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A Meta-Analysis of Structural and Functional Brain Imaging in Dementia of the Alzheimer's Type: A Neuroimaging Profile

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We conducted a quantitative review of the imaging literature using meta-analytic methodology to characterize further the magnitude of hippocampal deficit in probable Alzheimer's disease (AD) and to determine whether other neuroanatomic structures in AD can better discriminate the disease from normal aging. Additionally, we parceled the discriminability of neuroanatomic structures by duration of disease to determine those structures most sensitive to AD in its early and late stages. One hundred twenty-one studies published between 1984 and 2000 met criteria for inclusion in the present analysis. In total, structural (i.e., CT and MRI) and functional (i.e., SPECT and PET) neuroimaging results from 3511 patients with AD, and 1632 normal healthy controls were recorded across meta-analyses. Our results include neuroimaging profiles for both early onset and longer duration patients with AD. In sum, these profiles yield a signature of diagnostic markers in both cortical and subcortical neuroanatomic areas. This signature is consistent with the clinical phenomenology of Alzheimer's dementia and should aid in the positive identification of AD.

KEY WORDS: Alzheimer's disease; neuroimaging; MRI; CT; SPECT; PET; review.

Alzheimer's disease (AD) can cripple an individual of his/her existence and cause profound suffering for families. It is the most common form of dementia over the age of 65 years, and its occurrence in this population is rapidly increasing. Although adequate care of the burgeoning population of demented individuals with AD requires a knowledgeable approach to diagnosis and management, it is of no coincidence that research into its pathophysiology and behavioral expression has grown in concert with its prevalence.

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The *in vivo* anatomic techniques available during the 1970s like computerized tomography (CT) and, more recently, magnetic resonance imaging (MRI), single photon emission computerized tomography (SPECT), and positron emission tomography (PET) have been eloquently applied to the problem of finding evidence of abnormal brain structure and physiology in this disease (e.g., Kidron et al., 1997; Kumar et al., 1991; Laakso et al., 1996). But to what extent are these structures really defective in AD?

The accumulated literature has most often generated support for hippocampal deficit in AD in the form of statistically significant patient and control group differences. This evidence has been reviewed by several researchers (e.g., Charletta, Bennett, and Wilson, 1993; Mentis, 2000). These reviews, however, do not reveal the magnitude of hippocampal deficit in accumulated CT, MRI, SPECT, and PET studies of patients with AD. That is, traditional narrative reviews conflate statistically significant group differences with evidence for hippocampal deficits and do not give due consideration to the magnitude of such differences. Moreover, it is not uncommon to discover

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statistically significant group differences between patients with AD and normal controls in neuroanatomic areas beyond hippocampal cortices (e.g., Krasuski et al., 1998; Pietrini et al., 1996; Waldemar et al., 1994). Thus, although most interpretations of the literature suggest hippocampal impairment in many patients, the strength and consistency of this evidence has not been evaluated and synthesized quantitatively, nor immediately distinguished in terms of magnitude versus other cortical and subcortical structures.

Estimates of deficit magnitude require the quantitative methods of research synthesis provided by meta-analysis (Zakzanis, 1998a). For example, the magnitude, in standard deviation units, of AD-control group differences in hippocampal volume and regional cerebral blood flow (rCBF) was addressed recently in a quantitative review of the published literature (see Zakzanis, 1998b). A moderately large and reliable deficit in whole hippocampal volume and left hippocampal rCBF in patients with AD was found. The average magnitude of effect size, however, suggested that a significant proportion of any given AD sample, perhaps 20%, would be indistinguishable from healthy control subjects. Incomplete hippocampal differentiation between patients with AD and normal controls may reflect changes in hippocampal volume and rCBF in "normal" control persons who eventually developed AD but did not meet criteria for the disease at the time of initial evaluation. Indeed, it has been demonstrated that significant hippocampal volume loss due to normal aging may approach 46 mm^3 per year over the age of 65, with a near-linear decline (Jack et al., 1997). Yet *in vivo* hippocampal comparison between patients with AD and normal controls is believed to have produced the clearest distinction between these two groups (Mega, Thompson, Toga, and Cummings, 2000). Given the wealth of evidence accumulated across studies and institutions showing significant hippocampal loss in AD compared with elderly controls, there is now no longer a need for any future studies to confirm that the hippocampus in AD is reduced in volume and blood flow compared with normal-aged individuals (Mega et al., 2000). The present challenge is to characterize further the magnitude of hippocampal volume and blood flow in AD and to determine whether other neuroanatomic structures can better discriminate the disease from normal aging; particularly those structures that are least compromised by normal aging.

Accordingly, we conducted a quantitative review of the imaging literature, using meta-analytic methodology. Neuroimaging methods considered for our review included structural MRI and CT, which are noninvasive techniques for measuring the anatomy of the brain. Magnetic resonance imaging allows for an image of higher resolution than CT, but both have been applied to measuring brain volume in AD. Spectroscopic MRI and functional MRI remain in their infancy as research tools in AD, and therefore this literature was not reviewed because of an insufficient number of primary studies. Also reviewed were functional neuroimaging findings that offer the advantage of physiological rather than structural anatomical imaging. The most frequently indexed aspects of physiological function in AD include glucose metabolism and blood flow as measured with PET and SPECT, both of which were tracked in our literature review. It is important to note that each of these imaging methods has its strengths and limitations in clinical practice. Accordingly, these various techniques are considered complementary to one another in terms of diagnosis and documenting the clinical progression of disease in general (e.g., Buchpiguel, Alavi, Alavi, and Kenyon, 1995; Wagner and Conti, 1991).

Two broad questions were formulated to guide our analyses:

1. Are there neuroanatomic structures other than the hippocampus that provide better discriminators between AD and normal aging?
2. Is there a relationship between duration of disease and discriminability of neuroanatomic structures?

Hence, the goal of this review was to profile the Alzheimer brain in terms of *in vivo* neuroanatomy and by way of disease duration by determining the consistency, strength, and sensitivity of structural and functional neuroimaging findings. Consistency refers to the reliability of the findings, strength refers to the magnitude of effect, and sensitivity refers to how capable a given measure is in terms of identifying impairment.

METHODS

Meta-Analysis

We employed standard meta-analytic techniques to our review of the neuroimaging literature in AD (see Cooper and Hedges, 1994; Hedges and Olkin, 1985; Rosenthal, 1991, 1995). In addition to solving problems with traditional narrative reviews (see Wolf, 1986), meta-analysis provides tools for the analysis of magnitude. Magnitude can be indexed with the effect size estimate *d* that is meant to reflect the degree to which the dependent variable is present in the sample group or the degree to which the null hypothesis is false (Cohen, 1988). In mathematical terms, *d* is the difference between patient and control means calibrated in pooled standard deviation units. Eligible research studies comprising a common dependent variable and statistics that can be transformed into effect sizes

are viewed as a population to be systematically sampled and surveyed. Individual study results (typically means and standard deviations from each group) and moderator variables (e.g., duration of disease, gender, age) are then abstracted, quantified and coded, and assembled into a database that is statistically analyzed (Lipsey and Wilson, 1993). The main statistic presented in a meta-analysis is the mean effect size, which is meant to reflect the average individual effect size across the sample of studies included in the synthesis. Moderator variables are then correlated to the effect size to tease out relationships of subject characteristics that may influence the magnitude of the size of effect between the groups being compared.

