Genetic Risk Factors of Imaging Measures Associated with Late-Onset Alzheimer’s Disease

Christiane Reitz¹,²,³

¹Taub Institute for Research on Alzheimer’s Disease and the Aging Brain
College of Physicians and Surgeons, Columbia University, New York, NY
²Department of Neurology, College of Physicians and Surgeons
Columbia University, New York, NY
³Gertrude H. Sergievsky Center, College of Physicians and Surgeons
Columbia University, New York, NY
USA

1. Introduction

Late-onset Alzheimer's disease (LOAD) is the most common cause of dementia and the fifth leading cause of death in Americans older than 65 years.¹ Although other major causes of death have decreased, deaths due to LOAD have been rising dramatically over the past two decades, between 2000 and 2006 they increased by 46.1%.¹ Clinically, LOAD is characterized by progressive cognitive decline in particular in the memory domain. Neuropathologically it is characterized by the aggregation and deposition of misfolded proteins, in particular aggregated β-amyloid (Aβ) peptide in the form of extracellular senile (or neuritic) “plaques,” and hyperphosphorylated tau (τ) protein in the form of intracellular neurofibrillary “tangles” (NFTs). These changes are often accompanied by microvascular damage, vascular amyloid deposits, inflammation, microgliosis, and loss of neurons and synapses.

Although twin studies suggest that 37% to 78% of the variance in the age-at-onset of LOAD can be attributed to additive genetic effects,² few genes have been identified and validated, and these genes likely explain less than 50% of the genetic contribution to LOAD. This is the upper bound of explained heritability in other complex diseases for which— unlike LOAD— significant association has been demonstrated for several common loci of large effect (i.e., ORs > 2 to > 3), such as age-related macular degeneration. Thus, a substantial proportion of the heritability for LOAD remains unexplained by the currently known susceptibility genes. A likely explanation for the difficulty in gene identification is that LOAD is a multifactorial complex disorder with both genetic and environmental components, and that multiple genes with small effects are likely to contribute.

Several neuroimaging measures correlate with LOAD risk and progression, in particular the volumes of the hippocampus, parahippocampus and entorhinal cortex, and the cerebral grey matter. Also these measures appear to have a substantial genetic contribution reflected...
by heritability estimates ranging from 40% to 80%. Advances in brain imaging and high throughput genotyping enable new approaches to study the influence of genetic variation on brain structure and function. As a result, imaging genetics has become an emergent transdisciplinary research field, where genetic variation is evaluated using imaging measures as quantitative traits (QTs) or continuous phenotypes. Imaging genetics studies have advantages over traditional case-control designs. An important consideration is that QT association studies have increased statistical power and thus decreased sample size requirements. Additionally, imaging phenotypes may be closer to the underlying biological etiology of AD, making it easier to identify underlying genes. Together with studies of the genetics of brain structure and function among normal individuals which have been extended to the entire human lifespan from childhood through extreme old age, the data of such studies provide an invaluable backdrop for understanding the genetic influences on neuroanatomy and neurophysiology and are powerful tools for understanding the genetics of neurodegenerative diseases associated with changes in these brain structures such as LOAD. In this chapter, we summarize the current evidence relating genetic variation with LOAD and review the usefulness of imaging endophenotypes in identification of genes increasing susceptibility to LOAD.

2. Imaging endophenotypes in LOAD

**Structural MRI.** On structural magnetic resonance imaging (LOAD) is characterized by atrophy of the medial temporal lobe, foremostly the hippocampus and the amygdala (Figure 1), which may further involve the posterior cortex, occipital lobes, precuneus and posterior cingulate. Atrophy in the hippocampus and entorhinal cortex is associated with a decline in memory function, progression of memory impairment and an increased risk of LOAD. However, these structural changes on MRI are not specific to LOAD and not sufficient to establish a definitive diagnosis of LOAD, as similar atrophy is observed in other neurodegenerative disorders and normal aging. In addition, while nonspecific white matter changes appear frequently in healthy elderly individuals, such changes are also common in elderly people with cognitive decline, stroke or MCI. Nevertheless, several studies have suggested that certain structural MRI biomarkers possess some degree of discriminative diagnostic power. For example, evidence exists that in LOAD, the corpus callosum (particularly the anterior area) exhibits atrophy. This change helps to distinguish LOAD from frontotemporal dementia, in which the posterior area of the corpus callosum shows greater atrophy than the anterior area of this brain structure. There is also evidence that among patients with amnestic MCI, those who convert to LOAD show greater atrophy in the hippocampus and the inferior and middle temporal gyri than those who do not convert to LOAD.

