Neuroimaging to predict preclinical Alzheimer's disease

Veena Kumari, Martina T Mitterschiffthaler, Tonmoy Sharma

Alzheimer's disease is common in the elderly and causes tremendous distress to patients and their carers. With the advent of newer pharmacological treatments, significant improvement in the early diagnosis of Alzheimer's disease is required. This article examines the usefulness of neuroimaging techniques to predict Alzheimer's disease in prediagnosis individuals.

Alzheimer's disease (AD) is a brain disorder characterized by a progressive dementia. It is the major probable cause of dementia in the elderly, and its incidence rises from about 5% in those aged 65 years and over to about 25% in those aged 85 years and older (Small et al, 1997). As the elderly population is increasing, this trend can lead to great strain on the available health-service resources, along with deterioration in the quality of life of the sufferer and increased burden of care in caregivers.

With the advent of newer pharmacological treatments for symptoms, it may be possible to put an end to at least some of the negative effects of AD. The potential for more effective treatment has led to recent efforts to identify AD as accurately and early as possible in high-risk populations. It may be possible to achieve full characterization of preclinical (probable) AD, which antedates illness onset by about 1–2 years, with a multimodal approach involving a combination of neuroimaging, neuropsychological, genetic and clinical measures.

CLINICAL CRITERIA FOR THE DIAGNOSIS OF AD

The clinical criteria for the diagnosis of probable, possible and definite AD are listed below. These are as described by the Work Group of the National Institute of Ageing and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (McKahnn et al, 1984), which are also compatible with the diagnostic criteria according to the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV; American Psychiatric Association, 1994).

Clinical diagnosis of probable AD

- Dementia established by clinical examination and documented by the mini mental state examination, a brief test of mental status and cognitive function (MMSE; Folstein et al, 1975), or by the Blessed test, another quick test (approximately 10 minutes) of cognition assessing activities of daily living and memory, concentration and orientation (Blessed et al, 1968), and confirmed by further neuropsychological tests
- Deficits in two or more areas of cognition
- Progressive worsening of memory and other cognitive functions
- No disturbance of consciousness
- Onset between the ages of 40–90 years
- Absence of systemic diseases or other brain diseases that could explain the cognitive changes.

The diagnosis of probable AD is supported by:

- Progressive deterioration of specific cognitive functions such as language, motor skills and perception (aphasia, apraxia and agnosia respectively)
- Impaired activities of daily living
- Positive family history, particularly if documented neuropathologically
- Laboratory results: normal lumbar puncture, electroencephalogram and evidence of cerebral atrophy on computed tomography (CT) or magnetic resonance imaging (MRI).

Other clinical features consistent with the diagnosis of probable AD, after exclusion of other causes of dementia, include:

- Plateaus in clinical course
- Associated symptoms: depression, insomnia, incontinence, delusions, illusions, hallucinations, catastrophic verbal, emotional or physical outbursts, sexual disorders and weight loss

Dr Veena Kumari is Beit Memorial Research Fellow with Senior Lecturer Status, **Ms Martina T Mitterschiffthaler** is Research Psychologist in the Section of Cognitive Psychopharmacology, Division of Psychological Medicine and Department of Psychology, Institute of Psychiatry, London SE5 8AF, and **Professor Tonmoy Sharma** is Consultant Psychiatrist and Director of Clinical Neuroscience Research Centre, Stonehouse Hospital, Dartford, Kent

Correspondence to: Dr V Kumari

- Other neurological abnormalities in some patients, especially those with more advanced disease, and including motor signs such as increased motor tone, myoclonus and gait disorder
- Seizures in advanced disease
- CT normal for age.

Features that make the diagnosis of probable AD unlikely or uncertain:

- Sudden apoplectic onset
- Local neurological findings such as hemiparesis, sensory loss, visual field deficits and incoordination early in the course of the illness
- Seizures or gait disturbances at the onset or very early in the course of the illness.

Clinical diagnosis of possible AD

- May be made on the basis of the dementia syndrome, in the absence of other neurological, psychiatric or systemic disorders sufficient to cause dementia, and in the presence of variations in the onset, in the presentation or in the clinical course
- May be made in the presence of a second systemic or brain disorder sufficient to produce dementia, which is not considered to be the cause of the dementia
- Should be used in research studies when a single, gradually progressive, severe, cognitive deficit is identified in the absence of other identifiable cause.