Moreover, the effect size can then be transformed into a nonoverlap percentage (*U*), using Cohen's idealized distributions (Cohen, 1988), that can be used to indicate potential clinical markers for a disease and hence, aid in the differential diagnosis of neurological and psychiatric disease (see Zakzanis, Leach, and Kaplan, 1999). The *U* statistic represents the degree of nonoverlap associated with *d* and the distribution of scores between groups (Cohen, 1988). As in our previous work (see Zakzanis et al., 1999), we converted the *U* statistic to represent the degree of overlap by subtracting the nonoverlap from 100. Where appropriate, this hypothetical overlap statistic (OL%; overlap percentage) will be mentioned to aid in the interpretation of the data. Accordingly, the OL% statistic used here represents the degree of overlap between patients with AD and normal control participants in the distributions of structural and physiological measures of the cerebrum. For example, if the mean effect size between patients with AD and normal controls corresponded to an OL% of ∼5.0, this would mean that ∼95% of the patients with AD had, for instance, temporal lobe volume unlike any of the normal controls. Conversely it would mean that 5% of the patients and controls had similar temporal lobe volumetry. Moreover, if the corresponding overlap for an effect size was 10%, it would mean that 90% of the patients and controls had, again for example, similar temporal lobe volumetry (for a review, see Zakzanis, 2001).

Indeed meta-analytic findings have implications for basic science, diagnostic use, and treatment effects. For example, in 1982, Hunter and colleagues introduced meta-analytic procedures that focused on comparing the observed variation in psychotherapy study outcomes with that expected by chance to refute Eyesenck's long-accepted claim that psychotherapy was no better in terms of efficacy than no therapy (see Cooper and Hedges, 1994). Since then, meta-analytic studies of treatment efficacy for both psychological and pharmacologic modalities have become unequivocally the most popular methodological venue for evaluating treatment efficacy (e.g., Beasley et al., 2000; Gloaguen, Cottraux, Cucherat, and Blackburn, 1998; Gould, Mueser, Bolton, Mays, and Goff, 2001). Meta-analysis has also resolved basic science questions. For example, Russo and Spinnler (1994) have found that patients with AD show impairment in stem completion in comparison to word identification whereas the experimental literature had long accepted that patients with AD present with preserved repetition priming. Finally, meta-analytic procedures have also been used to create diagnostic profiles that can be used to differentiate disorders on the basis of effect size magnitudes of commonly employed clinical neuropsychological measures (see Zakzanis et al., 1999). Moreover, effect size statistics have also been used to aid in the differentiation of dementia from depression (e.g., Lachner and Engel, 1994).

Finally, it should be noted that the statistical analysis employed in meta-analytic studies is not entirely uncontroversial (see Hunter and Schmidt, 1990). As reviewed by Wolf (1986), there are some limitations surrounding this technique. A particular problem with any meta-analytic review of the literature is that primary studies vary in sample size, and that independent variables are not uncorrelated. As Van Horn and McManus (1992) did, we have used a correlational analysis to assess the independent effects of moderator variables, and have made no attempt to weight the various studies according to their sample sizes. In so doing, we are also aware of the problem emphasized by Hunter and Schmidt (1990, p. 86) that in examining meta-analytic data for the effects of moderator variables the crucial characteristic is the number of studies and not the number of subjects, which paradoxically can sometimes mean that their statistical power is surprisingly low, despite apparently large subject numbers (Van Horn and McManus, 1992). In using both univariate and multivariate analysis, we have followed Van Horn and McManus (1992) in not attempting to take any account of the differing sample sizes in studies. Despite the concerns of Hedges and Olkin (1985), we have also accepted the argument of Hunter and Schmidt (1990, p. 408) that such problems pale into insignificance in comparison to the problems posed by low power in such studies. In assessing the potential effects of moderator variables, we have therefore used unweighted population estimates from individual studies (see Van Horn and McManus, 1992).

Literature Search

We began our review of the literature by conducting a manual search through the volumes of journals that publish a high volume of relevant papers year by year as recommended by Cooper and Hedges (1994). This was done with every issue for the following journals:

American Journal of Psychiatry; *Annals of Neurology*; *Archives of Clinical Neuropsychology*; *Archives of General Psychiatry*; *Archives of Neurology*; *Biological Psychiatry*; *Brain*; *British Journal of Psychiatry*; *Dementia*; *Journal of Clinical and Experimental Neuropsychology*; *Journal of Neuropsychiatry and Clinical Neurosciences*; *Journal of Nervous and Mental Disease*; *Journal of the International Neuropsychological Society*; *Neurology*; *Neuropsychology*; *Neuropsychiatry, Neuropsychology, and Behavioral Neurology*; *Neuropsychopharmacology*; *Psychiatry Research.* To reduce the likelihood that bias was involved in the manual search outcome, we also located potential studies by conducting a computer-based search, using the *PsychInfo* and *Medline* databases. The key words used in the database search were "Alzheimer's" with independent matched searches with the key word(s) "PET," "positron emission tomography," "MRI," "magnetic resonance," "CT," "computed tomography," "CAT," "computed axial tomography," "brain metabolism," "blood flow," "neuroimaging," and "imaging." The studies located by the computer search were limited to published English written studies. Studies were obtained at two large Canadian Universities and through interlibrary loan.

Study Inclusion Criteria

Papers were included if they met the following criteria: (1) publication between 1984 and 2000; (2) research designs with a control group comprising healthy participants that had no reported history of neurological or psychiatric disease or any chronic medical disorder including a history of substance abuse where reported; (3) study statistics convertible to effect size *d* (e.g., means, standard deviations, *F*, *t*, *X*; see Wolf, 1986). Pre-1984 papers were not gathered in keeping with the introduction and use of more systematic and reliable diagnostic criteria for AD (i.e., NINCDS ADRDA criteria; see McKhann et al., 1984; hence, all patients in primary studies met NINCDS ADRDA criteria). If these criteria were met, the paper was then assessed for methodological rigor. Namely, the researcher(s) must have been blind to the subjects' diagnosis (i.e., either subject with AD or normal control) when reading the scans. This stipulation was made to ensure that the quality of the neuroimaging evaluation in each study was held relatively constant and did not influence the findings (see Damasio and Damasio, 1989). If the research paper met the preceding criteria, its content variable(s) was included in our review. In the case of separately published studies that used the same subject samples, the decision rule adopted was to treat these studies as a single study with multiple independent variables (see Hedges and Olkin, 1985). The *d* statistic (Cohen, 1988) was calculated for each comparison as the difference between Alzheimer and control group means normalized by the pooled standard deviation. Effect sizes were derived whenever means and standard deviations were reported. Effect sizes were also calculated from inferential statistics on the basis of formulas provided by Wolf (1986) when primary studies did not report central tendency and dispersion data. Effect sizes were not derived from *p* values.

Recorded Variables

Recorded variables for each article used in our meta-analysis included the full study reference, any moderator variables reported [e.g., age, onset age, duration of illness, percent male, and total score on the Mini-Mental State Examination (MMSE); Folstein, Folstein, and McHugh, 1975]. These study characteristics were used to describe the study set retrieved and treated uniformly for moderator variable analysis.

Computed Tomography and Magnetic Resonance Imaging. The brain volumetry literature involving CT scanning is concentrated in the late 1980s and early 1990s, when this imaging modality was well established and more widely available than MRI. In comparison, the MRI literature on this subject spans this period up to the present and reflects the increased use of MRI primarily due to the improved soft tissue contrast exhibited by neural tissues with this modality. Not surprisingly, there are large variations in the quality of the extracted volumetric measures in both the CT and MRI literature. In particular, the presentation of data which controlled for head size occurred in only 7 of 13 CT papers, and 19 of 36 MRI papers.

