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Recent Advances in Imaging Alzheimer's Disease

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Abstract

Advances in brain imaging technology in the past five years have contributed greatly to the understanding of Alzheimer's disease (AD). Here, we review recent research related to amyloid imaging, new methods for magnetic resonance imaging analyses, and statistical methods. We also review research that evaluates AD risk factors and brain imaging, in the context of AD prediction and progression. We selected a variety of illustrative studies, describing how they advanced the field and are leading AD research in promising new directions.

Keywords

Alzheimer's disease; amyloid; imaging; magnetic resonance imaging; methods; positron emission tomography; prediction; progression; risk factors

Alzheimer's disease (AD) is the most prevalent neurodegenerative disorder worldwide. It is the sixth most common cause of death in the US. All of us are at risk, and there is no known cure. About 13.2 million Americans will be diagnosed with AD by the year 2050 [1]. Late onset AD, the more common form of the disease, is 58–74% heritable [2–4]. Apolipoprotein E ε4 allele (*APOE4*) is a long-standing known AD risk gene [5], that thus far increases late-onset AD risk by the greatest factor [6]. However, in the last three years, large multiple-cohort genome-wide association studies (GWAS) have found several new single nucleotide polymorphisms (SNPs) that each affect the lifetime odds ratios for developing AD by approximately ±0.10–0.20 [7–10]. However, much of the genetic risk for AD is still unexplained, probably because a large number of genetic variants, each with a small effect, combine with environmental factors to contribute to AD onset. As we will show later, neuroimaging can help reveal the function of these new AD risk variants and how they influence brain integrity over the lifespan.

By the time AD can be detected using standard clinical assessments, the brain typically has undergone widespread irreversible neuronal and synaptic loss [12]. This neurodegeneration may be promoted by long-standing toxic processes such as amyloid aggregation and neurofibrillary tangle formation (the hallmarks of AD) and inflammation. To avert the

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looming AD crisis, we must identify better ways to track and treat AD in its earliest stages, even in people who are presymptomatic. Neuroimaging is an ideal tool for this; in the past five years alone, it has helped to show how controllable lifestyle factors, including exercise, education, and dietary factors such as folate and iron levels, affect brain integrity and disease risk later in life [13–18]. Neuroimaging advances, such as *in vivo* mapping of amyloid plaques and tau neurofibrillary tangles, and increasingly sensitive techniques for detecting atrophy on magnetic resonance images (MRI) have also made it easier to track AD progression. Large-scale genetic and epidemiological analyses of brain images may also discover factors that promote and deter atrophy. Only in the last few years have we routinely seen analyses of hundreds to thousands of brain scans. The largest neuroimaging genetics study to date [19] offered ~99.92% power to detect genetic variants that affect as little as 1% of the variance in hippocampal volume. Given this new level of power to distinguish risk gene effects on the brain [20], whole new lines of discovery are possible. We now know how multiple AD risk-conferring genes affect brain function and structure [21], and we are beginning to discover networks of genetic risk factors that affect the brain simultaneously. Finally, a major line goal of AD imaging is to identify at-risk older adults who are most likely to decline cognitively. If a drug trial uses neuroimaging as an outcome measure, the time and cost of the trial will be greatly reduced if imminent decliners can be selected in advance. In this paper we note ways in which imaging help identify decliners, boosting power for AD-related clinical trials.

AMYLOID IMAGING

A major advance in AD research over the past 5 years has been the ability to assess levels of amyloid plaques and tau neurofibrillary tangles in the living brain. Before amyloid imaging was possible, AD could only be definitively diagnosed at autopsy based on characteristic microscopic features [22]. Some early pioneering studies linked postmortem pathology to *in vivo* patterns of glucose metabolism measured using fluorodeoxyglucose (FDG) positron emission tomography (PET) [23]. However, typically, the unpredictable interval between the patients' last clinical assessments and their deaths make it difficult to compare clinical symptoms to AD pathology. By contrast, amyloid PET scans of the living brain make it possible to evaluate longitudinal changes in AD pathology, and to relate them to clinical changes assessed at the same time as the scans. A key goal has been to establish these PET measures as reliable biomarkers of clinical severity or disease risk. If a correlation is established with cognitive scores, or with future decline in those scores, the PET measures become more promising metrics to evaluate treatment and prevention efforts. Proof of concept for plaque and tangle PET imaging in living humans was established in 2002 [24] using 2-(1-(6-[(2-[18F]fluoroethyl)(methyl)amino]-2-naphthyl)ethylidene)malononitrile (also known as [^{18}F]FDDNP). In 2004, the PET probe, N-methyl-[11C]2-(4-methylaminophenyl)-6-hydroxy benzothiazole (also known as Pittsburgh Compound B or [^{11}C]PIB) was also introduced [25]. Like [^{18}F]FDDNP, [^{11}C]PIB allows PET imaging of amyloid plaques in the living brain. However, unlike [^{18}F]FDDNP, [^{11}C]PIB has a higher signal to noise ratio and is specific to senile amyloid plaques, while [^{18}F]FDDNP signal reflects senile and diffuse amyloid plaques as well as neurofibrillary tangle load [26]. [^{11}C]PIB has a shorter half-life, so scans must be performed very nearby, soon after probe