Criteria for diagnosis of definite AD

- Clinical criteria for probable AD
- Histopathological evidence obtained from a biopsy or autopsy.

TABLE 1.
Neuroanatomical, cognitive and behavioural changes in Alzheimer's disease

Neuroanatomical changes	Degenerative changes in the entorhinal cortex
	Bilateral hippocampus atrophy
	Deterioration of cholinergic neurons
Cognitive and behavioural changes	Difficulties with delayed recall
	Impaired performance on routine tasks
	Decreased ability to create complex sentences
	Disorientation of time and place
	Poor or decreased judgment
	Impaired abstract thinking
	Changes in mood and behaviour
	Personality changes
	Loss of initiative

From Alzheimer Society of Canada (2002)

COGNITIVE AND NEUROANATOMICAL CHANGES

Complex and distributed patterns of neuroanatomical changes, which are not easy to distinguish from structural alterations in normal ageing, accompany the onset of clinically evident AD (*Table 1*). The earliest degenerative changes of this disease begin in the entorhinal cortex (De Toledo-Morrell et al, 2000) and then involve the hippocampus before encompassing other parts of the cortex (Jack et al, 2000; Moffat et al, 2000; Small et al, 2000a; Xu et al, 2000). The annual rate of hippocampal atrophy has been found to be greater in patients with AD than that seen (1.5%) as part of normal ageing (Jack et al, 1998). A relationship has also been shown between the rate of global cerebral volume loss and rate of change in MMSE scores in patients with AD (Fox et al, 1999).

The earliest cognitive changes in AD are manifested as deficits in verbal and visual episodic memory (memory based on conscious experience in a way that it allows the possibility of retrieving specific aspects of such experiences) (*Table 1*). There is further evidence that gradually worsening memory in AD is linked to deterioration of the hippocampus and cortical cholinergic neurons, especially in people carrying a genetic risk for this illness (Moffat et al, 2000).

DETECTION OF PREDIAGNOSIS AD

Genetic factors are known to be involved in AD (Almkvist and Winblad, 1999). People with at least one first-degree relative with AD and testing positive for the epsilon4 allele of the apolipoprotein gene (APOE-4) have about a 40% risk of developing AD compared with low-risk (neither risk) individuals, who have about a 10% risk. However, the disease is likely to have a complex and heterogeneous aetiology and not everyone with probable symptoms or a genetic risk makes a transition to developing AD (Celsis, 2000). The existing evidence suggests that between 25% (Killiany et al, 2000) and 60% (Convit et al, 2000) of people with probable symptoms of AD convert to clinically evident AD over a period of 3 years.

Clinical onset of AD is generally preceded by a period of neuropathological deficits and mild cognitive impairments. The main cognitive marker of prediagnosis AD is poor performance on memory measures, especially on delayed recall (Laakso et al, 2000). However, given that a decline in mental abilities, characterized mainly by failing memory, is an accepted part of growing old, it can sometimes be difficult to

distinguish between memory loss associated with normal ageing and the early stages of AD. It would be useful to combine rate of memory loss with genetic risk and evidence of deteriorating functions and structures of the brain to diagnose AD in prediagnosis individuals. Recent neuroimaging techniques do not involve radioactivity and thus allow repeated measurements without causing any harm to subjects (see Sheringham et al in this issue for details of techniques).

Structural MRI

MRI of the hippocampus and entorhinal cortex has been found useful in discriminating people with prediagnosis AD from those with AD and normal controls (Xu et al, 2000). Prediagnosis AD subjects show slower rates of hippocampal volume loss compared with people with AD, but greater rates in comparison with healthy individuals (Jack et al, 1998; Du et al, 2001) (*Figure 1*).

The presence of the APOE-4 allele also predicts smaller volumes in the hippocampus, entorhinal cortex and anterior temporal lobes in AD (Geroldi et al, 1999). Importantly, MRI measures of the hippocampus and entorhinal cortex, which demonstrate neuropathological changes in early stages of AD, are found to be better at identifying different patients with prediagnosis AD than measurements that reflect alterations that develop later in the course of the disease, for example atrophy affecting the third ventricle (Killiany et al, 2000).

There is also evidence to confirm involvement of the caudal portion of anterior cingulate in the early stage of AD. This is a region known to develop severe neuronal loss in AD, and to be at least in part responsible for cognitive impairment (in particular impairment of executive function) seen in the early stage of AD (Killiany et al, 2000). Atrophy of the medial occipitotemporal, inferior and middle temporal gyri in non-demented elderly patients predicts decline in AD (Convit et al, 2000).