In the case of CT, data ranges upward in quality from studies that do not mention the in-plane or through-plane spatial resolution, or both (e.g., Burns, Jacoby, Philpot, and Levy, 1991; DeCarli et al., 1992; de Leon et al., 1989; Fazekas et al., 1989; Förstl, Burns, Jacoby, Eagger, and Levy, 1991a,b; Kido et al., 1989; Pfefferbaum et al., 1990; Smith et al., 1992), to protocols that are described meticulously, enabling detailed methodological evaluation (e.g., Kido et al., 1989; Obara, Meyer, Mortel, and Muramatsu, 1994). The size of brain voxels was typically $1 \times 1 \times 8$ mm, slightly larger than that reported in the MRI literature (see below). Neuroanatomical measurements were performed using numerous techniques ranging from mechanical planimetry (e.g., Burns et al., 1991) to careful manual tracing (e.g., Obara et al., 1994). Sophisticated image processing techniques to eliminate the effects of beam hardening, spectral shift, and streak artifacts were rarely adopted in addition to the

default image quality provided by the scanner (e.g., Shear et al., 1995). The majority of analyses were based on semiautomatic procedures that performed an initial tissue segmentation based on image intensity threshold, which was subsequently refined by a trained observer to identify large geometric regions of interest. These analyses were predominantly supported by preliminary assessments of inter- and intrarater variability.

Compared with CT, there is more variation in data quality associated with the MRI literature, given that there is considerably more flexibility in MRI scan protocol and sensitivity to more image parameters that govern image quality. Data are reported predominantly at the magnetic field strength of 1.5 T, the predominant strength currently installed worldwide. Several studies were performed at lower fields, however, notably 0.5 T (e.g., Biegon et al., 1994; DeCarli et al., 1995, 1996; Hampel et al., 1998; Krasuski et al., 1998; Murphy et al., 1993; Teipel et al., 1998; Vermersch et al., 1993) and even 0.02 T (e.g., Wahlund et al., 1993). The lower signal-to-noise ratio at these fields can be overcome by increasing voxel size, although this likely does not eliminate extra variability in volumetric or area measurements compared with those at 1.5 T. The improved capability to perform scans with oblique slice orientation enabled numerous studies to scan the cross-section of the hippocampus with ~1-mm in-plane spatial resolution (e.g., Cuénod et al., 1993; Krasuski et al., 1998; Lehtovirta et al., 1996; Pearlson et al., 1992; Vermersch et al., 1993). The typical slice thickness across all studies was 5 mm. Analyses varied upwards in quality from a single multislice spin echo acquisition followed by manually defined regions of interests, very similar to the procedure used in CT analysis (e.g., DeCarli et al., 1995, 1996; Wahlund et al., 1993), to multiple scans with intensity weightings reflecting two or three of the principal tissue parameters that determine image contrast in MRI: proton density, T2 relaxation time, and T1 relaxation time (e.g., Barta et al., 1997; Hampel et al., 1998; Kidron et al., 1997; Murphy et al., 1993; Pearlson et al., 1992; Teipel et al., 1998; Yamauchi et al., 1993). The latter approach also included as a subset the use of 3D MRI approaches to determine T1-weighted images with much-improved through-plane resolution (ranging from 1.3- to 3-mm slice thickness) (e.g., Hampel et al., 1998, Kidron et al., 1997; Teipel et al., 1998). The combined use of three image data sets with different image contrast and 3D MRI greatly improves the capabilities of semiautomated tissue segmentation (Kidron et al., 1997) and likely enables the best volumetric measures of convoluted neuroanatomy currently available.

Single Photon Emission Computed Tomography. Studies of the Alzheimer brain incorporating SPECT instrumentation were primarily interested in resting-state rCBF using both single- and multihead gamma-camera-based systems. The modern studies using single-head tomography have overcome many of the limitations of the original systems, such as poor head alignment, magnetic field aberrations, and inadequate uniformity and linearity for tomography. Most of the systems described in the primary studies provided high-resolution images with static tracers (7–10 mm). Moreover, several ^{99m}Tc-labeled and ^{123}I-labeled radiopharmaceuticals for the SPECT measurement of rCBF were used across studies. Static tracers included IMP, HIPDM, HMPAO, and ECD for use with rotating gamma cameras. Finally, receptor imaging studies were not gathered and, hence, not included in the meta-analysis.

Positron Emission Tomography. The PET findings that were gathered included cerebral blood flow studies that reflect the measurement of rCBF during continuous inhalation of $^{15}CO_2$. Activity was calculated in primary studies from cerebral blood flow after additional measurements of the oxygen extraction fraction (i.e., the percentage of the available blood oxygen extracted during its passage through the brain vasculature usually measured after inhalation of $^{15}CO_2$). Also gathered were studies of regional blood volume which is indexed by a correction for the percentage of any cerebral region that contains blood rather than brain (see Sawle, 1995). Finally, glucose metabolism studies were also gathered. These studies measured activation after intravenous injection of 2-[^{18}F]fluoro-2-deoxy-D-glucose (FDG), which is metabolized by hexokinase to FDG-6-phosphate. For the varying PET procedures, at-rest study conditions were used to compute effect sizes and no receptor imaging studies were included in the meta-analytic review.

To address the issue of improved imaging spatial resolution over time and its possible affect on the magnitude of the effect size, we computed an unweighted multiple regression with date of publication as a covariant which proved to be insignificant. We also analyzed, however, the different imaging techniques separately, rather than en mass, using Pearson product–moment correlations. We found a significant relation between SPECT effects and date of publication ($r = 0.40$, $p < 0.05$), but no such relation for the CT, MRI, and PET effects.

RESULTS

One hundred twenty-one studies published between 1984 and 2000 met criteria for inclusion in the present analysis. In total, neuroimaging results from 3511 patients with AD, and 1632 normal healthy controls were recorded across meta-analyses.

To determine whether the moderator variables (e.g., age, onset age, duration of illness, and gender) were related to the obtained effect sizes, we correlated each of the moderator variables with mean effect sizes computed from both structural and functional imaging modalities to compensate for insufficient power. (Note: Unilateral effect sizes were also combined.) We found a significant relation between duration of illness and hippocampal atrophy/metabolism ($r = –0.66$, $p < 0.01$), temporal lobe atrophy/metabolism ($r = –0.57$, $p < 0.05$), medial temporal lobe atrophy/metabolism ($r = –0.55$, $p < 0.05$), posterior temporal lobe atrophy/metabolism ($r = –0.45$, $p < 0.05$), parietal lobe atrophy/metabolism ($r = –0.41$, $p < 0.05$), and prefrontal cortex atrophy/metabolism ($r = –0.41$, $p < 0.05$). We also found a relationship between total MMSE score and age ($r = –0.59$, $p < 0.01$).

Table 1 includes a description of patient characteristics across all structural studies. Patients with AD included into structural imaging studies were on average 71 years of age, with a mean age at disease onset of 68. Patients were no more likely to be male than to be female and averaged a total score of 18 on the MMSE.