**Functional MRI.** Functional MRI (fMRI) can visualize neuronal activity either during rest or in association with a task that activates specific brain regions. The most common method is blood oxygen level-dependent (BOLD) fMRI, which measures alterations in blood flow on the basis of changes in deoxyhemoglobin. As the deoxyhemoglobin concentration depends on neuronal activity, BOLD reflects brain activity. This technique is widely used in research and in the diagnosis of various brain disorders because of its high sensitivity and easy implementation.
LOAD Endophenotypes on MRI

BOLD signals depend on several anatomical, physiological and imaging parameters, and can be interpreted qualitatively or semiquantitatively. As a result, interindividual and intraindividual variability limits the use of such signals in the differential diagnosis of dementia-causing disorders. Nevertheless, fMRI can facilitate the characterization of functional abnormalities in specific diseases. People with LOAD exhibit reduced brain activity in parietal and hippocampal regions in comparison with healthy controls when undergoing memory encoding tasks. In addition, some studies have found different neuronal activity patterns in healthy controls and patients with MCI. Recent advances in fMRI have allowed intrinsic functional networks in the human brain to be defined. The study of cognitive-behavioral function in the early stages of neurodegenerative disorders may allow the identification of the neuroanatomical networks affected by these diseases, and may assist in the differential diagnosis of the various disorders that underlie dementia.

PET and single-photon emission CT. PET and single-photon emission CT (SPECT) have been widely explored as diagnostic tools for dementia, and both techniques have shown good diagnostic and prognostic capabilities. PET studies have mostly used the tracer 2-[18F]-fluoro-2-deoxy-d-glucose (18F-FDG), which provides a measure of cerebral glucose metabolism and, hence, indirectly demonstrates synaptic activity. In the early stages of LOAD, 18F-FDG-PET reveals a characteristic pattern of symmetric hypometabolism in the posterior cingulate and parietotemporal regions that spreads to the prefrontal cortices (Figure 2a). These changes are distinct from the changes in cerebral glucose metabolism that are seen in healthy controls and cases of other forms of dementia, and the extent of hypometabolism inversely correlates with the degree of cognitive impairment. 18F-FDG-PET has a high sensitivity (94%) but a low specificity (73–78%) for the diagnosis of dementia. SPECT, which involves studying regional blood flow with Tc-hexamethylpropyleneamine oxime, has a similar specificity to 18F-FDG-PET for this condition. A number of low-molecular-weight tracers have been developed for PET to
assess Aβ deposits in vivo. The most frequently used tracer is Pittsburgh compound B (PIB). Compared with healthy controls, patients with LOAD show increased 11C-PIB retention in cortical regions targeted by Aβ deposits (Figure 2b). Deposition of this peptide seems to reach a plateau by the early stages of LOAD. In MCI, PIB binding is bimodal, with ≈ 50% of patients showing an increase in 11C-PIB binding, resembling the 11C-PIB retention that is seen in LOAD, while the other ≈ 50% of patients exhibit low levels of 11C-PIB binding that are similar to the levels seen in controls. In MRI studies, 11C-PIB binding correlated positively with atrophy in the amygdala and hippocampus but not other cortical areas, suggesting that various brain areas have different susceptibilities to Aβ deposit-mediated toxicity, or that amyloid deposition is nonessential for neurodegeneration. New PET tracers for amyloid deposits, such as 18F-FDDNP, are being developed. In studies comparing 11C-PIB and 18F-FDDNP, these tracers showed differences in regional binding and in the cognitive domains with which they seem to be associated, suggesting that these tracers measure related but different characteristics of LOAD.

Fig. 2. A) FDG PET patterns characteristic of metabolic activity in cognitively normal individuals and patients with LOAD. Red: high FDG uptake, Blue: low FDG uptake. Compared to persons aging normally, persons with LOAD show decreased bilateral glucose metabolism particularly in the temporal and parietal regions. B) PIB PET images characteristic of elderly individuals without cognitive impairment and patients with LOAD. Red: high PiB retention, Purple: low PiB retention. The image of the LOAD case shows red and yellow areas indicating high concentrations of PiB in the brain thereby suggesting high amounts of amyloid deposits.