Functional MRI

As brain function is likely to deteriorate well before structural changes are evident, functional MRI (fMRI) may provide better clues to early aetiopathology of the disease. Functional neuroimaging techniques, such as positron emission tomography (PET), have shown AD-related abnormalities, for example temporoparietal hypometabolism (Fazekas et al, 1989) (*Figure 2*).

The latest neuroimaging technique, fMRI, has several advantages over PET. It has superior spatial and temporal resolution and is a safe, non-invasive technique which does not require the use of radioactive substances, thus enabling investigation of brain functions on a longitudinal basis.

Bookheimer and colleagues (2000) have shown increased brain activation during cognitive tasks, especially during memory tasks (Burggren et al, 2002) in subjects thought to be at risk for AD. The authors proposed that these subjects performed additional cognitive work to accomplish tasks. However, Smith and colleagues (1999) earlier reported reduced brain activation in subjects at risk for AD even before clinical and cognitive symptoms or gross anatomical abnormalities emerge. Patients with AD themselves are found to show reduced brain activation (Johnson et al, 2000). It remains to be examined whether these seemingly discrepant findings represent different stages or types of the illness, or changes that may be task-specific (Burggren et al, 2002). Further within-subjects longitudinal (serial) data are required to explore how fMRI can be combined with genetic and cognitive measures to form a powerful predictor of AD in at-risk populations.

Proton magnetic resonance spectroscopy

Another useful neuroimaging tool to investigate markers of AD is proton magnetic resonance spectroscopy (MRS), which provides information on brain chemistry. Large decreases in brain N-acetylaspartate (NAA), a marker of neuroaxonal integrity, are commonly seen in patients with AD in cerebral gray and white matter (De

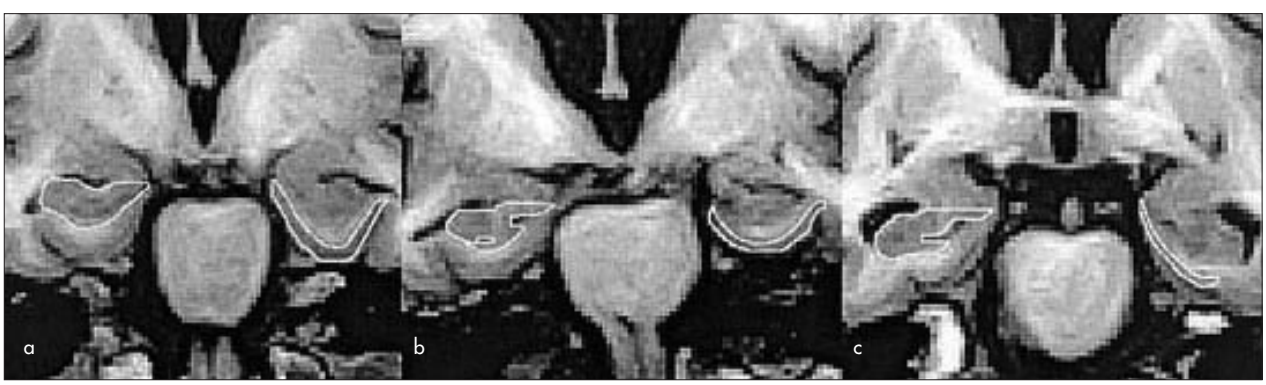

Figure 1. Entorhinal cortex (right) and hippocampal (left) volumes in groups of: (a) 40 individuals with normal cognition; (b) 36 individuals with mild cognitive impairment (preclinical Alzheimer's disease); and (c) 20 patients with Alzheimer's disease.

Stefano et al, 1999; Jessen et al, 2000; Huang et al, 2001) (*Figure 3*).

However, MRS abnormalities are also seen in other forms of dementia and are therefore not specific to AD. Nevertheless, levels of NAA may provide a useful predictor of progression to AD, since greater NAA decreases have been seen in brains of patients with clinically more severe disease. It is important to note that the brain metabolic changes seen with proton MRS can be independent of structural abnormalities detected by conventional MRI; however, as described above, quantitative measurements of regional brain volumes are also useful as predictors of AD. Thus, proton MRS, combined with other magnetic resonance techniques, can provide more sensitive predictors of AD and sensitive indices to monitor disease progression.