Table 2 includes the structural imaging mean effect sizes for each neuroanatomic variable parceled by major cerebral cortices and rank-ordered in terms of magnitude. Effect sizes were computed according to Cohen's *d* formula where the mean value of the control group was subtracted from the mean value of the patient group calibrated in pooled standard deviation units (see Cohen, 1988; Zakzanis, 2001). The table also includes the number of studies that contributed to the mean effect size, the standard deviation of the mean, the OL%, and the 95% confidence interval (CI). To address the issue of reliability of effect sizes, we calculated the number of studies needed to confirm an absence of a meaningful effect size. Cooper (1979) called this the Fail Safe *N* for the number of additional studies in a meta-analysis that would be necessary to reverse the overall probability obtained from our combined test to a value higher than our critical value for statistical significance, usually 0.05 or 0.01. Accordingly, we used Orwin's formula (Orwin, 1983) to provide a Fail Safe *N* for each mean *d* found in Table 2 at a criterion of 0.01.

Given that AD is a progressive disorder where its neuropathological signature evolves in keeping with disease duration, we parceled the effect sizes into two further profiles, using the median duration of illness as a midpoint. Accordingly, Table 3 includes structural imaging findings in patients with AD and duration of illness less than 4 years. Patients in this profile (AD: $N = 131$; Control: $N = 81$) were on average 70.3 (SD = 1.47) years of age with a mean duration of illness of 2.33 (SD = 1.15) years and an average onset age of 67.0 (SD = 1.20). Patients were no more likely to be male than to be female (male = 41.3%, SD = 10.01) and averaged a total score on the MMSE of 19.1 (SD = 2.68).

Table 4 includes structural imaging findings in patients with AD and duration of illness greater than 4 years. A total of 385 patients with AD and 274 controls made up this profile. Patients were on average 70.5 (SD = 5.46) years of age with a mean duration of illness of 5.04 (SD = 0.63) years and an average age at disease onset of 67.7 (SD = 4.9) years. Gender composition was divided equally (male = 48.8%, SD = 28.3) and the average total score on the MMSE (17.7, SD = 2.24) was significantly lower compared to patients with a disease duration less than 4 years ($p < 0.05$).

Table 5 includes a description of patient characteristics across all functional studies. Patients with AD included into functional imaging studies were significantly younger than those included in the structural studies with a corresponding statistically significant younger onset age. Patients' duration of illness, gender composition, and average total score on the MMSE did not differ significantly from those patients included into the structural imaging studies ($p > 0.05$).

Table 6 includes the functional imaging mean effect sizes, standard deviation, *N*, OL%, 95% CI, and a Fail Safe *N* for each neuroanatomic variable parceled by major cerebral cortices and rank-ordered in terms of magnitude.

We constructed a profile in Table 7 of functional imaging findings in patients with AD and duration of

Table 1. Patient Characteristics Across All Structural Studies ($N = 56$)

	Mean	Standard deviation	Minimum	Maximum
Age*	70.9	4.6	57.0	80.4
Onset age*	68.0	3.9	55.3	75.0
Duration of illness (in years)	4.3	1.5	1.0	6.0
Male (%)	45.5	19.2	10.0	100.0
Mini-mental state examination (total score)	18.3	3.6	8.6	24.0

*Significantly different from patient age and onset age across all functional studies at $p < 0.05$.

Table 2. Structural Brain Imaging (CT and MRI)

	N	Mean *d*	(*SD*)	OL%	95% C.I.	Fail Safe N
Whole brain						
Whole brain	11	–1.02	0.50	45	–1.36/–0.68	1111
L. hemisphere	1	–0.49	—	67	—	—
R. hemisphere	1	–0.44	—	70	—	—
Frontal lobes						
Prefrontal	1	–1.28	—	35	—	—
L. frontal lobe	8	–0.94	0.54	46	–1.39/–0.49	744
R. frontal lobe	7	–0.82	0.59	51	–1.37/–0.28	567
Frontal lobes	4	–0.65	0.21	59	–0.98/–0.32	256
Temporal lobes						
Superior temporal	1	–4.35	—	<2	—	—
Amygdala	3	–2.17	1.18	16	–5.10/0.75	648
R. amygdala	9	–1.84	0.87	21	–2.33/–1.35	1647
L. amygdala	9	–1.82	0.82	22	–2.45/–1.19	1629
L. temporal horn	2	1.75	0.58	23	–3.26/7.16	348
R. hippocampus	15	–1.71	0.87	24	–2.19/–1.22	2550
R. medial temporal	2	–1.66	1.78	25	–17.67/14.35	330
Whole hippocampus	6	–1.66	0.56	25	–2.25/–1.07	990
R. temporal horn	2	1.63	0.17	26	0.10/3.15	324
L. hippocampus	15	–1.58	0.87	27	–2.06/–1.10	2355
Sylvian fissure	5	1.51	0.25	29	1.19/1.82	750
R. enthorhinal	4	–1.46	0.46	30	–2.18/–0.73	580
L. temporal lobe	5	–1.33	0.75	33	–2.27/–0.40	660
Whole temporal lobe	4	–1.32	0.54	34	–2.19/–0.46	524
Temporal horns	3	1.31	0.42	34	–2.00/–0.49	393
L. enthorhinal	4	–1.19	0.68	38	–2.27/–0.10	472
L. sylvian fissure	5	1.12	0.27	41	0.79/1.44	555
Hypothalamus	1	–1.04	—	43	—	—
L. temporal pole	2	–1.02	0.18	44	–2.67/0.63	202
R. subiculum	1	–1.01	—	44	—	—
Medial temporal	1	–0.98	—	45	—	—
L. medial temporal	2	–0.97	1.24	45	–12.08/10.15	192
R. temporal lobe	5	–0.79	0.45	53	–1.35/–0.23	390
R. sylvian fissure	4	0.74	0.30	54	0.26/1.22	292
Parahippocampus	3	–0.71	0.34	57	–1.55/0.12	213
R. temporal pole	2	–0.66	0.13	59	–1.80/0.48	130
Parietal lobes						
Whole parietal	2	–1.56	0.97	28	–10.27/7.14	310
Posterior parietal	1	–1.31	—	34	—	—
L. sensorimotor	1	–0.64	—	60	—	—
L. parietal	5	–0.55	0.53	64	–1.19/0.10	270
R. parietal	5	–0.46	0.39	70	–0.94/0.20	225
Occipital lobes						
Occipital	1	–0.49	—	67	—	—
R. occipital	1	–0.21	—	85	—	—
L. occipital	1	–0.17	—	88	—	—
Subcortical anatomy						
Thalamus	3	–1.73	0.77	23	–3.65/0.19	516
R. cerebellum	1	–1.46	—	30	—	—
R. ventricle	4	1.31	0.77	34	–8.17/2.53	520
Globus pallidus	1	–1.26	—	36	—	—
Ventricles	18	1.24	0.35	35	1.07/1.41	2214
Third ventricle	16	1.19	0.53	38	0.90/1.46	1888
Corpus callosum	8	–1.01	0.43	44	–1.37/–0.65	800
Basal ganglia	2	–0.92	0.22	47	–1.56/–0.28	182
Caudate	2	–0.91	0.47	48	–5.16/3.35	180
L. ventricle	4	0.88	0.52	49	–5.42/1.70	348
L. subiculum	1	–0.84	—	51	—	—

Table 2. (*Continued*)

	N	Mean *d*	(*SD*)	OL%	95% C.I.	Fail Safe N
Basal forebrain	1	–0.83	—	51	—	—
Cerebellum	1	–0.82	—	52	—	—
R. caudate	4	–0.66	0.63	59	–1.67/0.35	260
L. caudate	4	–0.60	0.53	61	–1.58/0.27	236
Lenticular nucleus	1	–0.53	—	65	—	—
Putamen	3	–0.49	0.47	67	–1.66/0.67	144
Pons	1	–0.39	—	73	—	—
R. thalamus	5	–0.34	0.32	76	–0.73/5.61	165
L. thalamus	5	–0.28	0.26	80	–0.61/4.38	135
L. cerebellum	1	–0.27	—	80	—	—
Internal capsule	1	–0.20	—	85	—	—
Multiple cortices						
L. temporal–parietal	1	–1.99	—	19	—	—
R. temporal–parietal	1	–1.42	—	31	—	—
Parietal–occipital	2	–1.06	0.38	42	–4.49/2.37	210
Temporal–parietal	1	–0.47	—	68	—	—

Note. Where SD is missing, the mean *d* was based on a single effect size.

illness less than 4 years on the basis of 397 patients and 174 controls. Patients included into these functional studies had an average total MMSE score of 20.0 (SD = 4.30), a mean age of 67.4 (SD = 4.01), an average duration of illness of 2.98 (SD = 0.65) years, and a mean onset age of 64.3 (SD = 2.88) years. Gender composition was equally distributed (male = 41.0%, SD = 13.7).

