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Imaging, Cerebral Topography and Alzheimer's Disease

S. R. Rapoport H. Petit
D. Leys Y. Christen (Eds.)

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Rapoport, Stanley I., M.D.
Laboratory of Neurosciences
National Institute on Aging
National Institutes of Health
Bethesda, MA 20892, USA

Petit, Henri, M.D.
A.D.E.R.M.A., Faculté de Médecine
Université de Lille
1, place de Verdun
F-59045 Lille Cédex

Leys, Didier, M.D.
A.D.E.R.M.A., Faculté de Médecine
Université de Lille
1, place de Verdun
F-59045 Lille Cédex

Christen, Yves, Ph. D.
Fondation IPSEN pour la Recherche Thérapeutique,
30, rue Cambronne, F-75737 Paris Cédex

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Preface

This volume contains the proceedings of the fifth Colloque Médecine et Recherche organized by the Fondation Ipsen pour la Recherche Thérapeutique and devoted to Alzheimer's disease. It was held in Lille on October 16, 1989 and dedicated to imaging, cerebral topography and Alzheimer's disease.

The proceedings of the previous meetings were published as the present one in the same series: *Immunology and Alzheimer's disease* (A. Pouplard-Barthelaix, J. Emile, Y. Christen eds.), *Genetics in Alzheimer's disease* (P.-M. Sinet, Y. Lamour, Y. Christen eds.) in 1988, *Neuronal grafting and Alzheimer's disease* (F. Gage, A. Privat, Y. Christen eds.), *Biological markers of Alzheimer's disease* (F. Boller, R. Katzman, A. Rascol, J.-L. Signoret, Y. Christen eds.) in 1989.

The next meeting of the series entitled ***growth factors and Alzheimer's disease*** was being held in Strasbourg on April 25, 1990. The proceedings will be published by the end of this year.

Yves Christen
Vice-Président of the Fondation Ipsen pour la Recherche Thérapeutique

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Contributors

Agniel, A.
INSERM U. 230 et Service de Neurologie, CHU Purpan, 31059 Toulouse Cédex, France

Baron, J. C.
INSERM U. 320 and Cyceron B.P. 5027, 14021 Caen Cédex, France

Bouras, C.
Département de Psychiatrie, IUPG Bel Air, Université de Genève, 1225 Chêne-Bourg, Geneva, Switzerland

Bowen, D. M.
Miriam Marks Department of Neurochemistry, Institute of Neurology (Queen Square), 1, Wakefield Street, London WC1N 1PJ, UK

Campbell, M. J.
Fishberg Research Center for Neurobiology and Department of Geriatrics and Adult Development, Box 1065, Mount Sinai School of Medicine, One Gustave L. Levy Place, New York, NY 10029, USA

Celsis, P.
INSERM U. 230 et Service de Neurologie, CHU Purpan, 31059 Toulouse Cédex, France

Clarisse, J.
Departments of Neuroradiology, Université de Lille, Faculté de Médecine, 1 place de Verdun, 59045 Lille Cédex, France

Cox, K.
Department of Neurosciences, University of California, School of Medicine San Diego, La Jolla, CA 92093, USA

Creasey, H.
Department of Geriatric Medicine, University of Sydney, Concord RG Hospital, Concord 2139, Australia

Cross, A. J.
Astra Neuroscience Research Unit, Institute of Neurology (Queen Square), 1, Wakefield Street, London WC1N 1PJ, UK

Défossez, A.
Laboratories of Histology (INSERM U. 156), Université de Lille, Faculté de Médecine, 1 place de Verdun, 59045 Lille Cédex, France

Delacourte, A.
Laboratories of Neurosciences (INSERM U. 16), Université de Lille, Faculté de Médecine, 1 place de Verdun, 59045 Lille Cédex, France

Delaère, P.
Laboratoire de Neuropathologie R. Escourolle, FRA Association Claude Bernard, Hôpital de La Salpêtrière, 47 bd de l'Hôpital, 75651 Paris Cédex 13, France

De Lima, A. D.
Max-Planck-Institut für Entwicklungsbiologie, Spemannstraße 35/I, 7400 Tübingen, FRG

Démonet, J. F.
INSERM U. 230 et Service de Neurologie, CHU Purpan, 31059 Toulouse Cédex, France