3. Genetic influences on brain morphological endophenotypes

Elucidating the extent to which genetic and environmental factors influence normal brain structure is of great importance for understanding age-related normal and pathological changes in brain and cognition. Twin studies, which estimate heritability based on data from monozygotic (MZ) and dizygotic (DZ) twin pairs, provide the optimal genetic method for clarifying this issue because they allow decomposing the variance of any variable into genetic, shared environmental influences, and unique individual-specific environmental influences.
As MZ twin pairs are genetically identical (with rare exceptions due to somatic mutations) while DZ twin pairs share on average 50% of their segregating genes, variation of a certain measure is considered heritable if MZ twin pairs resemble each other for this measure more closely than DZ twin pairs. An influence of shared environmental factors is suspected when correlations in DZ twin pairs are >50% of the MZ twin pair correlation. Unique environmental factors determine the extent to which MZ twins do not resemble each other. Extended twin-studies include additional relatives thereby increasing the statistical power to detect the influences of environmental influences shared by members from the same family.

**Heritability of Brain Volumes and Structures.** To date, more than 30 twin studies on brain imaging measures have been performed that aim to define the genetic contribution to brain structures (reviewed by Krasuski et al. and Karas et al). Overall, these studies demonstrated substantial heritability of these endophenotypes, particularly for larger structures.

Twin studies using magnetic resonance imaging (MRI), found high heritability estimates of global brain measures including intracranial volume (>72%), total brain volume (66–97%), lobar tissue (in particular the temporal and parietal cortices), total gray matter volume and total white matter volume. Brain areas that in contrast seem to be under stronger environmental control include the gyral patterning of the cortex, the volume of the lateral ventricles, and the volume of the hippocampus. It is important to point out that some of these studies did not correct for total cranial volume or height when measuring brain volumes. Although it is likely that the ratio of brain volume/total cranial volume is comparable among monozygotic twins, it remains possible that this lack of correction has led in some studies to spurious results.

More recent studies have predominantly examined possible genetic effects on specific brain areas using voxel-based morphometry and cortical thickness measures. Overall, these studies confirmed in particular the high heritabilities for the frontal, parietal and temporal cortices. In a study by Thompson et al., that constructed detailed three-dimensional maps based on a genetic continuum of similarity in grey matter in groups of unrelated subjects as well as DZ and MZ twins, genetic factors influenced in particular anatomical regions that include frontal and language-related cortices (ie., sensorimotor, middle frontal, anterior temporal and Wernicke’s cortices; r²(MZ) > 0.8, p < 0.05). In a study by Holshoff Pol et al., which examined both gray and white matter density in a large sample of 54 monozygotic and 58 dizygotic twin pairs and 34 of their siblings, genetic factors significantly influenced white matter density of the superior occipitofrontal fascicle, corpus callosum, optic radiation, and corticospinal tract, as well as grey matter density of the medial frontal, superior frontal, superior temporal, occipital, postcentral, posterior cingulate, and parahippocampal cortices (heritability>0.69). In a study by Wright et al., voxel-based morphometry revealed moderate heritabilities (42-66%) for temporal/parietal neocortical areas and paralimbic structures. In a study by Rijsdijk et al., heritability estimates were only significant for left posterior cingulate and right dorsal anterior cingulate gray matter concentrations (46% and 37%, respectively). In a recent study that derived both surface-based and voxel-based representations of brain structure, both heritability estimates for thickness and surface area were highest for the temporal and parietal lobes. In addition, this
study suggested that grey matter volume is more closely related to surface area than cortical thickness suggesting that surface area and cortical thickness measurements should be considered separately and preferred over gray matter volumes for imaging genetic studies. Only one study has measured the heritability estimates for changes in brain volumes over time. In this study which used structural MRI, the genetic contributions to variability in intracranial volume, corpus callosum, and lateral ventricles in healthy elderly were high (88-92%) but did not change after 4 years follow-up.40

