Psychosis in Alzheimer's Disease Is Associated With Frontal Metabolic Impairment and Accelerated Decline in Working Memory: Findings From the Alzheimer's Disease Neuroimaging Initiative

Jeremy Koppel, M.D., Suzanne Sunday, Ph.D., Terry E. Goldberg, Peter Davies, Ph.D., Erica Christen, M.S., Blaine S. Greenwald, M.D., for the Alzheimer's Disease Neuroimaging Initiative

Objective: *An ascendant body of evidence suggests that Alzheimer disease with psychosis (AD+P) is a distinct variant of illness with its own genetic diathesis and a unique clinical course. Impaired frontal lobe function has been previously implicated in AD+P. The current exploratory study, presented in two parts, evaluates both the regional brain metabolic and psychometric correlates of psychosis in a longitudinal sample of subjects with AD, made available by the Alzheimer's Disease Neuroimaging Initiative (ADNI).* **Methods:** *In Part 1 of the study, 21 ADNI participants with AD who developed psychotic symptoms during the study but were not psychotic at baseline were matched with 21 participants with AD who never became psychotic during the study period, and mean brain [F^{18}]fluorodeoxyglucose positron emission tomography (FDG-PET) Cerebral metabolic rate for glucose (CMRgl) by regions of interest (ROIs) were compared Additionally, 39 participants with active psychosis at the time of image acquisition were matched with 39 participants who were never psychotic during the study period, and mean brain FDG-PET CMRgl by sROI were compared. In Part 2 of the study, 354 ADNI participants with AD who were followed for 24 months with serial psychometric testing were identified, and cognitive performance and decline were evaluated for correlation with psychotic symptoms.* **Results:** *Part 1: There were no regional brain metabolic differences between those with AD destined to become psychotic and those who did not become psychotic. There was a significant reduction in mean orbitofrontal brain metabolism in those with active psychosis. Part 2: Over the course of study follow-up, psychosis was associated with accelerated decline in functional performance as measured by the Functional Assessment Questionnaire, the Mini-Mental State Examination, and Forward Digit Span.*

Received November 2, 2011; revised September 20, 2012; accepted October 26, 2012. From the Litwin Zucker Alzheimer's Research Center (JK, SS, TG, PD, EC, BG), Manhasset, NY. Send correspondence and reprint request to Jeremy Koppel, the Litwin Zucker Alzheimer's Research Center, Manhasset, NY. e-mail: jkoppel@nshs.edu

http://dx.doi.org/10.1016/j.jagp.2012.10.028

Conclusion: *In a sample drawn from the ADNI dataset, our exploratory FDG-PET findings and longitudinal cognitive outcomes support the hypofrontality model of AD+P. Focal frontal vulnerability may mediate the accelerated decline seen in AD+P.*
(Am J Geriatr Psychiatry 2013; ■:■−■)

Key Words: Alzheimer disease, psychosis, working memory, frontal, hypofrontality

The notion that psychotic Alzheimer disease (AD+P) represents a variant distinct from Alzheimer disease without psychosis (AD-P) has gained traction in recent years from studies suggesting unique clinical outcomes in those manifesting delusions or hallucinations during the course of illness and from data suggesting a genetic diathesis to AD+P. Several clinical and epidemiologic characteristics can distinguish AD+P from AD-P, including a greater burden of cognitive impairment,[1,2] functional impairment,[3,4] a more rapid velocity of decline,[5] and an increased risk of AD+P in siblings of affected probands.[6]

A complete understanding of the biology underlying AD+P has yet to be achieved. A hypofrontality model describing impaired frontal lobe function in AD+P has been suggested as a potential mediator of both exacerbated cognitive impairment and the emergence of psychotic symptoms. Evidence supporting this model include the results of one cognitive study comparing AD+P with AD-P in which subjects who were of similar duration of illness, age, and education demonstrated specific differences in tasks of frontal lobe function[1] and include suggestions of frontal impairment from small functional neuroimaging studies of AD+P.[7–9]

If the hypofrontality model is valid, this focal impairment may have a distinguishing cognitive signature separate from the psychiatric symptomatology. Recently, our group reported on an association between AD+P and impairment on one task of working memory, the digit span test,[10] which may represent the cognitive expression of hypofrontality in AD+P. Approaches to evaluating frontal function in vivo include both cognitive assessment on frontal tasks and functional neuroimaging comparing regional brain metabolism. To test the hypofrontality model of AD+P in a longitudinal cognitive and functional neuroimaging outcomes study, the Alzheimer's Disease Neuroimaging Initiative (ADNI) database, which includes both longitudinal cognitive assessment and functional imaging, was accessed. Although the ideal methods for testing this model would be a coordinated assessment of longitudinal change over time in both cognitive and metabolic brain parameters and the interactions between the two, limitations in the availability of psychotic subjects in the ADNI database for subjects with both serial functional neuroimaging and cognitive data made this impossible. Therefore, the study is divided into two parts that address the relationship between psychosis and brain metabolism and psychosis and cognition separately. Two specific hypotheses were tested: 1) subjects with AD+P would have evidence of frontal hypometabolism, and 2) AD+P would be associated with a more rapid decline in the digit span performance.

In Part 1 of this report, in an effort to test the hypothesis that frontal impairment is associated with AD+P, we analyzed [F^{18}]fluorodeoxyglucose positron emission tomography (FDG-PET) data using a matched design to control for confounding variables. Subjects with psychosis were matched one-to-one on available demographic and disease-related variables with subjects who were not psychotic during the study, and cross-sectional regional brain glucose metabolism and cognition were compared in two different analyses. To determine whether any perturbations in frontal brain glucose metabolism associated with psychosis precede the psychosis (and could potentially represent a premorbid hypofrontality resulting from a genetic or neurodevelopmental "trait" effect) or whether any changes in regional brain glucose metabolism only coincide with the psychotic "state" itself, we divided these data into two analyses. In the first analysis, subjects not yet psychotic at baseline but who became psychotic during the study were matched with subjects who were never psychotic, and cross-sectional brain glucose metabolism and cognitive performance were compared. In a subsequent analysis, subjects already psychotic were matched to subjects