PREDICTION OF PRECLINICAL AD

The progressive deterioration of memory functions and other symptoms of AD might be altered by treatment with cholinesterase inhibitors (Krall et al, 1999). Research has consistently shown that performance on both short-term (such as span tests and the recency portion of free recall) and long-term memory tasks (such as the primacy portion of free recall, logical memory and recalling learnt associations) is affected in AD. Similar deficits have been found in research on anticholinergic blockade in healthy subjects (Zachariah et al, 2002). It is believed that the level of memory functioning in AD can be preserved by using selective acetylcholinesterase inhibitors, such as rivastigmine, which make more acetylcholine available in the brain. There are also recent data showing improved brain metabolism and cognitive functions with cholinergic treatment in AD (Potkin et al, 2001).

KEY POINTS

- Alzheimer's disease (AD) is the major probable cause of dementia in the elderly.
- With more people living well into old age, AD is an increasing problem.
- Gradually worsening memory and temporal lobe involvement are the earliest and most prominent features of AD.
- The level of memory functioning in AD can be preserved by using selective acetylcholinesterase inhibitors, which make more acetylcholine available in the brain.
- Initiation of treatment early in the course of the disease has the potential to alter the course and improve the prognosis of this disease in 'at-risk' individuals.
- The ability to evaluate the integrity of brain functions with recent neuroimaging techniques can substantially aid the understanding of mechanisms and the early detection of the disease, and may enable the testing of potential pharmacological interventions for this condition.

One of the major shortfalls of procholinergic treatment in AD, however, is that when treatment is initiated, most cholinergic neurons have already died. While some amount of upregulated functioning may be produced by treatment with procholinergic drugs, the increase in activity is likely to be less than would be seen when the cholinergic system is still relatively intact. Studies aiming to intervene in individuals who are not yet showing clinical signs of AD need to ensure that only those individuals with clearly defined AD and those at a high probability of risk of developing AD be subjected to any intervention. Characterization of the 'preclinical stage', which is reliably associated with onset of AD, would help to enable intervention in those at risk of developing AD.

CONCLUSIONS

There appear to be several individual prediagnosis markers of AD. However, the specificity and relative strengths of these markers have not yet been established in a single investigation. A multimodal, repeated-measures approach involving standard clinical, neuropsychological and genetic testing as well as neuroimaging techniques would help to elucidate the abnormalities that alone, or in combination, differentiate 'at risk' for AD subjects from healthy subjects in general, and specific abnormalities that characterize prediagnosis AD in particular. Identification of specific objective brain abnormalities that accompany and/or predict the transition from prediagnosis to a clinical diagnosis of AD within the 'at-risk' populations may enable, in the future, measures to be taken to prevent or at least delay the onset of clinically evident AD in true prediagnosis subjects. This has the potential to alter the course of the disease and improve the outcome for affected individuals. HM

Figure 1 *is reproduced by kind permission of the BMJ Publishing Group from Du et al (2001).* Figure 2 *is reproduced by kind permission of the National Academy of Sciences from Small et al (2000b).* Figure 3 *is reproduced by kind permission of Lippincott, Williams and Wilkins from Huang et al (2001).*
Conflict of interest: none.

Almkvist O, Winblad B (1999) Early diagnosis of Alzheimer's dementia based on clinical and biological factors. *Eur Arch Psych Clin Neurosci* **249** (suppl 3): 3–9

Alzheimer Society of Canada (2002) Alzheimer Disease: 10 Warning Signs. Alzheimer Society of Canada, Toronto (http://www.alzheimer.ca/english/disease/warningsigns.htm)

American Psychiatric Association (1994) *Diagnostic and Statistical Manual of Mental Disorders*. 4th edn. American Psychiatric Association, Washington DC

Blessed G, Tomlinson BE, Roth M (1968) The association between quantitative measures of dementia and of senile change in the cerebral grey matter of elderly subjects. *Br J Psych* **114**(512): 797–811

Bookheimer SY, Strojwas MH, Cohen MS et al (2000) Patterns of brain activation in people at risk for Alzheimer's disease. *N Engl J Med* **343**(7): 450–6

Burggren AC, Small GW, Sabb FW, Bookheimer SY (2002) Specificity of brain activation patterns in people at genetic risk for Alzheimer disease. *Am J Geriatr Psych* **10**(1): 44–51