4. Genetic epidemiology of LOAD

Genetically, AD is categorized into two forms: (1) familial cases with Mendelian inheritance of predominantly early-onset (<60 years, early-onset familial AD [EOFAD]), and (2) “sporadic” cases with less apparent or no familial aggregation and later age of onset (≥60 years, late-onset AD [LOAD]). It is important to note that this traditional dichotomization is overly simplistic as there are cases of early-onset AD without evidence for Mendelian transmission while, conversely, LOAD is frequently observed with a strong familial clustering, sometimes resembling a Mendelian pattern. In contrast to early-onset Alzheimer’s disease which is caused by autosomal dominant mutations in the APP (amyloid precursor protein), PSEN1 (presenilin 1) and PSEN2 (presenilin 2) genes, the genetics of LOAD is more complex. The genes involved in LOAD increase disease risk and are not inherited in a Mendelian fashion. First-degree relatives of patients with LOAD have twice the expected lifetime risk of this disease of people who do not have a LOAD-affected first-degree relative.41 In addition, LOAD occurs more frequently in monozygotic than in dizygotic co-twins, suggesting a substantial genetic contribution to this disorder. In the largest twin study of dementia, involving 11,884 participants in the Swedish registry who were aged >65 years, 395 twin pairs were identified in which either one or both twins had LOAD.42 This study demonstrated a heritability of 58–79% for LOAD, depending on the model that was used in the data analysis.

Apolipoprotein E. APOE is the only established susceptibility gene for LOAD and maps to chromosome 19 in a cluster with the genes encoding translocase of outer mitochondrial membrane 40 (TOMM40), apolipoprotein C1 and apolipoprotein C2. APOE is a lipid-binding protein that is expressed in humans as one of three common isoforms, which are encoded by three different alleles, namely APOE ε2, APOE ε3 and APOE ε4. The presence of a single APOE ε4 allele is associated with a 2–3-fold increase in the risk of LOAD, while the presence of two copies of this allele is associated with a fivefold increase in the risk of this disease. Each inherited APOE ε4 allele lowers the age of LOAD onset by 6–7 years. Furthermore, the presence of this allele is associated with memory impairment, MCI, and progression from MCI to dementia. APOE ε4 has been suggested to account for as much as 20–30% of LOAD risk. Despite the studies linking APOE ε4 with LOAD, the presence of this allele is neither necessary nor sufficient for disease: among participants in the Framingham study, 55% of those who were homozygous for APOEε4, 27% of those with one copy of this allele and 9% of those without an APOE ε4 allele developed LOAD by 85 years of age. Segregation analyses conducted in families of patients with LOAD support the presence of at least four to six additional major LOAD risk genes.43 Additional genetic risk variants. After APOE,
the best-validated gene LOAD risk is the sortilin-related receptor 1 (SORL1) gene, which is located on chromosome 11q23. SorL1 belongs to a group of five type I transmembrane receptors (the others being sortilin, SorCS1, SorCS2 and SorCS3) that are highly expressed in the CNS and are characterized by a luminal, extracellular vacuolar protein sorting 10 domain. From family-based and population-based studies that, together, included over 6,000 individuals from four ethnic groups, Rogaeva et al. identified two haplotypes in the 3' and 5' regions of SORL1 that are associated with LOAD risk. In addition, these researchers demonstrated that SorL1 promotes the translocation and retention of APP in subcellular compartments that exhibit low secretase activity, thereby reducing the extent of proteolytic breakdown into both amyloidogenic and nonamyloidogenic products. As a consequence, underexpression of SORL1 leads to overexpression of Aβ and an increased risk of LOAD. Several subsequent studies replicated these initial genetic association findings, and the results were further validated by a collaborative, unbiased metaanalysis of all published genetic data sets that included a total of 12,464 LOAD cases and 17,929 controls. In the past year, several studies demonstrated that, in addition, genetic variation in the SORCS1 homolog SORCS1 influences LOAD risk, cognitive performance, APP processing and Aβ1–40 and Aβ1–42 levels through an effect on γ-secretase processing of APP, further emphasizing the role of sortilin-related proteins in LOAD etiology.

Genome-wide association studies for LOAD using large numbers of cases and controls have revealed modest effect sizes for several genes on LOAD risk, with odds ratios in the range of 1.1–1.5, although most of these studies have only confirmed the association of APOE with this disease. One such study showed that variants of TOMM40—which is proximally located to and in linkage disequilibrium with APOE—were associated with LOAD risk, but whether these genetic associations are independent of the APOE locus remains unclear.