Finally, in Table 8 we display functional imaging findings in patients with AD with duration of illness greater than 4 years. A total of 268 patients with AD and 114 controls made up this profile. Patients were on average 68.3 (SD = 3.8) years of age with a mean duration of illness of 6.02 (SD = 1.76) years and an average age at disease onset of 63.1 (SD = 4.24) years. Gender composition was divided equally (male = 57.3%, SD = 10.1) and the average total score on the MMSE (17.2, SD = 3.0) was significantly lower when compared to patients with a disease duration of less than 4 years.

Table 3. Structural Imaging Findings in Patients with AD with Duration of Illness Less than 4 Years

	N	Mean *d*	(*SD*)	OL%
Hippocampus left	2	–2.82	1.10	7
Hippocampus right	2	–2.48	1.01	12
Amygdala left	2	–2.22	0.40	15
Amygdala right	2	–2.13	0.39	18
Frontal lobe left	2	–1.49	0.30	30
Frontal lobe right	2	–1.38	0.16	32
Temporal lobe left	1	–0.89	—	49
Temporal lobe right	1	–0.57	—	63
Whole brain atrophy	1	–0.57	—	63

Note. Where SD is missing, the mean *d* was based on a single effect size.

Table 4. Structural Imaging Findings in Patients with AD with Duration of Illness Greater than 4 Years

	N	Mean *d*	(*SD*)	OL%
Medial temporal lobe right	1	–2.92	—	7
Medial temporal lobe left	1	–1.84	—	21
Temporal lobe left	1	–1.71	—	24
Sylvian fissure	2	–1.67	0.37	25
Ventricles	2	1.53	0.58	28
III Ventricle	2	1.30	0.39	34
Globus pallidus	1	–1.26	—	36
Hippocampus right	3	–1.24	0.51	35
Caudate	1	–1.23	—	35
Enthorhinal left	1	–1.14	—	40
Sylvian fissure left	1	–1.12	—	41
Enthorhinal right	1	–1.06	—	42
Hippocampus left	3	–1.06	0.38	42
Parietal–occipital	2	–1.06	0.38	42
Putamen	1	–1.03	—	43
Sylvian fissure right	1	–1.03	—	43
Temporal lobe right	1	–0.95	—	47
Whole brain atrophy	3	–0.85	0.64	52
Frontal lobes	2	–0.74	0.30	54
Parietal lobe left	1	–0.62	—	60
Frontal lobe left	1	–0.33	—	76
Frontal lobe right	1	–0.32	—	77
Parietal lobe right	1	–0.31	—	78

Note. Where SD is missing, the mean *d* was based on a single effect size.

Table 5. Patient Characteristics Across All Structural Studies ($N = 65$)

	Mean	Standard deviation	Minimum	Maximum
Age*	67.4	4.0	58.2	74.0
Onset age*	63.9	3.5	55.5	70.0
Duration of illness (in years)	4.2	2.3	2.0	14.0
Male (%)	49.4	17.7	9.0	100.0
Mini-mental state examination (total score)	19.4	3.2	12.8	30.0

*Significantly different from patient age and onset age across all structural studies at $p < 0.05$.

DISCUSSION

We conducted a quantitative review of the imaging literature, using meta-analytic methodology to characterize further the magnitude of hippocampal deficit in AD and to determine whether other neuroanatomic structures in AD can better discriminate the disease from normal aging. Additionally, we parceled the discriminability of neuroanatomic structures by duration of disease to determine those structures most capable of discriminating AD in its early and late stages.

In terms of structural imaging, we found volume loss within the superior temporal lobes, right/left and whole amygdala, thalamus, temporal horns, left temporoparietal cortices, and right/left and whole hippocampi, to best discriminate between patients with AD and normal controls. When duration of illness was taken into consideration however, volume loss within the hippocampus was the most reliable discriminatory measure between patients with AD and normal controls in its early stages (i.e., duration of illness less than 4 years). Conversely, volume loss within the medial temporal lobes was the most sensitive measure to identify AD in patients with a duration of illness greater than 4 years. Hence, in keeping with the neuropathological evolution of the disease, these findings would seem to fit well with longitudinal observations where hippocampal atrophy and its behavioral manifestation (e.g., episodic memory impairment) typically occur early in the disease, and more widespread medial temporal lobe volume loss and its behavioral manifestation (e.g., naming deficits) tend to occur a little later in duration (see Cummings and Benson, 1992).

In terms of functional, as compared to structural, imaging instrumentation, we found an overall pattern of greater sensitivity for many neuroanatomic structures. We also found that patients included into functional imaging studies were significantly younger and had a younger age of onset than did patients included into structural imaging studies. We might speculate that the cause of this selection bias may reflect the more stringent inclusion criteria for functional versus structural studies. That is, the signal-to-noise ratio for functional studies is likely less than for images of brain anatomy, which might bias investigators toward looking at patients a little worse off in terms of illness severity. This could be a systemic factor as functional studies with large sample sizes are few. At this time, whether the difference in age and age of onset between patients recruited into functional and structural imaging studies have any impact on our findings remains quantitatively unresolved.

From another perspective, it is important to consider that fMRI hemodynamic responses appear to change with age (see Grady and Craik, 2000). More specifically, recent evidence from functional neuroimaging experiments has revealed that, depending on the task, older adults can display greater or lesser activity in task-relevant brain areas than can younger adults. Hence, it appears that some brain changes seen with age may be compensatory in nature and in this case, possibly reflective of cognitive reserve. Cognitive reserve refers to the not-uncommon observation that an imperfect relationship exists between the degree of neuropathology and the actual expression of clinical symptoms. This difference is likely mediated by counteracting mechanisms that follow brain damage such as an increased efficiency within existing networks or the recruitment of alternative pathways (Stern, 2002). Given the inherent differences between structural and functional imaging modalities, a large proportion of the variation between these techniques may also be attributable to a differential expression of cognitive reserve phenomena.