Duyckaerts, C.
Laboratoire de Neuropathologie R. Escourolle, FRA Association Claude Bernard, Hôpital de La Salpêtrière, 47 bd de l'Hôpital, 75651 Paris Cédex 13, France

Frackowiak, R. S. J.
National Hospital, Queen Square and MRC Cyclotron Unit, Royal Postgraduate Medical School, London, UK

Francis, P. T.
Miriam Marks Departments of Neurochemistry, Institute of Neurology (Queen Square), 1, Wakefield Street, London WC1N 1PJ, UK

Grady, C. L.
Laboratory of Neurosciences, National Institute on Aging, Bldg 10, Room 6C414, National Institutes of Health, Bethesda, MD 20892, USA

Green, A. R.
Astra Neuroscience Research Unit, Institute of Neurology (Queen Square), 1, Wakefield Street, London WC1N 1PJ, UK

Hauw, J.-J.
Laboratoire de Neuropathologie R. Escourolle, FRA Association Claude Bernard, Hôpital de La Salpêtrière, 47 bd de l'Hôpital, 75651 Paris Cédex 13, France

Haxby, J. V.
Laboratory of Neurosciences, National Institute on Aging, Bldg 10, Room 6C414, National Institutes of Health, Bethesda, MD 20892, USA

Hof, P. R.
Fishberg Research Center for Neurobiology and Department of Geriatrics and Adult Development, Box 1065, Mount Sinai School of Medicine, One Gustave L. Levy Place, New York, NY 10029, USA

Klunk, W. E.
University of Pittsburgh, Western Psychiatric Institute and Clinic, The Graduate School of Public Health, 130 DeSoto St., Crabtree Hall, Pittsburgh, PA 15261, USA

Lassen, N. A.
Department of Neurology, Rigshospitalet, 9, Blegdamsvej, 2100 Copenhagen, Denmark

Leys, D.
Departments of Neurology, Université de Lille, Faculté de Médecine, 1 place de Verdun, 59045 Lille Cédex, France

Lowe, S. L.
Miriam Marks Department of Neurochemistry, Institute of Neurology (Queen Square), 1, Wakefield Street, London WC1N 1PJ, UK

Luxenberg, J.
Laboratory of Neurosciences, National Institute on Aging, National Institutes of Health, Bethesda, MD 20892, USA

Marc-Vergnes, J. P.
INSERM U. 230 et Service de Neurologie, CHU Purpan, 31059 Toulouse Cédex, France

Morrison, J. H.
Fishberg Research Center for Neurobiology and Department of Geriatrics and Adult Development, Box 1065, Mount Sinai School of Medicine, One Gustave L. Levy Place, New York, NY 10029, USA

Parent, M.
Laboratories of Neuropathology, Université de Lille, Faculté de Médecine, 1 place de Verdun, 59045 Lille Cédex, France

Paulson, O. B.
Department of Neurology, Rigshospitalet, 9, Blegdamsvej, 2100 Copenhagen, Denmark

Petit, H.
Departments of Neurology, Université de Lille, Faculté de Médecine, 1 place de Verdun, 59045 Lille Cédex, France

Pettegrew, J. W.
University of Pittsburgh, Western Psychiatric Institute and Clinic, The Graduate School of Public Health, 130 DeSoto St., Crabtree Hall, Pittsburgh, PA 15261, USA

Piette, F.
Hôpital Charles Foix, 7, avenue de la République, 94205 Ivry/Seine, France

Procter, A. W.
Miriam Marks Department of Neurochemistry, Institute of Neurology (Queen Square), 1, Wakefield Street, London WC1N 1PJ, UK

Pruvo, J.-P.
Departments of Neuroradiology, Université de Lille, Faculté de Médecine, 1 place de Verdun, 59045 Lille Cédex, France

Puel, M.
INSERM U. 230 et Service de Neurologie, CHU Purpan, 31059 Toulouse Cédex, France

Rapoport, A.
Departments of Neurology, Université de Lille, Faculté de Médecine, 1 place de Verdun, 59045 Lille Cédex, France

Rapoport, S. I.
Laboratory of Neurosciences, National Institute on Aging, National Institutes of Health, Bethesda, MD 20892, USA

Rascol, A.
INSERM U. 230 et Service de Neurologie, CHU Purpan, 31059 Toulouse Cédex, France

Rossor, M. N.
National Hospital, Queen Square and MRC Cyclotron Unit, Royal Postgraduate Medical School, London, UK