Together, two genome-wide association studies identified variants in the clusterin gene (CLU), the phosphatidylinositol-binding clathrin assembly protein gene (PICALM) and complement receptor type 1 gene (CR1) as being associated with LOAD and several subsequent studies replicated these findings, but functional data confirming the roles in LOAD of the proteins encoded by these genes are still lacking. Clusterin is a lipoprotein that is expressed in mammalian tissues and is incorporated into amyloid plaques. This protein binds to soluble Aβ in CSF, forming complexes that can penetrate the BBB. Clusterin levels are positively correlated with the number of APOE ε4 alleles, suggesting a compensatory induction of CLU in the brains of LOAD patients with the APOE ε4 allele, who show low brain levels of APOE. CR1 encodes a protein that is likely to contribute to Aβ clearance from the brain, while PICALM protein is involved in clathrin-mediated endocytosis, allowing intracellular trafficking of proteins and lipids such as nutrients, growth factors and neurotransmitters. PICALM protein also has a role in the trafficking of vesicle-associated membrane protein 2, a soluble N-ethylmaleimide-sensitive factor attachment protein receptor that is involved in the fusion of synaptic vesicles to the presynaptic membrane in neurotransmitter release. A third large genome-wide association study confirmed the associations of PICALM and CLU with LOAD and reported two additional loci as being associated with LOAD52: rs744373, which is near the bridging integrator 1 gene (BIN1) on chromosome 2q14.3, and rs597668, which is located on chromosome 19q13.3. BIN1 is a member of the BAR (BIN–amphiphysin–Rvs) adaptor family, which has been implicated in caspase-independent apoptosis and membrane dynamics, including vesicle fusion and
trafficking, neuronal membrane organization, and clathrin-mediated synaptic vesicle formation. Of note, the latter process is disrupted by Aβ. Changes in BIN1 expression have also been shown in aging mice and in transgenic mouse models of LOAD. The locus rs597668 is not in linkage disequilibrium with APOE, suggesting that the effect of this locus on LOAD risk is independent. Six genes are found in this region, of which at least two (genes encoding biogenesis of lysosomal organelles complex 1 subunit 3 and microtubule-associated protein–microtubule affinity-regulating kinase 4) are implicated in molecular pathways linked to LOAD or other brain disorders.

It is important to note, that the results of the published genome-wide association studies are informative, but that the genetic associations need functional validation. Indeed, such studies alone cannot prove causality or assess the biological significance of an observed genetic association. Genomewide association studies represent a method of screening the genome, but are limited in their ability to detect true associations.

5. Genetic variation and neuroimaging measures in LOAD

As described above, multiple neuroimaging measures that correlate with LOAD risk and progression appear to have genetic underpinnings, with heritability estimates ranging from 40% to 80%. Recent studies that aimed to determine whether the discovered genetic risk factors for LOAD also influence these neuroimaging traits suggest that several of these candidate genes also influence specific LOAD imaging endophenotypes. Most studies chose hippocampal volume as the quantitative phenotype because of its sensitivity to the changes of early LOAD, and by far the best studied gene is APOE. In line with the strong and consistent results for APOE when using LOAD as the phenotype, most T-1 weighted MRI studies reported an association of APOE e4 with accelerated LOAD-related volume loss in the hippocampal region. This is supported by several studies exploring the effect of the APOE e4 allele on glucose metabolism using FDG-PET, or amyloid deposition using ([^11C] PiB-PET.

Few studies have examined the association between other genes and LOAD imaging measures, and most of these were GWAS studies. In a GWAS of 381 participants of the Alzheimer’s Disease Neuroimaging Initiative (ADNI) cohort, 21 chromosomal areas were associated with hippocampal atrophy. These candidate regions included the APOE, EFNA5, CAND1, MAGI2, ARSB, and PRUNE2 genes, which are involved in the regulation of protein degradation, apoptosis, neuronal loss and neurodevelopment. In the same study, APOE and TOMM40 were confirmed when LOAD was used as the phenotype of interest. Additional studies by the same group, that included a larger set of imaging phenotypes and used T1-weighted MRI, voxel-based surface-based methods, or 3D mapping of temporal lobe volume differences using tensor-based morphometry, confirmed SNPs in APOE and TOMM40 as strongly associated with multiple brain regions (including hippocampal volume, entorhinal cortex volume, amygdala volume, cortical thickness measures, grey-matter density) and revealed other SNPs in or close to candidate genes that have been repeatedly associated with LOAD as described above (PICALM, SORL1, SORCS1, APP, CR1, BIN1). In addition these studies reported novel SNPs in proximity to the EPHA4, TP63, NXPH1, GRIN2B, NEDD9, DAPK1, IL1B, MYH13, TNK1, ACE, PRNP, PCK1 and GAPDH genes. Several
of these genes are biologically plausible. NXPH1 codes for neurexophilin-1, a protein implicated in synaptogenesis, that forms a tight complex with alpha neurexins, a group of proteins that promote adhesion between dendrites and axons. This adhesion is a key factor in synaptic integrity, the loss of which is a hallmark of AD. GRIN2B encodes the N-methyl-D-aspartate glutamate receptor NR2B subunit, which is a target for memantine therapy to decrease excitotoxic damage. ACE has been shown to cleave amyloid beta in vitro and is in addition involved in blood pressure regulation. Both high and low blood pressure have been associated with LOAD.