creation. Depending on study goals, each probe may offer advantages. [^{18}F]FDDNP is particularly useful for examining medial temporal lobe pathology, where neurofibrillary tangles are likely to predominate in preclinical AD [27], while [^{11}C]PIB is useful for studies that focus specifically on amyloid deposition. Higher levels of both [^{11}C]PIB and [^{18}F]FDDNP are correlated with lower cerebrospinal fluid (CSF) levels of amyloid-β 42 ($A\beta_{42}$) [28, 29], the main building block for amyloid plaques, and higher levels of CSF tau [29], the building block for neurofibrillary tangles. This provides converging evidence for the validity of these tools.

PET imaging of AD pathology has helped chart the trajectory of pathology as it spreads in the living brain. [^{18}F]FDDNP has shown regional plaque and tangle load differences between cognitively intact older adults and those with mild cognitive impairment (MCI) [30]. Cognitive performance was linked to the plaque and tangle load, and the associations were displayed across the brain in 3D [31]. PET measures were correlated with subtle cognitive differences even in the normal elderly, and thus show promise for gauging presymptomatic disease progression. In a cross-sectional study, we found that those with lower cognitive ability had higher [^{18}F]FDDNP signal in regions that approximated the classic Braak and Braak trajectory; as performance declined, pathology increased in lateral temporal, parietal, and frontal cortices [31] (Fig. 1). Cognitive performance was also related to [^{11}C]PIB signal in normal elderly and MCI subjects. In one study, the relationship between amyloid load and episodic memory was mediated by hippocampal volume [32].

Higher levels of [^{11}C]PIB signal in the brain are heritable [33], associated with family history of AD [34], and similar in monozygotic twins discordant for AD [35]. *APOE* genotype, the strongest genetic risk factor for late onset AD, is related to both [^{11}C]PIB and [^{18}F]FDDNP signal in cognitively intact older adults [36, 37]. However, it does not fully explain the heritability of [^{11}C]PIB signal [33], suggesting that amyloid imaging on a large scale may eventually uncover new genetic risk factors for late onset AD. Longitudinal [^{11}C]PIB and structural MRI have also offered insight into disease progression, showing that amyloid deposition occurs at a constant slow rate while neurodegeneration accelerates; clinical symptoms were related more strongly to neurodegeneration than to amyloid deposition, which typically occurs before cognitive decline is evident [38]. However, [^{11}C]PIB signal levels can still predict conversion from normal cognition and amnestic MCI to AD [39–41]. Additionally, [^{11}C]PIB data were complementary to MRI data and together, both allowed for a more accurate AD diagnosis [42]. [^{11}C]PIB has even been used to evaluate how an AD drug treatment (bapineuzumab) affects amyloid plaque load *in vivo* [43]. Other [^{11}C]PIB studies explored the cognitive reserve hypothesis, which suggests that people with brains that better compensate for physiological deficits may accumulate more pathology before clinical symptoms are evident [44]. Education modulates the relationship between [^{11}C]PIB signal and cognition, with greater plaque deposition relating to cognition less strongly in more highly educated adults [45, 46]. Amyloid imaging has also been useful for evaluating disruptions to the default mode network (DMN), a co-activated network of cortical brain regions that show more functional MRI activity at rest than during a directed task. The DMN shows deficits in AD patients [47], and DMN activity strength correlates with working memory performance [48]. Both [^{18}F]FDDNP and [^{11}C]PIB have shown that

higher AD pathology is associated with lower DMN activity, even in cognitively intact older adults [49–53].

New PET amyloid probes such as [(18)F]3′-F-PiB (Flutemetamol) [54], (18)F-AV-45 (Florbetapir) [55], and (18)F-AV-1 (Florbetaben) [56] are now being investigated. These combine the specificity of [^{11}C]PIB with the longer half-life of [^{18}F]FDDNP, so the amyloid-specific probe can be created at a separate location and shipped. A promising lead, [^{18}F]-THK523, also exists for *in vivo* imaging of neurofibrillary tangles, but has not yet been human-tested [57].