Schapiro, M.
Laboratory of Neurosciences, National Institute on Aging, Bldg 10, Room 6C414, National Institutes of Health, Bethesda, MD 20892, USA

Soetaert, G.
Katholiek Universiteit Leuven, Leuven, Belgium

Steele, J. E.
Miriam Marks Department of Neurochemistry, Institute of Neurology (Queen Square), 1, Wakefield Street, London WC1N 1PJ, UK

Steinling, M.
NMR Imaging, Hôpital B. Lille, 1 place de Verdun, 59037 Lille Cédex, France

Stratmann, G. C.
Miriam Marks Department of Neurochemistry, Institute of Neurology (Queen Square), 1, Wakefield Street, London WC1N 1PJ, UK

Tyrrell, P.J.
National Hospital, Queen Square and MRC Cyclotron Unit, Royal Postgraduate Medical School, London, UK

Vermersch, P.
Departments of Neurology, Université de Lille, Faculté de Médecine, 1 place de Verdun, 59045 Lille Cédex, France

Voigt, T.
Max-Planck-Institut für Entwicklungsbiologie, Spemannstraße 35/I, 7400 Tübingen, FRG

Waldemar, G.
Department of Neurology, Rigshospitalet, 9, Blegdamsvej, 2100 Copenhagen, Denmark

Young, W. G.
Department of Neuropharmacology, Research Institute of Scripps Clinic, BCR-1, 10666 North Torrey Pines Road, La Jolla, CA 92037, USA

Contents

Topography of Alzheimer's Disease: Involvement of Association Neocortices and Connected Regions; Pathological, Metabolic and Cognitive Correlations; Relation to Evolution

S. I. Rapoport

Summary

Alzheimer's disease (AD) patients display reduced glucose metabolism and increased right-left metabolic asymmetries in the association neocortices early and throughout the clinical course, with relative sparing of primary sensory and motor neocortical regions. The metabolic asymmetries precede and predict neocortically mediated cognitive deficits. They also correspond with the distribution of AD neuropathology in the association, as compared with primary sensory and motor, neocortices. Outside of the neocortex, pathology is distributed mainly in brain regions functionally and anatomically connected with the association neocortex – medial septal nucleus, nucleus basalis of Meynert, CA1 and subicular subfields of hippocampal formation, layers II and IV of entorhinal cortex, corticobasal nuclear group of amygdaloid formation, cortically projecting neurons of the dorsal raphe and locus coeruleus. Comparative anatomical studies suggest that many of these regions evolved disproportionately in higher primates, particularly in hominids, by a process termed "integrative phylogeny." Thus, the topographic distribution of functional and pathological abnormalities in AD suggests that AD is a phylogenic disease. Regional vulnerability to the disease may have been introduced into the primate genome during evolution, possibly by regulatory mutations. The topographic correspondence of neuropathology and functional deficits in AD and demented adults with Down's syndrome suggests, furthermore, that a genomic change equivalent to increased expression of genes on human chromosome 21 introduced the AD process during evolution.

Why Determine the Topography of Neurodegenerative Disorders?

In the last decade, it has become possible to examine the topography of certain human neurodegenerative diseases by means of positron emission tomography (PET), early and throughout their clinical course (Huang et al. 1980). For example, with an appropriate positron emitting isotope, such as [^{18}F]2-fluoro-2-deoxy-D-glucose (^{18}FDG), and a sensitive PET scanner, we can now examine regional cerebral metabolic rates for glucose ($rCMR_{glc}$) within areas of the human brain as small as 6 mm in diameter, on the cortical surface as well as subcortically

(Grady et al. 1989a). As glucose is the major substrate for brain oxidative metabolism, its rate of consumption is a direct measure of regional brain functional activity.

Positron emission tomography studies during life, if consistent with postmortem neuropathology and neurochemistry, make it easier to guess which brain regions are initially affected in a given disorder, and which degenerate in a secondary manner. This is important because postmortem studies alone cannot identify the order of pathological events, but only the final picture. By using PET to ascertain which brain regions are affected early in the course of a disease, it should be possible to generate hypotheses and experimental approaches to better understand its pathogenesis, with regard to factors such as genetics, environmental exposure, regional connectivity, or regional metabolic, molecular biological or neurotransmitter differences. Furthermore, because man is an animal who reached his present form through genetic mutation, natural selection and adaptation to changing environments (Darwin 1871), regional differences in disease vulnerability can also be considered in terms of evolutionary principles (Hughlings Jackson 1884; Roofe and Matzky 1968; Rapoport 1988a, b, 1989).