Nonetheless, we did find that volume loss of the superior, medial, left inferior, and whole parietal lobe, right/left amygdala, anterior cingulate, left entorhinal, putamen, and right/left hippocampi, to best discriminate between patients with AD and normal controls. Surprisingly, when duration of illness was less than 4 years, volume loss within the putamen served to be the structure with the greatest discriminability, although this finding can be questioned in terms of its reliability as a large associated standard deviation surrounding its mean effect size was found. Indeed, it should be emphasized that what is listed and described in our tables are sometimes not really

Table 6. Functional Brain Imaging (SPECT and PET)

	N	Mean *d*	(*SD*)	OL%	95% C.I.	Fail Safe N
Whole brain						
Whole brain	16	–1.28	0.78	35	–1.70/–0.87	2032
R. hemisphere	1	–0.39	—	73	—	—
L. hemisphere	1	–0.15	—	88	—	—
Frontal lobes						
Anterior cingulated	10	–1.93	1.21	20	–2.81/–1.06	1920
L. orbital frontal	5	–1.62	1.12	26	–3.01/–0.21	805
R. orbital frontal	5	–1.54	1.02	28	–2.80/–0.28	765
Frontal lobes	23	–1.21	0.86	37	–1.58/–0.83	2760
L. primary motor	7	–1.10	1.14	41	–1.33/–0.62	763
R. primary motor	7	–1.04	1.04	43	–1.29/–0.59	728
Prefrontal	14	–1.03	0.61	43	–1.38/–0.67	1428
Orbital frontal	8	–1.02	0.69	44	–1.58/–0.44	808
L. frontal lobe	19	–0.96	0.74	47	–1.32/–0.60	1824
Primary motor	8	–0.95	0.60	47	–1.45/–0.45	752
R. frontal lobe	20	–0.80	0.76	51	–1.16/–0.44	1580
Temporal lobes						
L. amygdala	5	–2.17	0.92	16	–3.31/–1.02	1080
Inferior temporal	6	–1.96	0.70	19	–2.70/–1.21	1170
L. enthorhinal	1	–1.94	—	19	—	—
L. hippocampus	5	–1.92	1.34	20	–3.58/–0.25	955
R. hippocampus	5	–1.76	1.26	22	–3.32/–0.19	875
Medial temporal	9	–1.73	0.72	23	–2.29/–1.18	1548
R. amygdala	5	–1.69	0.49	24	–2.30/–1.08	840
Temporal pole	2	–1.65	0.10	25	–2.60/–0.69	328
L. temporal	5	–1.62	0.68	26	–2.46/–0.77	805
R. temporal	6	–1.56	0.96	28	–2.58/–0.55	930
Hippocampus	5	–1.56	1.02	28	–2.83/–0.28	775
R. medial temporal	7	–1.54	1.06	29	–2.51/–0.55	1071
L. medial temporal	6	–1.53	0.93	29	–2.50/–0.55	912
Superior temporal	10	–1.50	0.56	29	–1.90/–1.10	1490
Temporal lobes	19	–1.37	0.83	32	–1.77/–0.97	2584
R. enthorhinal	1	–1.36	—	32	—	—
Posterior temporal	3	–1.30	1.42	34	–4.82/2.22	387
L. temporal pole	7	–1.18	0.91	38	–2.02/–0.33	819
R. inferior temporal	2	–1.04	0.61	43	–6.56/4.49	206
L. posterior temporal	3	–1.01	0.86	44	–3.13/1.12	300
R. temporal pole	7	–0.93	0.88	47	–1.74/–0.11	644
R. posterior temporal	3	–0.85	0.74	51	–2.69/1.00	252
R. superior temporal	5	–0.69	0.59	57	–1.43/–0.10	340
L. superior temporal	5	–0.59	0.76	62	–1.54/–0.37	290
L. inferior temporal	2	–0.58	0.77	62	–7.50/6.35	116
Amygdala	1	–0.42	—	73	—	—
Parietal lobes						
R. medial parietal	2	–3.29	2.83	5	–28.7/22.2	656
R. superior parietal	3	–2.25	0.69	15	–4.00/–1.39	672
R. sensorimotor	3	–2.16	1.42	16	–5.69/1.37	645
Posterior parietal	2	–1.92	0.17	20	–3.44/–0.39	382
L. medial parietal	2	–1.79	0.25	22	–4.00/0.44	356
Whole parietal	22	–1.77	1.07	22	–2.25/–1.29	3872
L. superior parietal	3	–1.76	0.75	23	–3.63/0.11	525
L. inferior parietal	4	–1.68	1.33	25	–3.79/–0.20	668
L. sensorimotor	3	–1.67	1.47	25	–5.33/2.00	498
Posterior cingulated	7	–1.61	0.73	26	–2.29/–0.94	1120
Anterior parietal	2	–1.57	0.17	27	–3.09/–0.02	312
Superior parietal	4	–1.44	0.50	31	–3.97/–0.54	572
Medial parietal	3	–1.37	0.43	32	–2.46/–0.28	408
Inferior parietal	5	–1.34	0.48	33	–1.95/–0.73	665

Table 6. (*Continued*)

	N	Mean *d*	(*SD*)	OL%	95% C.I.	Fail Safe N
L. posterior parietal	2	–1.34	0.36	33	–4.58/1.91	266
L. parietal	13	–1.25	0.89	35	–1.80/–0.71	1612
Angular gyrus	1	–1.22	—	36	—	—
R. posterior parietal	2	–1.21	0.42	37	–1.65/–0.76	240
R. parietal	13	–1.16	0.84	38	–1.68/–0.65	1495
R. inferior parietal	4	–1.12	0.71	41	–2.28/–0.02	444
Sensorimotor	17	–0.86	1.01	50	–1.38/–0.34	1445
L. anterior parietal	1	–0.59	—	61	—	—
R. anterior parietal	1	–0.24	—	83	—	—
Occipital lobes						
L. occipital	13	–0.98	1.00	45	–1.59/–0.37	1261
R. occipital	12	–0.89	0.98	48	–1.51/–0.26	1056
L. calcarine fissure	2	–0.74	0.50	54	–5.24/3.77	146
R. calcarine fissure	2	–0.73	0.53	54	–5.49/4.04	144
Occipital	25	–0.70	0.46	57	–0.89/–0.52	1725
Subcortical anatomy						
Putamen	5	–2.10	2.06	18	–4.66/0.47	1045
Striatum	2	–1.19	1.61	38	–15.67/13.29	236
Caudate	4	–1.18	0.20	38	–1.51/–0.86	468
Basal ganglia	13	–1.16	1.44	39	–2.04/–0.29	1495
R. thalamus	4	–1.04	1.27	43	–3.07/1.00	412
L. insula	2	–1.03	0.41	43	–4.72/2.65	204
R. caudate	3	–0.98	0.98	45	–3.42/1.46	291
L. thalamus	4	–0.91	0.85	48	–2.26/0.45	360
Thalamus	18	–0.85	1.01	51	–1.35/–0.34	1512
Lenticular nucleus	1	–0.79	—	53	—	—
L. basal ganglia	2	–0.70	1.02	57	–9.90/8.51	138
R. insula	2	–0.69	0.52	58	–5.39/4.01	136
L. caudate	3	–0.68	0.31	59	–1.46/0.10	201
R. basal ganglia	2	–0.66	0.54	60	–5.54/4.24	130
Pons	2	–0.45	0.10	69	–1.40/0.51	88
L. cerebellum	2	–0.39	0.12	73	–1.47/0.70	76
R. cerebellum	2	–0.37	0.08	74	–1.26/0.51	72
Cerebellum	16	–0.17	0.90	87	–0.65/0.31	32
Vermis	1	–0.02	—	0	—	—
Brainstem	4	0.00	0.88	0	–0.63/2.18	—
Multiple cortices						
Temporal–parietal	6	–1.33	0.34	33	–1.68/–0.97	792
L. temporal–parietal	1	–1.31	—	34	—	—
R. temporal–parietal	1	–1.19	—	38	—	—
Frontoparietal	1	–0.94	—	46	—	—
Frontotemporal	1	–0.74	—	54	—	—
Parietal–occipital	1	–0.14	—	88	—	—

Note. Where SD is missing, the mean *d* was based on a single effect size.