NEW METHODS FOR MRI ANALYSIS

Both greater ventricular volume [58–61] and lower medial temporal lobe structure volumes, especially of the hippocampus [60–65], predict cognitive decline and are associated with AD and genetic risk for AD. However, manual segmentation of these structures is time-consuming and is a limiting factor when a large study sample size is needed to obtain reliable results. Methods for fully automatic segmentation of subcortical structures have greatly improved in recent years. Large numbers of subjects can now be processed accurately and quickly, with high reproducibility. This allows researchers to detect subtle relationships more efficiently, while controlling for multiple confounds simultaneously. For example, the Enhancing NeuroImaging Genetics through Meta-Analysis (ENIGMA) project recently analyzed hippocampal volume using automated methods in 21,000 subjects scanned at over 20 sites worldwide [19]. This was the first study in history to identify new genetic variants that influence hippocampal volumes; clearly, traditional manual tracing would not have been feasible in such a sample size.

One new hippocampal segmentation method is a machine learning method based on “adaptive boosting”, in which an automated method learns from expert manual tracings; it can also learn from its mistakes. AdaBoost [66] is a meta-algorithm that combines weak classifiers (those that do not perform perfectly on their own but perform better than chance) such that regions with hippocampal segmentation errors receive more attention in subsequent iterations. This method has been extended to segment hippocampi of large numbers of AD and MCI patients automatically. The level of agreement between automated segmentations and manual ones was similar to agreement between two expert trained raters working independently. However, automated segmentation can be used to analyze hundreds of scans in a few hours [67]. The segmentation of MRI data from large samples, such as the Alzheimer’s Disease Neuroimaging Initiative (ADNI) cohort, has led to detailed calculations of sample sizes required to detect correlations between hippocampal structure, clinical assessments, and CSF biomarkers [68]. Work is still underway to determine which segmentation methods agree best with manual tracings. The ENIGMA consortium, which performed the largest-ever hippocampal volume analysis, concluded that the most accurate software depends on the dataset, but the methods correlate well with each other, as long as some manual quality control is performed [19]. Shape-based morphometry studies have attempted to evaluate measures of hippocampal structure more complex than volume, as subregional measures may better distinguish diagnostic groups or predict imminent decline. One study combined radial distance (the distance from the medial core of structure to each

surface point) and multivariate tensor-based morphometry (mTBM; which uses spatial derivatives of the deformation maps used to register each brain image to a template image) [69] to study hippocampal structure in AD and MCI patients and normal controls [70]. This combines complementary information from radial distance, which measures hippocampal size in terms of the surface normal direction, and mTBM, which measures deformation within surfaces, to identify differences in hippocampal and lateral ventricle structure that relate to diagnosis (Fig. 2). Except for group differences between AD and MCI in the hippocampus (where mTBM performed the best), these combined methods detected diagnostic group differences at least as well as mTBM, TBM, or radial distance alone, allowing statistically significant differences to be detected in smaller samples [70]. This may be partly because TBM resolves more diffuse atrophy (such as in the temporal lobe as a whole) more sensitively than smaller-scale changes (such as in the hippocampus) [71].

Other methods target the ventricular system. Ventricular enlargement is the most prominent radiological marker of atrophy on brain MRI, albeit a relatively nonspecific one. Our laboratory recently created and validated an automated three-dimensional surface-meshing tool to automatically extract the lateral ventricles of the brain [72]. Previously, the narrowness of the inferior and posterior horns made it difficult for a computer program to label all regions of the ventricles consistently, but this new tool used surface models from several manually traced images, and aligned them to a new scan using a warping algorithm. By averaging several estimates of the segmentation, we obtained highly accurate and robust results. Such an approach, termed multi-atlas segmentation, decreased segmentation error and increased the statistical power to differentiate AD patients from controls [72]. When used to map ventricular changes in the ADNI cohort, baseline ventricular morphology was correlated with a cognitive decline over the following year, and was related to CSF $A\beta_{42}$ levels [73]. This confirms earlier study findings that ventricular morphology is both AD-relevant and predictive of clinical symptoms. Such information is invaluable in AD prevention trials where an enriched sample is necessary to evaluate treatments using a reasonable sample size.