Comparative anatomical data suggest that the brain not only increased in size during recent primate evolution but also underwent disproportionate expansion and differentiation of certain systems of related regions (cf. Luria 1973) according to the principle of "integrated phylogeny" (Rapoport 1988a, 1989, in preparation). Furthermore, human neurological disorders may affect such systems according to the recency of their evolutionary modifications during primate (and particularly hominid) evolution (cf. Hughlings Jackson 1884). In such cases, a neurological disease can be rightly termed "phylogenic" (Roofe and Matzke 1968; Sarnat and Netsky 1981; Rapoport 1989).

Integrative Phylogeny of Association Brain Regions

It has been proposed that several systems or ensembles of functionally and anatomically connected brain regions underwent integrated phylogeny during recent evolution of primates, particularly of hominids (Rapoport, in preparation). As illustrated in Table 1, System I regions include the association neocortices and non-neocortical telencephalic regions within the hippocampal formation (CA1 and subicular subfields), entorhinal cortex (layers II and IV), amygdaloid complex [corticobasolateral nuclear group, as defined by Stephan and Andy (1977)], nucleus basalis of Meynert and medial septal nucleus. System II regions include several frontal cortical regions, as well as parts of the thalamus, basal ganglia and substantia nigra which constitute segregated circuits contributing to motor movements and motor-related memory and other cognitive abilities (Alexander et al. 1986; Rapoport, in preparation). System III regions include the neodentate nucleus of the cerebellum, and certain neurons of pontine and mesencephalic nuclei. In general, many of the non-neocortical brain regions and their subdivisions, which expanded or differentiated disproportionately during primate evolution, are anatomically and functionally related to the association neocortices (Rapoport 1988a,b; 1989, in preparation).

Table 1. Progression studies of telencephalic brain regions in higher primates[a]

Brain region	PI[b] man	Division with maximal progression during primate evolution
System I[c]: Telencephalic regions, including amygdala and hippocampal formation		
Neocortex	156	Association areas, including Prefrontal cortex Visual association Broca's speech area (44 and 45, Brodman) Inferior parietal lobule (39 and 40, Brodman) Brodman area 37 (part of Wernicke's speech area)
Corpus callosum	↑	
Amygdaloid complex	3.9	Corticobasolateral group
Hippocampal formation	4.2	Subiculum, CA1 regions
Entorhinal cortex	5.5	
Septum	4.0	
Nucleus basalis of Meynert	↑	

[a] Data summarized by Rapoport (in preparation) from Stephan and Andy (1970, 1977), Stephan et al. (1970, 1987), Andy and Stephan (1966) and Gorry (1963)
[b] PI, progression index in *Homo sapiens* (ratio of weight of human brain to weight of brain in insectivore of equivalent body weight). ↑, PI > 1 but value not known in man
[c] See text for details

Several human neurological disorders probably involve brain regions of System II. These include obsessive compulsive disorder (in which metabolic abnormalities are localized in the orbitofrontal cortex, anterior cingulate gyrus, prefrontal cortex and caudate nucleus, and where the anatomy of the caudate nucleus is abnormal) (Baxter et al. 1987; Luxenberg et al. 1988; Wise and Rapoport 1988; Swedo et al. 1989), Huntington's disease (in which the caudate nucleus degenerates), and Parkinson's disease (with pathology in the substantia nigra and caudate nucleus) (Heindel et al. 1989; Rapoport, in preparation).

On the other hand, System I regions appear to be preferentially involved in Alzheimer's disease (AD), Pick's disease and Down's syndrome (Rapoport 1988a, b, 1989; Haxby et al., this volume; Schapiro et al., 1986 and this volume). In this paper, I summarize neuropathological, PET and cognitive data which argue for System I regional predilection to AD, and in turn suggest that AD is a human phylogenic disease. This latter interpretation implies, I believe, that understanding the genetic basis of evolution of the human brain, and particularly of AD-vulnerable regions, may elucidate the genetic basis of AD.