There have been few studies exploring the effects of specific candidate genes (other than APOE) on brain imaging phenotypes. Ho et al.\textsuperscript{68} investigated the relationship between an obesity-associated candidate gene (FTO) and regional brain volume differences in 206 ADNI control participants. Systematic brain volume deficits were detected in cognitively normal obesity-associated risk allele carriers, as well as in subjects with increased body mass index indicating that this obesity susceptibility gene is associated with detectable deficits in brain structure, which may indirectly influence future risk for neurodegenerative disease. In 129 hypertensive individuals from a family-based cohort sampled from a Dutch genetically isolated population,\textsuperscript{69} four SNPs located at the 3'-end of SORL1 (rs1699102, rs3824968, rs2282649, rs1010159) were associated with frequency of microbleeds which is potentially related to amyloid angiopathy. In the MIRAGE Study\textsuperscript{70} several SORL1 SNPs that have been reported to be associated with LOAD, were associated with hippocampal atrophy, cerebrovascular disease, and white matter hyperintensities. In a candidate gene study that used (FDG-PET) measurements as a quantitative pre-symptomatic endophenotype in 158 cognitively normal late-middle-aged APOE\(\varepsilon\)4 homozygotes, heterozygotes, and non-carriers,\textsuperscript{71} the GAB2 protective haplotype was associated with higher regional-to-whole brain FDG uptake in APOE\(\varepsilon\)4 carriers.

6. Discussion

The work reviewed above indicates that there are various brain imaging measures that are useful endophenotypes associated with genetic liability for LOAD. The strongest evidence of heritability, linkage and/or association in studies of normal brain aging have been found for the medial frontal cortex, Heschl’s gyrus and postcentral gyrus, Broca’s area, anterior cingulate, gray matter of the parahippocampal gyrus and white matter of the superior occipitofrontal fasciculus. The high heritability for these endophenotypes seems to be present throughout life and seems to be functionally relevant. In contrast, the heritability of volume of the hippocampus, which is central to the formation of new memories and memory consolidation, the process for converting short-term memory into stored or long-term memory,\textsuperscript{72} seems to be modest. Support for an environmental component of hippocampus volume comes from a twin study of Ammon’s horn sclerosis\textsuperscript{73} in which only the twin of MZ pairs who had experienced prolonged, childhood febrile seizures developed sclerosis. This discordance in hippocampal response to trauma suggests susceptibility of this structure to environmental events. Mammalian studies reporting neurogenesis of the hippocampal dentate gyrus in adult animals even into senescence\textsuperscript{74, 75} suggest that the relatively stable size of the hippocampus throughout adulthood\textsuperscript{76, 77} may reflect a lifelong relative maintenance of volume\textsuperscript{78, 79} through mechanisms such as neurogenesis and synaptogenesis with rich environmental stimulation\textsuperscript{75} even when genetically
This speculation must, however, be tempered by the relatively small number of new neurons generated in confined regions of the hippocampus and the lack of evidence that volume necessarily reflects cell number. In any case, if neurogenesis could be adequately and functionally amplified, it may carry new promise for conditions affecting the hippocampus such as LOAD.

The GWAS and candidate gene studies, however, which explored the impact of genetic variation on imaging endophenotypes of LOAD, do support an impact of genetic factors. In particular studies exploring the effect of APOE genotype on morphological changes consistently suggest a modulation of volume/structure dependent on level of genetic risk. Thus, taken together these studies of the genetics of brain structure and function among normal individuals suggest that variation in brain structure and function can be expected and that pathological states represent the extremes of this variation. They further indicate that the morphological characteristics of several brain structures represent both differential vulnerability to environmental influences and phenotypical expressions of different sets of genes, which may operate on morphology at different times throughout development and aging. As a consequence, these data provide a valuable background for understanding the genetics of neurodegenerative diseases associated with changes in brain structures including LOAD. They suggest that using these quantitative imaging traits may provide an informative phenotype and may increase statistical power.

