunction associated with delusions.[16,17] Thus, delusions and poor insight may have a shared relationship with right frontal cortex dysfunction. Further elucidation of the clinical and neuropathologic associations among delusions, memory, and insight can help to identify critical mechanisms underlying cognitive and neuropsychiatric symptoms in AD and can help to inform clinical treatment.

The goals of this study were to examine the clinical associations among delusional thoughts, memory deficits, and poor insight in mild to moderate AD and to explore the neurobiologic basis and possible shared mechanisms for these symptoms using fluorodeoxyglucose positron emission tomography (FDG-PET). We hypothesized that both delusions and poor insight would be associated with right lateral/inferior frontal cortex hypometabolism and that memory deficits would be associated with inferior and medial temporal cortex hypometabolism.

METHODS

Participants

Eighty-eight participants with AD were recruited from outpatient clinics that included the VA Greater Los Angeles Healthcare System Memory Clinic and Geropsychiatry Clinic. Participants completed a clinical evaluation of neurologic, psychiatric, and cognitive functioning and a structural neuroimaging scan. Final diagnosis was based on the criteria for probable AD established by the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association and is consistent with National Institute of Aging/Alzheimer's Association criteria for probable AD.[18] Exclusion criteria were history of psychotic disorder unrelated to dementia, history of head trauma with loss of consciousness, history or neuroimaging evidence of stroke or cerebrovascular disease, seizure disorder, substance use disorder, severe aphasia, or systemic illness or other neurologic illness that could account for cognitive deficits. Thirty-two participants were on a stable dose (3 months or more) of cholinesterase inhibitor medication and 21 were on a stable dose of selective serotonin reuptake inhibitor antidepressant. No participants were being treated with an antipsychotic, benzodiazepine, or other psychotropic medication. The study was reviewed and approved by the local institutional review board.