Neuropathology of Association Regions in the Alzheimer Brain

Abundant senile (neuritic) plaques, neurofibrillary tangles with paired helical filaments, and neuronal dropout characterize the AD brain (Terry and Wisniewski 1972; Ball and Nuttall 1981; Ball et al. 1985; Arendt et al. 1985). This

Table 2. Brain regions affected by Alzheimer pathology[a]

Association neocortices much more than primary motor or sensory neocortices
Neurofibrillary tangles in pyramidal neurons of layers III and V; cell loss
Non-neocortical regions connected with association neocortices
Posterior cingulate gyrus
Entorhinal cortex (layers II and IV)
Hippocampal formation (subiculum, CA 1 pyramidal field, dentate gyrus)
Amygdaloid formation, corticobasal group
Cholinergic nucleus basalis of Meynert (Ch 4)
Medial septal nucleus (Ch 1)
Locus coeruleus, noradrenergic cortically projecting neurons
Dorsal raphe, serotonergic cortically projecting neurons

[a] See text for references

Table 3. Distribution of neurofibrillary tangles in cortical visual regions of patients with AD[a]

Age (years)	Cortical region[b]		
	17	18	20
82	0.2 ± 0.1	9.8 ± 1.5	7.8 ± 1.1
74	0.1 ± 0.1	13.0 ± 0.7	24.4 ± 1.6
71	0.1 ± 0.1	15.0 ± 1.5	22.1 ± 1.3
68	0.5 ± 0.3	19.9 ± 2.2	57.5 ± 3.9
63	2.0 ± 0.6	30.3 ± 1.6	63.5 ± 5.2
62	2.4 ± 0.5	30.4 ± 2.3	37.5 ± 2.0
Mean	0.9 ± 1.0*	19.7 ± 3.6**	35.5 ± 8.8***

[a] Data from Lewis et al. (1987)

[b] Values for each case are the mean ± SE number of tangles in a 250-μm-wide cortical traverse from ten sections. Values not sharing same superscript are significantly different from each of the others ($p < 0.05$)

neuropathology is more severe in System I regions than in System II or other nonassociation brain regions (Table 2) (Rapoport 1988 b, in preparation). Thus, the association neocortices are more severely pathological than are primary sensory and motor regions (Brun and Gustafson 1976; Pearson et al., 1985). Although senile plaques are commonly found throughout the neocortex, neurofibrillary tangles are more common within large pyramidal neurons of layers III and V of association than of primary sensory and motor areas, as illustrated, for example, for visual regions (Table 3) (Pearson et al. 1985; Rogers and Morrison 1985; Lewis et al. 1987). Layer III and V neurons are the source of corticocortical fibers, whereas layer V neurons also give rise to corticofugal fibers (Wise and Jones 1977), and their involvement indicates disorganization of long cortical-cortical and corticofugal connections (Horwitz et al. 1987; Morrison, this volume).

Outside of the neocortex, neurofibrillary tangles are found in neurons which are closely connected, directly or indirectly, with the association neocortex, and

belong mainly to the System I regions which underwent integrated phylogeny (Table 1). These cells are in layers II and IV of the entorhinal cortex, and in the subiculum, CA1 subfield and outer two-thirds of the molecular layer of the dentate gyrus of the hippocampal formation (Ball and Nuttall 1981; Kemper 1984; Hyman et al. 1984, 1986). The subiculum and entorhinal cortex connect the hippocampal formation reciprocally with the association neocortices, and their pathology in AD may functionally disconnect the hippocampal formation from these regions (Hyman et al. 1984).

Cell loss and neuropathology are also found in the posterior cingulate gyrus (Brun and Gustafson 1976), which has important connections with the association neocortex. The corticobasal nuclear group of the amygdaloid complex, closely connected with the posterior hippocampal formation, entorhinal cortex and association neocortex, is more usually affected in AD than is the centromedial group, which is less association related (Jamada and Mahraein 1968; Stephan and Andy 1977; Kemper 1984). Regions of the basal forebrain are frequently pathological. The medial septal nucleus, which exchanges fibers with the posterior cingulate gyrus and hippocampal formation, is often affected (Arendt et al. 1985), as is the nucleus basalis of Meynert, which provides most of the cholinergic innervation to the neocortex (Whitehouse et al. 1982; Mesulam et al. 1983; Arendt et al. 1985).