Although encouraging, this also raises some additional questions and challenges. First, are the genes mediating each endophenotype involved in abnormal brain aging and cognition at least partially distinct from each other? This is a key assumption of the endophenotype approach, yet empirical proof of this remains to be determined. A substantial degree of overlap appears likely for a number of the known genes associated with early- and late-onset AD, at least including the APP, PSEN1, PSEN2, APOE, SORL1 and SORCS1, given that these genes are involved in either the production or processing of the β-amyloid peptide. Nevertheless, each gene has a unique role in this cascade and it thus seems likely these loci will differ in their magnitudes of influence across the brain systems affected in this disorder. How do these genes (along with others that remain to be identified) coalesce in influencing liability to overt expression of LOAD? Are their effects additive or interactive? The answers to these questions depend on large-scale studies of genetically at-risk samples with and without environmental exposures and the use of sophisticated statistical modeling algorithms that can powerfully probe the resulting datasets for evidence of gene-gene and gene-environment interactions. Finally, are these endophenotypes and associated genes unique to cognitive impairment in LOAD, or are they shared by other diseases such as Dementia with Lewy Bodies, Parkinson’s disease or depression? Lewy body inclusions and Lewy neurites, the key pathological hallmarks of dementia with Lewy Bodies and Parkinson’s disease, are a frequent coexistent pathologic change observed in autopsy-confirmed LOAD.

The questions posed above raise considerable challenges for investigators attempting to unravel the genetic complexity of LOAD. Nevertheless, we have entered a new era in which conjoint advances in molecular genetics and dissection of the dementing phenotype are enabling rapid progress with multiple gene discoveries. These discoveries validate the dissection of this disorder into its more discretely determined subcomponents in order to elucidate the mechanisms underlying cognitive impairment in the elderly.
<table>
<thead>
<tr>
<th>Author</th>
<th>Subjects</th>
<th>Age in years, mean (range)</th>
<th>Brain region</th>
<th>Heritability in % (95% CI)</th>
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<tbody>
<tr>
<td>Reveley et al.33 (1984)</td>
<td>18 MZ, 18 DZ</td>
<td>NA</td>
<td>LV</td>
<td>82-85% (NA)</td>
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<td>Bartley et al.27 (1997)</td>
<td>10 MZ, 9 DZ</td>
<td>MZ: 31 (19-54), DZ: 33 (18-29)</td>
<td>TB</td>
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<td>Carmelli et al.25 (1998)</td>
<td>74 MZ, 71 DZ</td>
<td>68-79 years</td>
<td>IC</td>
<td>91% (NA)</td>
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<tr>
<td>Pfefferbaum et al.26 (2000)</td>
<td>45 MZ, 40 DZ</td>
<td>MZ: 72.2, DZ: 71.4, range: 68-78</td>
<td>Subcortex IC CC LV</td>
<td>70% (NA) 81% (72-90) 79% (69-89) 79% (55-100)</td>
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<tr>
<td>Sullivan et al.34 (2001)</td>
<td>45 MZ, 40 DZ</td>
<td>MZ: 72.2, DZ: 71.4, range: 68-78</td>
<td>HIP</td>
<td>40% (NA)</td>
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<tr>
<td>Thompson et al.5 (2001)</td>
<td>10 MZ, 10 DZ</td>
<td>48.2 ±3.4</td>
<td>Middle frontal sensimotor and anterior temporal cortices, Broca’s and Wernicke’s region (cortical thickness)</td>
<td>90-95% (NA)</td>
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<tr>
<td>Baaré et al.24 (2001)</td>
<td>54 MZ, 58 DZ, 34 sibs 15 MZ, 18 DZ</td>
<td>MZM: 31.2, MZF: 34.1, DZM: 30.3, DZF: 30.6, OS: 30.3, sibs: 29.0; range: 19-69 75.7 ± years</td>
<td>IC TB GM WM LV Size CC Microstructure CC (DTI)</td>
<td>88% (82-92) 90% (85-93) 82% (73-88) 87% (80-91) C: 59% (47-69), E: 41% (31-53) 5:1 (NA) 3:1 (NA)</td>
</tr>
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<td>Geschwind et al.30 (2002)</td>
<td>72 MZ, 67 DZ</td>
<td>MZ: 72.3, DZ: 71.8</td>
<td>Cerebral hemispheres</td>
<td>65% (NA)</td>
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<tr>
<td>Author</td>
<td>Subjects</td>
<td>Age in years, mean (range)</td>
<td>Brain region</td>
<td>Heritability in % (95% CI)</td>
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<tr>
<td>Wright et al.²⁹ (2002)</td>
<td>10 MZ, 10 DZ</td>
<td>MZ: 31 (19-54), DZ: 23 (18-29)</td>
<td>TB, LV, CB, Ventrolateral FR, cingulate, anterior/superior/transverse temp, retrosplenium</td>
<td>66% (17-100) C: 48% (0-97), E: 50% (32-84) 63%, E: 22% (NA) 58-73% (NA)</td>
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<td>White et al.⁸³ (2002)</td>
<td>12 MZ, 12 control pairs</td>
<td>MZ: 24.5±7.2, controls: 24.4±7.2</td>
<td>TB, GM, WM, CB, CAU, PUT, THAL, cortical depth</td>
<td>r&gt;0.90, r&gt;0.75</td>
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<td>Scamvouge ras et al.⁸⁴ (2003)</td>
<td>14 MZ, 12 DZ</td>
<td>MZ: 16-41, DZ: 18-32</td>
<td>CC</td>
<td>94% (NA)</td>
</tr>
<tr>
<td>Pfefferbaum et al.⁴⁰ (2004)</td>
<td>34 MZ, 37 DZ</td>
<td>4-year longitudinal follow-up T1: 68-80 years, T2: 72-84 years</td>
<td>CC (T1), CC (T2), LV (T1), LV (T2)</td>
<td>89% (NA) 92% (NA) 92% (NA) 88% (NA)</td>
</tr>
<tr>
<td>Wallace et al.³¹ (2006)</td>
<td>90 MZ, 37 DZ</td>
<td>MZ: 11.9, DZ: 10.9, range: 5-19</td>
<td>TB, GM, WM, FR, TEMP, PAR, CB, LV</td>
<td>89% (67-92) 82% (50-87) 85% (56-90) 77-88% (50-90) 49% (13-83) 31% (0-67), C: 24% (0-58), E: 45% (33-60)</td>
</tr>
</tbody>
</table>