Celsis P (2000) Age-related cognitive decline, mild cognitive

impairment or preclinical Alzheimer's disease. *Ann Med* **32**(1): 6–14
Convit A, De Asis J, de Leon MJ, Tarshih CY, de Santi S, Rusinek H (2000) Atrophy of the medial occipitotemporal, inferior, and middle temporal gyri in non-demented elderly predict decline to Alzheimer's disease. *Neurobiol Aging* **21**(1): 19–26
De Stefano N, Mortilla M, Federico A (1999) Proton magnetic resonance spectroscopy of the brain in dementia. *Ital J Neurol Sci* **20:** S258–S264
De Toledo-Morrell L, Goncharova I, Dickerson B, Wilson RS, Bennett DA (2000) From healthy ageing to early Alzheimer's disease: in vivo detection of entorhinal cortex atrophy. *Ann N Y Acad Sci* **911:** 240–53
Du AT, Schuff N, Amend D et al (2001) Magnetic resonance imaging of the entorhinal cortex and hippocampus in mild cognitive impairment and Alzheimer's disease. *J Neurol Neurosurg Psych* **71**(4): 441–77
Fazekas F, Alavi A, Chawluk JB et al (1989) Comparison of CT, MR, and PET in Alzheimer's dementia and normal aging. *J Nucl Med* **30**(10): 1607–15
Folstein MF, Folstein SE, McHugh PR (1975) 'Mini-Mental State': a practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res* **12:** 196–8
Fox NC, Scahill RI, Crum WR, Rossor MN (1999) Correlation between rates of brain atrophy and cognitive decline in AD. *Neurology* **52**(8): 1687–9
Geroldi C, Pihlajamaki M, Laasko MP et al (1999) APOE-epsilon4 is associated with less frontal and more medial temporal lobe atrophy in AD. *Neurology* **53**(8): 1825–32
Huang W, Alexander GE, Chang L et al (2001) Brain metabolite concentration and dementia severity in Alzheimer's disease: a (1)H MRS study. *Neurology* **57**(4): 626–32
Jack CJ, Peterson R, Xu Y et al (1998) Rate of medial temporal lobe atrophy in typical ageing and Alzheimer's disease. *Neurology* **51:** 933–9
Jack CR Jr, Peresen RC, Xu Y et al (2000) Rates of hippocampal atrophy correlate with change in clinical status in ageing and AD. *Neurology* **55**(4): 484–9
Jessen F, Block W, Traber F et al (2000) Proton MR spectroscopy detects a relative decrease of N-acetylaspartate in the medial temporal lobe of patients with AD. *Neurology* **55**(5): 684–8
Johnson SC, Saykin AJ, Baxter LC et al (2000) The relationship between fMRI activation and cerebral atrophy: comparison of normal aging and Alzheimer's disease. *Neuroimage* **11:** 179–87
Killiany RJ, Gomez-Isla T, Moss M et al (2000) Use of structural magnetic resonance imaging to predict who will get Alzheimer's disease. *Ann Neurol* **47**(4): 430–9
Krall WJ, Sramek JJ, Cutler NR (1999) Cholinesterase inhibitors: a therapeutic strategy for Alzheimer's disease. *Ann Pharmacother* **33**(4): 441–50
Laakso MP, Hallikainen M, Hanninen T, Partanen K, Soininen H (2000) Diagnosis of Alzheimer disease: MRI of the hippocampus *vs* delayed recall. *Neuropsychologia* **38**(5): 579–84
McKahnn G, Drachman D, Folstein M, Katzman R, Price D, Stadlam EM (1984) Clinical diagnosis of the Alzheimer disease: report of the NINCDS-ADRDA Work Group under the auspices of the department of Health and Human Services Task Force on Alzheimer disease. *Neurology* **34:** 939–44
Moffat SD, Szekely CA, Zonderman AB, Kabani NJ, Resnick SM (2000) Longitudinal change in hippocampal volume as a function of apolipoprotein E genotype. *Neurology* **55**(1): 134–6
Potkin SG, Anand R, Fleming K et al (2001) Brain metabolic and clinical effects of rivastigmine in Alzheimer's disease. *Int J Neuropsychopharmacol* **3:** 23–30
Small GW, Rabins PP, Barry PP et al (1997) Diagnosis and treatment of Alzheimer's disease and related disorders: consensus statement of the American Association for Geriatric Psychiatry, the Alzheimer's association, and the American Geriatrics Society. *JAMA* **278:** 1363–71
Small SA, Nava AS, Perera GM, Delapaz R, Stern Y (2000a) Evaluating the function of hippocampal subregions with high-resolution MRI in Alzheimer's disease and ageing. *Microsc Res Tech* **51**(1): 101–8
Small GW, Ercoli LM, Silverman DH et al (2000b) Cerebral metabolic and cognitive decline in persons at genetic risk for Alzheimer's disease. *Proc Natl Acad Sci USA* **97**(11): 6037–42
Smith CD, Andersen AH, Kryscio RJ et al (1999) Altered brain activation in cognitively intact individuals at high risk for Alzheimer's disease. *Neurology* **53:** 1391–6
Xu Y, Jack CR, O'Brien PC et al (2000) Usefulness of MRI measures of entorhinal cortex versus hippocampus in AD. *Neurology* **54:** 1760–7
Zachariah E, Kumari V, Galea G et al (2002) Effects of oral procyclidine administration on cognitive functions in healthy subjects: implications for schizophrenia. *Int J Clin Psychopharmacol* **22**(2): 224–6