Additionally affected nuclear groups in AD usually are connected with the neocortex. Thus, cortically projecting serotonergic neurons within the dorsal raphe nuclei are affected, as compared with the central superior nucleus (Zweig et al. 1988). Furthermore, dorsally situated noradrenergic neurons within the locus coeruleus (as compared with central neurons which project to the basal ganglia, cerebellum and spinal cord) are lost in the AD brain (Marcyniuk et al. 1986; Mann et al. 1987). The thalamus, caudate nucleus and substantia nigra are less frequently involved. The olfactory bulb, which regresses along the ascending primate scale and has connections with the amygdaloid complex, is also pathological (Mann et al. 1988).

The paired helical filaments of neurofibrillary tangles contain an abnormally phosphorylated, microfilament-associated protein tau, the protein ubiquitin, and high molecular weight protein aggregates (Grundke-Iqbal et al. 1986). These filaments are also found in the neurites of senile plaques. A precursor, a nonphosphorylated tau-like neurofilament protein, has been demonstrated within neurons of layers III and V of the association neocortices, the subiculum, layers II and IV of the entorhinal cortex, and the pyramidal and hilar regions of the hippocampus, all of which demonstrate neurofibrillary tangles in AD (Morrison et al. 1987). When the tangles are evident, however, labeling of the nonphosphorylated precursor disappears.

Alzheimer's disease is accompanied by brain atrophy and neuronal loss. Even early in its clinical course, progressive ventricular dilatation can be demonstrated by serial quantitative computed tomography (Creasey et al. 1986 and this volume; Luxenberg et al., 1987). In the postmortem AD brain, atrophy is more severe in association than in primary cortical regions (Najlerahim and Bowen 1988; Bowen et al.; this volume), where it is evidenced as reduced thickness and reduced length of the cortical ribbon (Duyckaerts et al. 1985; Mann et al. 1985). Neuronal loss

in subcortical structures frequently is correlated with plaque, tangle or cell counts in connected cortical areas (Mann et al. 1985; Arendt et al. 1985).

Down's syndrome (trisomy 21) subjects older than 35 years of age display the characteristic neuropathology of AD, although neurofibrillary tangles with paired helical filaments may occur years after high numbers of senile plaques appear in the Down's syndrome brain (Burger and Vogel 1973; Wisnieswki et al. 1985; Mann and Esiri 1989; Schapiro et al. this volume). Furthermore, the topography of neuropathology in the Down's syndrome brain does not differ from the topography in brains of AD patients (Ball and Nuttall 1981; Mann et al. 1984, 1987; Casanova et al. 1985; Schapiro et al., 1986; Marcyniuk et al. 1988). Finally, functional, metabolic and neurochemical disturbances in demented older Down's syndrome subjects are quite similar to those found in AD patients (see below) (Schapiro et al., this volume). These correspondences attest to the similarity of the neurodegenerative processes in Down's syndrome and AD (see "Discussion" below).

Brain Metabolism and Cognition in AD

Positron emission tomography studies of $rCMR_{glc}$ in patients with AD clearly demonstrate early and selective involvement of the association, as compared with primary sensory and motor, cortices in this disorder. In our research program at the Laboratory of Neurosciences, $rCMR_{glc}$ was studied in relation to severity of dementia in AD patients and in age-matched healthy controls. PET was performed on subjects at rest and with reduced visual and auditory inputs, using an ECAT II scanner (ORTEC, Life Sciences, Oak Ridge, TN; FWHM = 17 mm). The AD patients were screened for illnesses other than AD which might contribute to cerebral dysfunction, and the controls were screened very carefully as well. AD (possible or probable) was diagnosed according to NINCDS-ADRDA criteria for choosing patients for research purposes (McKhann et al. 1984). Severity of dementia was assessed with the Mini-Mental State Examination (Folstein et al., 1975); mild, score = 21–30; moderate, score = 11–20; severe, score = 0–10. Subjects were also administered an extensive neuropsychological test battery (Wechsler 1955; Haxby et al. 1986).

Mean scores derived from this battery are summarized in Table 4 for mildly and moderately demented AD patients. Whereas moderately demented patients differed from controls on a wide range of neuropsychological tests, mildly demented patients differed only on the tests of memory ($p < 0.01$). Indeed, a significant and isolated memory impairment, with normal scores on all tests of language and visuospatial function, characterized five of the ten mildly demented patients in Table 4 (Haxby et al. 1986).

Differences between mean $rCMR_{glc}$ values in mildly demented AD patients and controls were difficult to demonstrate statistically because of the large standard deviation of absolute PET data (Duara et al. 1986). However, standard deviations could be reduced to about 5% of the means by calculating ratios of