AMYG, amygdala; CAU, caudate; CB, cerebellum; CC, corpus callosum; CI, confidence interval; CING, cingulate; CST, corticospinal tract; DTI, diffusion tensor imaging; DZ, dizygotic; DZF, dizygotic female; DZM, dizygotic male; FR, frontal lobe; GM, gray matter; HIP, hippocampus; IC, intracranial volume; LH, left handed; LV, lateral ventricles; MFL, medial frontal lobe; MZ, monozygotic; MZF, monozygotic female; MZM, monozygotic male; NA, not available; OCC, occipital lobe; occ-front-temp, occipito-frontal temporal; PAR, parietal lobe; PARAHIP, parahippocampal gyrus; PUT, putamen; SOF, superior orbitofrontal; TB, total brain; TEMP, temporal lobe; THAL, thalamus; SFL, superior frontal lobe; STL, superior temporal lobe; WM, white matter.

Table 1. Studies on heritability of human brain volumes
It is important to note that - despite their utility in the context of etiological research on LOAD - endophenotypes have not proven to have great utility in the clinical distinction of dementing disorders. As described above, the different forms of dementia show substantial clinical and pathological overlap, and likely do not reflect completely separate underlying pathologies or genetic causes but rather a continuous spectrum of disease. Therefore, although they more realistically reflect variation in the underlying causes of illness, the use of endophenotypic assessments in diagnostic or treatment contexts is difficult.

In conclusion, given that the pathways from genotypes to end-stage phenotypes are circuitous at best, discernment of endophenotypes more proximal to the effects of genetic variation can improve statistical power and thereby be a powerful tool in the identification of genes linked to complex disorders. They can help understand how environmental and genetic factors interact to influence disease susceptibility and expression, and can help identify targets for the development of new treatment and prevention strategies.

7. Acknowledgements

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8. References


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Neuroimaging methodologies continue to develop at a remarkable rate, providing ever more sophisticated techniques for investigating brain structure and function. The scope of this book is not to provide a comprehensive overview of methods and applications but to provide a 'snapshot' of current approaches using well established and newly emerging techniques. Taken together, these chapters provide a broad sense of how the limits of what is achievable with neuroimaging methods are being stretched.

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