STATISTICAL METHODS

Recent publications have provided useful guidelines for the most efficient use of resources in future studies. By assessing changes in groups of subjects scanned longitudinally, several studies have empirically determined the best methods for boosting statistical power, often by calculating sample sizes needed to evaluate certain effects. For instance, in a large (n= 1,030) longitudinal TBM study, the ability to detect structural atrophy over time was enhanced by summarizing changes in statistically defined regions of interest derived from a training sample of 22 AD patients. Sample sizes needed to detect brain changes using the best MRI analysis methods were far lower than those needed to detect cognitive change using typical clinical tests [74]. In general, longer follow-up periods (such as 24 months) increased the power to detect change. Even so, many subjects drop out of longitudinal studies, so the added power of a long trial must be traded-off against the risk of losing too many subjects. The attrition rate for ADNI is only around 7% per year, but, in simulations, when more than 15–16% of subjects dropped out annually, a shorter time period (such as 12 months) provided more statistical power [75].

Cerebral glucose metabolism rate changes over one year are also easier to detect using statistically-defined regions of interest derived from a training subsample of the data [76]. Even so, for a statistically-designed region of interest to be approved by the FDA as a reasonable outcome measure in a clinical trial, some criteria would have to be determined to identify it from a subset of the data. Given the power of statistical brain maps and the range of methods to analyze them, detailed head-to-head comparisons with more standard volumetric measures are needed [77]. In related work, our lab used a Support Vector Machine algorithm to combine numerous types of biomarkers, including brain imaging, to classify subjects as AD, MCI, or healthy elderly controls [78]. MRI measures best identified AD subjects, but PET-FDG and CSF biomarkers (particularly $A\beta_{42}$) better identified subjects as having MCI. This work also showed that if those most likely to decline can be identified, fewer subjects are required to detect a specific slowing of the atrophy rate over time in response to a given treatment [78]. Finally, many studies combine multiple biomarkers for predicting decline, but some of the biomarker data are often unavailable for some of the subjects. For instance, in ADNI, only half the subjects had FDG-PET and still fewer had amyloid imaging or lumbar puncture to assess CSF analytes. Sparse coding methods, an innovation from mathematics, are being used to address the problem of missing data in predictive models [79].

RISK FACTORS

Both genetic and environmental factors influence AD risk, and in recent years, many of these factors have also been shown to influence brain structure and function in regions relevant to AD. Numerous studies have demonstrated that possession of *APOE4* is related to brain differences in healthy and cognitively impaired older adults [80]. In recent years, several GWAS have identified and confirmed new genetic risk factors for late onset AD [7–9, 81, 82]. Some top AD polymorphisms have since been associated with differences in brain structure [83] and function [84,85]. For instance, diffusion tensor imaging has shown that the allele C in the clusterin (*CLU*) gene at rs11136000 is associated with lower white matter integrity in healthy young adults in many regions affected in AD [11] (Fig. 3). At least one copy of this adverse allele is carried by approximately 84% of non-demented Caucasians [6], and the C allele increases the lifetime odds of AD by 1.14 in Caucasians [6]. This suggests a developmental vulnerability to AD in these young people. The *CLU* risk allele has also been associated with differences in brain function, assessed using functional MRI [84, 85]. Variants in other top AD-related genes such as *PICALM*, *CR1*, and *BIN1* have been associated with AD-relevant measures such as hippocampal volume or gray matter density, entorhinal cortex thickness [86, 87]. Several new studies have also found that maternal versus paternal (or no) family history of AD may affect brain structure in ways that are important to AD risk [88–92]. Maternal family history may be useful to include in future genetic studies of AD, and AD family history in general may be useful for selecting people for clinical trials, especially when study efficiency relies on identifying those likely to decline cognitively.

Most of the newly discovered AD risk genes increase a person's aggregate risk only mildly [6], so some tools aim to evaluate the effects of multiple genetic variants simultaneously. A few studies have used polygenic scores to assess the cumulative effect of certain AD risk

variants on brain structure. In these studies, each subject is assigned a score based on the number of allele copies for certain previously identified risk variants, in some cases using odd ratios to weight the importance of different genes. This allows researchers to assess cumulative effects of several genetic risk factors on brain measures related to AD [86, 93]. In addition, several new tools are available that offer more flexibility for exploring genetic risk than a single weighted value can provide. For instance, our lab created a tool that allowed a genome-wide search for gene variants that are associated with brain structure [94]. This tool identified one gene variant, in the *GRIN2B* gene, that was associated with temporal lobe volume in AD and MCI patients and healthy older controls (Fig. 3). The protein encoded by *GRIN2B* is the N-methyl-*D*-aspartate (NMDA) glutamate receptor NR2B subunit, which is important in learning and memory and is already a target for AD research [94]. Another new tool allows for a voxelwise gene-wide association, which searches the whole brain, point-by-point, for evidence of gene effects [95]. Each gene may contain multiple SNPs, many of which may be highly correlated, so this method tests all SNPs in a gene at once, reducing the number of tests performed, and thus increasing statistical power to detect effects (as there is a less heavy correction for multiple comparisons).