Figure 2. Examples of positron emission tomography (PET) images coregistered to each subject's baseline magnetic resonance image (MRI): (a) from an 81-year-old non-demented woman (APOE 3/3 genotype); (b) from a 76-year-old non-demented woman (APOE 3/4 genotype); (c) from a 79-year-old woman with Alzheimer's disease (APOE 3/4 genotype). The last column shows 2-year follow-up scans for the non-demented women. Compared with the non-demented subject without APOE-4, the non-demented APOE-4 carrier showed 18% (right) and 12% (left) lower inferior parietal cortical metabolism, whereas the demented woman's parietal cortical metabolism was 20% (right) and 22% (left) lower with more widespread metabolic dysfunction as a result of disease progression. Two-year follow-up scans showed minimal parietal cortical decline for the woman without APOE-4, but bilateral parietal cortical decline for the non-demented woman with APOE-4 who reached clinical criteria for mild Alzheimer's disease at follow-up. MRI scans were within normal limits.

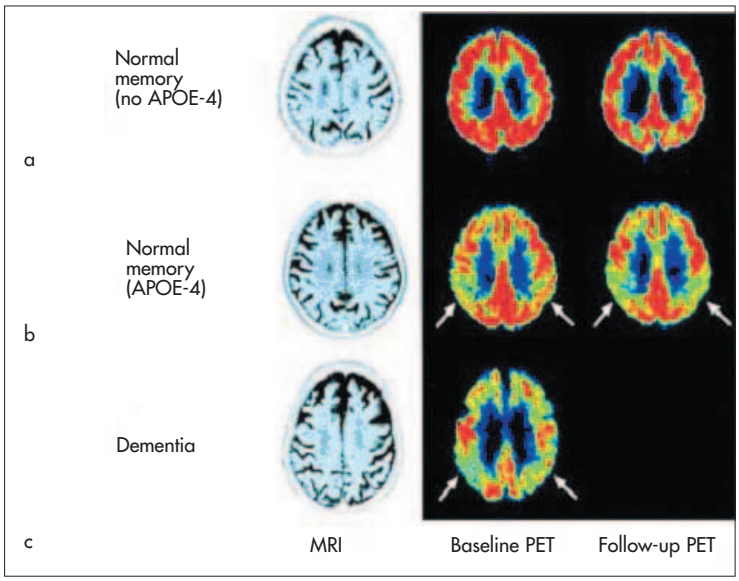

Figure 3. Representative proton (hydrogen-1) magnetic resonance spectra from: (a) the occipital region of a 65-year-old subject with Alzheimer's disease (AD) and a 69-year-old control; (b) the right parietal region of a 65-year-old subject with AD and a 65-year-old control; and (c) the left parietal regions of a 69-year-old subject with AD and a 68-year-old control. The identified resonance peaks in the control spectrum of (a) are: N-acetylaspartate (NAA), 2.02 parts per million (ppm); creatine (Cr), 3.03 ppm; choline (Cho), 3.23 ppm; myo-inositol (mI), 3.56 ppm. The upward and downward arrows indicate increases of mI and decreases of NAA peak amplitudes in subjects with AD compared with controls respectively.