mean effect sizes for each and every dependent measure. Rather, often a single effect size is reported. Accordingly, the small *N* sizes do limit the generalizability of the findings. Hence, volume loss within the hippocampi may again be the most reliable discriminatory measure between patients with AD and normal controls in its early stages. With duration of illness greater than 4 years, volume loss within the anterior cingulate was the most sensitive measure of AD-normal control discriminability. Other structures with considerable sensitivity in later stage AD included the inferior and medial temporal lobes, the basal ganglia, and the amygdala. These findings are consistent with most observations in PET and SPECT studies of AD (e.g., Baron et al., 2001). That is, in very early AD, blood flow and metabolism reduces first in the posterior cingulate gyrus and precuneus (Fox et al., 2001). This reduction may arise from functional deafferentation caused by primary neural degeneration in the remote area of the entorhinal cortex and

Table 7. Functional Imaging Findings in Patients with AD with Duration of Illness Less than 4 Years

	N	Mean *d*	(*SD*)	OL%
Putamen	2	–4.10	1.78	<2
Hippocampus left	2	–3.35	0.08	5
Hippocampus right	2	–3.10	0.01	6
Parietal lobes	7	–2.06	0.90	18
Posterior temporal lobe left	1	–1.87	—	20
Posterior parietal lobes	1	–1.80	—	22
Amygdala left	2	–1.71	0.54	24
Amygdala right	2	–1.66	0.76	25
Temporal lobes	4	–1.66	0.48	25
Posterior temporal lobe right	1	–1.65	—	25
Inferior parietal lobes	1	–1.64	—	26
Temporal pole	2	–1.64	0.11	26
Parietal lobe left	2	–1.63	0.91	26
Superior parietal lobes	1	–1.61	—	27
Hippocampus	4	–1.60	1.17	27
Inferior temporal lobes	3	–1.57	0.33	27
Posterior cingulate	1	–1.56	—	27
Superior temporal lobes	4	–1.54	0.71	28
Parietal lobe right	2	–1.53	0.38	28
Medial temporal lobes	4	–1.50	0.47	29
Anterior parietal lobes	1	–1.45	—	30
Basal ganglia left	1	–1.42	—	31
Temporal lobe left	1	–1.25	—	35
Frontal lobe left	4	–1.24	0.40	35
Whole brain atrophy	4	–1.24	0.13	35
Angular gyrus	1	–1.22	—	36
Anterior cingulate	2	–1.17	0.13	39
Frontal lobe right	4	–1.15	0.39	40
Orbital frontal	3	–1.13	0.61	40
Frontal lobes	3	–1.11	0.43	41
Temporal pole left	2	–1.05	1.48	43
Prefrontal cortex	6	–1.04	0.68	43
Basal ganglia right	1	–1.04	—	43
Caudate nucleus	2	–1.03	0.01	43
Medial temporal lobes left	1	–1.01	—	44
Temporal lobe right	1	–0.86	—	50
Lenticular nucleus	1	–0.79	—	53
Sensory cortex	2	–0.76	0.14	54
Motor cortex	3	–0.74	0.10	54
Medial temporal lobes right	1	–0.71	—	57
Thalamus	7	–0.55	0.62	64
Occipital lobes	6	–0.54	0.21	64
Pons	1	–0.52	—	65
Occipital lobe left	3	–0.50	0.33	66
Occipital lobe right	3	–0.49	0.25	67
Amygdala	1	–0.42	—	72
Basal ganglia	3	–0.24	0.11	83
Cerebellum	5	–0.16	0.47	89

Note. Where SD is missing, the mean *d* was based on a single effect size.

hippocampi that are the first to be pathologically affected in AD. Then medial temporal structures and parietotemporal association cortex show flow or metabolic reduction as the disease progresses (see Matsuda, 2001). The reason why flow or metabolism in medial temporal

Table 8. Functional Imaging Finding in Patients with AD with Duration of Illness Greater than 4 Years

	N	Mean *d*	(*SD*)	OL%
Anterior cingulate	3	–3.50	0.45	4
Inferior temporal lobes	1	–2.98	—	7
Medial temporal lobes	1	–2.88	—	7
Posterior temporal lobes	1	–2.87	—	7
Basal ganglia	2	–2.59	2.14	10
Amygdala right	1	–2.23	—	15
Amygdala left	1	–2.20	—	15
Parietal lobes	3	–1.76	—	23
Medial temporal lobes left	1	–1.72	—	24
Temporal lobes left	4	–1.71	0.75	24
Orbital frontal left	2	–1.70	0.84	24
Superior parietal lobe right	1	–1.68	—	24
Inferior parietal lobe left	1	–1.67	—	25
Parietal lobe left	4	–1.66	0.95	25
Superior temporal lobes	2	–1.65	0.01	25
Medial parietal lobe left	1	–1.61	—	26
Thalamus right	2	–1.58	1.87	27
Motor cortex left	2	–1.50	0.43	29
Superior parietal lobe left	1	–1.47	—	30
Parietal lobe right	4	–1.41	1.13	31
Motor cortex	1	–1.41	—	31
Medial temporal lobes right	1	–1.40	—	31
Thalamus left	2	–1.38	1.01	33
Temporal lobes right	4	–1.36	0.74	33
Orbital frontal right	2	–1.35	1.05	33
Motor cortex right	2	–1.33	0.51	33
Superior parietal lobes	2	–1.31	0.81	34
Medial parietal lobe right	1	–1.28	—	34
Inferior parietal lobes	2	–1.25	0.81	35
Posterior parietal lobe right	1	–1.24	—	35
Inferior parietal lobe right	1	–1.22	—	36
Temporal–parietal cortices	1	–1.20	—	38
Whole brain	3	–1.20	0.32	38
Medial parietal lobes	2	–1.19	0.44	38
Temporal lobes	3	–1.17	0.65	37
Frontal lobes	5	–1.14	1.04	40
Inferior temporal lobes left	1	–1.12	—	41
Prefrontal cortex	1	–1.12	—	41
Occipital lobe	4	–1.08	0.23	42
Posterior parietal lobe left	1	–1.08	—	42
Superior temporal lobes right	1	–1.04	—	43
Occipital lobe left	4	–1.00	1.01	44
Posterior temporal lobe left	1	–0.99	—	44
Frontal lobe left	5	–0.97	0.64	45
Sensory cortex	3	–0.93	1.76	47
Temporal pole right	1	–0.93	—	47
Temporal pole left	1	–0.88	—	49
Occipital lobe right	4	–0.84	0.88	51
Frontal lobe right	5	–0.83	0.73	51
Sensory cortex left	1	–0.76	—	53
Insula left	1	–0.74	—	54
Posterior temporal lobes right	1	–0.71	—	57
Thalamus	1	–0.63	—	60
Inferior temporal lobe right	1	–0.60	—	61
Caudate nucleus left	1	–0.57	—	63
Sensory cortext right	1	–0.57	—	63
Caudate nucleus left	1	–0.53	—	65

Table 8. (*Continued*)

	N	Mean *d*	(*SD*)	OL%
Calcarine fissure left	1	–0.38	—	74
Calcaring fissure right	1	–0.35	—	76
Insula right	1	–0.32	—	77
Cerebellum right	1	–0.30	—	78
Cerebellum left	1	–0.29	—	79
Cerebellum	2	–0.21	0.22	85
Lentiform	1	–0.10	—	92
Vermis	1	–0.02	—	0

Note. Where SD is missing, the mean *d* was based on a single effect size.

structures shows delay in starting to reduce in spite of the earliest pathological developments remains to be elucidated. Yet, as Matsuda (2001) notes, it is likely that the anterior cingulate gyrus is functionally involved, because attention is the first non-memory domain to be affected, before language and visuospatial functions. Hence, its usefulness in diagnostic imaging of AD typically increases with disease duration.

