Cognitive Deficits and Local Metabolic Changes in Dementia of the Alzheimer Type

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Summary

Relations between neuropsychological and regional cerebral metabolic alterations were studied cross-sectionally and longitudinally in patients with dementia of the Alzheimer type and were compared to controls. Reductions in regional cerebral metabolism, measured in the resting state with positron emission tomography and $^{18}$F]fluorodeoxyglucose, were greatest in the association cortices relative to the primary sensory and motor cortices and to the thalamus and basal ganglia. Individual patients demonstrated different patterns of association cortex metabolic reductions. Reductions in homologous right and left hemisphere association regions were often asymmetric. Parietal and frontal metabolic reductions were also often disproportionate relative to each other. Neuropsychological impairments in patients with dementia of the Alzheimer type were also selective and heterogeneous. Memory impairment was often the first symptom followed by impaired ability to maintain attention to complex or shifting sets. As the disease progressed, language and visuospatial functions became impaired. Whereas the memory impairment was usually global and severe, patterns of nonmemory impairments varied markedly from patient to patient. For example, some patients had disproportionately severe language impairments relative to milder visuospatial impairments and other patients demonstrated the opposite pattern. In patients with moderate dementia of the Alzheimer type, patterns of nonmemory impairments were related to the distribution of association cortex metabolic reductions. At initial evaluation, mildly impaired patients did not have significant nonmemory language and visuospatial impairments but did have significant neocortical metabolic reductions that were not correlated with neuropsychological test scores. After a mean of 2 years of longitudinal study, significant language and visuospatial impairments developed, and right-left metabolic asymmetries were significantly correlated with visuospatial-language discrepancies. These results suggest that neocortical metabolic abnormalities can be observed with positron emission tomography before associated impairments of neocortically mediated visuospatial and language functions are demonstrable.
Introduction

Alzheimer’s disease is a progressive, degenerative brain disease whose principal clinical symptoms are disorders of memory, language and cognition. Other brain functions, such as simple sensory and motor function, are not impaired in patients with Alzheimer’s disease or are impaired only in late stages after the dementia has become severe. The development of noninvasive methods to measure regional brain blood flow and metabolism has made it possible to examine relations between neuropsychological impairments and the regional distribution of disease-related alterations in blood flow and metabolism. In the Laboratory of Neurosciences, National Institute on Aging, we have been conducting a longitudinal study of patients with clinically diagnosed dementia of the Alzheimer type (DAT) for the past 7 years. At yearly intervals, patients are given positron emission tomography (PET) scans to measure regional cerebral metabolic rates for glucose (rCMRglc), computed tomography (CT) and MRI scans to examine brain structure, and an extensive battery of neuropsychological tests. In this paper, the major findings regarding the neuropsychological impairments associated with DAT and their relation to alterations in rCMRglc are reviewed. The emphasis in this review is on interindividual variations in the pattern of neuropsychological impairments and how these variations are related to patterns of rCMRglc reductions. These studies have helped to elucidate the neurobiological basis for disorders of language and visuospatial functions in DAT. Other prominent neuropsychological disorders of DAT, namely those of memory and attention, however, have not yet been related to regional brain alterations as measured with PET. The review concludes with a discussion of what the neurobiological basis of these disorders may be, why PET studies have heretofore not contributed to our understanding of these functions, and how future PET studies may be able to give us new insights in these areas.

Methods

Subjects

All patients with DAT met NINCDS-ADRDA diagnostic criteria for possible or probable Alzheimer’s disease (McKhann et al. 1984) when studied initially. To study the full course of Alzheimer’s disease, five patients were studied initially when they had an isolated memory impairment with no demonstrable impairments of nonmemory language or cognitive functions. Because dementia is a syndrome that by definition involves impairment of more than one area of cognitive function, these patients were not demented at the time of their first evaluation and met criteria for possible but not probable Alzheimer’s disease. Subsequent evaluations of these patients demonstrated the development of nonmemory neuropsychological impairments in all five patients, and two have died with autopsy confirmation of Alzheimer’s disease. Patients were divided into subgroups based