Taken together, our meta-analyses provide compelling quantitative evidence for the early involvement of the hippocampal formation in the natural history of AD. Early AD-type histopathologic changes limited to the hippocampus have been described (e.g., Pitkänen et al., 1996) and may be seen in normal aging subjects, given the complete lack of discriminability of effect sizes found in this meta-analysis. The sites of maximal loss in the hippocampal formation are in the CA1, subiculum, and entorhinal cortex (de Leon et al., 1997). These pathological changes are consistent with what is typically expected in terms of behavioral expression. That is, the earliest symptom is usually an insidious impairment of memory. In terms of subsequent neuropathology, the stereotypical evolution of AD has been well described in terms of neurofibrillary degeneration (e.g., Braak and Braak, 1991, 1997). Specifically, damage usually proceeds beyond medial temporal lobe structures into the association areas of neocortex and this is ultimately followed by the deterioration of primary neocortical regions (for a review, see Braak et al., 1999). Correspondingly, beyond deficits in memory, there is increasing impairment of language and other cognitive functions as the disease progresses (see Honig and Mayeux, 2001). Problems occur with naming and word finding, and later with verbal and written comprehension and expression. Visuospatial, analytic, and abstract reasoning abilities, judgment, and insight then become affected. Ultimately, there is loss of self-hygiene, eating, dressing, ambulatory abilities, and incontinence and motor dysfunction (see Cummings and Benson, 1992).

Accordingly, where the practicing and research neuropsychologist is in need of understanding assessment findings and behavioral alterations over the course of AD, our results may be of some aid. For example, when a patient presents with a 10-month history of progressive isolated memory loss, on the basis of the perusal of our profiles, the practicing/research neuropsychologist could support the patient's tentative diagnosis of AD (in keeping with the cognitive findings and clinical interview of such an example) if the patient presented with volume loss of the hippocampus (e.g., on MRI) based on our expected effect size found in Table 3. Conversely, if the patient presented with a 6-year history of memory decline and other cognitive dysfunction (e.g., visuospatial and naming deficits), and evidence of decreased anterior cingulate blood flow on SPECT, the perusal of our profiles (i.e., Table 8) would tell the practicing/research neuropsychologist that a diagnosis of AD is likely.

Finally, our profiles may aid the practicing/research neuropsychologist in thinking through future research studies that combine neuroimaging methods with neurocognitive methods in AD. For example, it would be important to know that conclusions drawn from a study of visuospatial ability in AD about brain–behavior relations may implicate several areas of "brain" that are not attributed to "behavior" in keeping with disease duration of the patients with AD. That is, it is evident from our profiles that differences between patients with AD and normal controls exist in varying magnitudes as articulated by the effect sizes. These differences are real, and often can sometimes go unnoticed when using statistical tests of significance and small sample sizes (see Zakzanis, 1998a, 2001). Of course, trivial effects can also be championed as statistically significant with large enough sample sizes, which further convolutes our ability to draw meaningful conclusions from the research literature.

Although almost every study in which imaging measures of global or hemispheric structure and function have been employed has identified a statistically significant difference between the mean value found in patients with AD and that found in control subjects, this quantitative review found that an invariable and substantial amount of overlap exists between these two populations, which in turn limits the clinical utility of this approach for diagnosis in individual patients. It is highly likely that this overlap between controls and patients with AD is due in part to the manner in which normal aging is defined when selecting subjects to serve as controls. Most studies have employed as controls individuals who would fall into the category of typical aging. The result is that most elderly control populations in imaging studies include subjects with conditions that are predisposed towards cerebral atrophy such as

hypertension, and some may be in the preclinical stages of dementia (see Bondi and Monsch, 1998; Scinto and Daffner, 2000). As noted, if significant hippocampal volume loss of normal aging is characteristic, then it should come as no surprise that the hippocampi become less sensitive to AD-control discriminability in keeping with disease duration. Accordingly, it is important to note which structures other than the hippocampi can provide reliable separation between patients with the disease and normal controls later in the disease, given that patients often present at first admission with significant neuropsychological deficits and both structural and functional brain alterations that implicate cortices beyond the hippocampus.

Moreover, the sensitivity and specificity of imaging measures of neuroanatomy as a marker of AD have generally been assessed by comparing both structural and functional volume measurements in patients with a clinical diagnosis of probable AD to a matched normal healthy control group. Although estimates of the statistical sensitivity of the discriminatory power of these measurements have been assessed in this review, the "clinical" specificity of imaging measures of neuroanatomy as a marker of AD can only be assessed by comparing these volume measurements among different patient groups; for example, AD versus frontotemporal dementia, or AD versus progressive supranuclear palsy. Few studies of this type have been done, and hence, this analysis of specificity could not be completed here. Accordingly, it will be important to quantify such studies as they accumulate in the published literature using meta-analytic strategies if these methods are to be used in the differential diagnosis of AD. At the same time, it is also important to emphasize the need for future studies to continue to investigate differences in volume loss between patients with AD and normal controls in a number of cortical and subcortical structures using both imaging modalities (i.e., structural and functional) to allow more direct comparisons to be made. For example, in comparing Tables 3 and 4 in our study, one would find that our dependent measures are not the same. Specifically, analyses of the medial temporal lobes are not included in Table 3. This directly reflects the need for a structural imaging investigation of the medial temporal lobes in early AD that utilizes a control group design. Accordingly, complete meaningful comparisons between all of our dependent measures cannot be made as a function of duration of illness at this time.

In addition, these future studies must include basic clinical and demographic characteristics of patient samples. From our review of the literature, we found an alarming omission of basic patient characteristics such as gender, education, duration of illness, and onset age. If these basic characteristics are not included in future publications, it will make it impossible to assess the relationship between these basic characteristics and the AD brain.

It should also be noted that global volume, metabolism, or perfusion is often abnormal in AD, and that optimal identification of regional patterns requires that the global effects be taken into account. A number of methods for doing this have been developed and applied to CT, MRI, PET, and SPECT. The technique of "normalization" divides regional volume or activity by mean volume or activity in another brain region, relatively unaffected in AD, such as the cerebellum, primary visual cortex, or pons (Jagust, Johnson, and Holman, 1995; Sperling, Sandson, and Johnson, 2000). Given that we found significant effect sizes in the primary visual cortex, pons, and cerebellum, using structural and functional imaging modalities, this quantitative review found the smallest effect sizes correspond to the brain stem in functional studies and the internal capsule in structural studies. Accordingly, these structures may be better suited to calibrate activity or volume in other brain regions in the AD brain. Given that these effect sizes were based on a small number of studies, this result awaits replication.

In sum, this review of structural and functional imaging has sought to identify a pattern of neuroanatomical pathology that corresponds to the clinical phenomenology of Alzheimer's dementia. Our results include neuroimaging profiles for both early onset and longer duration patients with AD. Briefly, early stages of AD are best distinguished from normal aging by hippocampal deterioration, whereas patients of longer duration were best distinguished by pathology within the medial temporal lobes and the anterior cingulate gyrus. It has been shown that this signature is consistent with the progressive clinical characteristics of Alzheimer's dementia. Such a signature image feature should aid in the positive identification of AD and could significantly contribute to improvements in the application of therapy as well as early differential diagnosis.

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