Yet another tool tested genome-wide association at each voxel in the brain, studying only the most associated variant at each voxel to reduce the number of multiple comparisons [96]. An additional new tool to emerge accepts input from the user as to which SNPs will be evaluated, and controls for the effect of each SNP when evaluating each other SNP in the input list [97]. One recent study used penalized linear discriminant analysis to first identify a characteristic pattern of AD-related brain differences. We then used that imaging signature as a biomarker in a genome-wide association, performed using sparse reduced-rank regression, to identify genetic variants of interest [98]. Tools such as these help researchers to evaluate how multiple genetic variants together increase AD risk. They can also identify new genetic risk variants, bringing us closer to determining key mechanisms in the disease process.

Several studies have revealed how environmental risk factors for AD, such as cardiovascular risk, homocysteine levels, and insulin resistance affect brain structure and function in AD-relevant ways. For instance, obesity and a commonly-carried risk gene for obesity (*FTO*) (Fig. 3) have been linked to more atrophied brains and smaller hippocampi in older adults [15, 17, 99–101]. Along with increased body mass, higher blood pressure has also been associated with differences in functional brain patterns in AD-relevant regions during a memory task [102], and blood cholesterol levels have been linked to hippocampal and other brain gray matter volume [103, 104]. Higher systolic blood pressure has even been associated with more amyloid deposition in AD-relevant brain regions in healthy older adults [105]. High levels of homocysteine (a derivative of the amino acid methionine) elevate risk for cardiovascular disease [106] and AD [107]. They have been linked to greater white matter atrophy in a large sample of older adults, and in the patients with MCI alone [18]. This effect may relate in part to a commonly-carried variant in the folate pathway gene, *MTHFR* [108]. Using B vitamins to lower homocysteine levels may slow the rate of brain atrophy in MCI patients [109]. Higher peripheral insulin is also associated with less AD-related brain atrophy and dementia severity in early AD [110]; in cognitively intact older

adults, insulin resistance was associated with hippocampal volume [111]. Finally, iron homeostasis is important for healthy brain functioning, and its disruption may lead to cognitive impairment [112]. Our laboratory found that levels of serum transferrin, a protein that transports iron in the body, and a variant in the hemochromatotic *HFE* gene were both associated with white matter integrity in young adults [13] (Fig. 3). Gaining a better understanding of how environmental risk factors affect brain structure aids AD research in at least three ways: 1) it provides focal points for treatment efforts, and a way to evaluate them even before clinical decline is evident; 2) it helps identify those most likely to decline cognitively, boosting statistical power for clinical trials; and 3) it uncovers possible factors that should be controlled for when examining other genetic and environmental effects.

PREDICTING COGNITIVE DECLINE OR CONVERSION TO AD

The ability to predict who will decline cognitively or develop AD over time is crucial to AD research. It provides a focus for treatment efforts, boosts power for clinical trials, and allows for further investigation of genetic and environmental factors that contribute to AD before clinical symptoms are evident and possibly before massive destruction of brain tissue has taken place. Predictors of cognitive decline in cognitively normal older adults include MRI measures of temporal and parietal structures [113] (particularly the CA1 of the hippocampus and the subiculum [114]) and the lateral ventricles [115]. Information from both MRI and CSF biomarkers was better for predicting cognitive decline than either measure alone [116]. Similarly, several other studies have found that multiple measures together best predict MCI patient conversion to AD. These measures typically included baseline cognitive tests [117–120], medial temporal lobe or hippocampal structure [117, 118, 120, 121], CSF biomarker levels [118], and cerebral glucose metabolism rates as measured by PET [119, 121]. Of studies that focused on individual biomarkers rather than combinations of them, two found that certain baseline MRI measures (medial temporal cortex or a structural abnormality score that reflect the degree of AD-like features) predict MCI conversion to AD somewhat better than CSF biomarker levels do [122, 123]. In fact, atrophy in a number of AD-related regions (such as the temporal and frontal lobes, temporoparietal cortex, anterior and posterior cingulate, and the precuneus) has been found to be greater in MCI patients who convert to AD within 3 years versus those who do not [124]. Other studies found that a smaller CA1 of the hippocampus or subiculum [125] and lower baseline right caudate volumes [126] were associated with increased conversion from MCI to AD. One study found that for those with moderate MCI, although hippocampal and ventricular volume predicted conversion to AD, baseline cognitive testing predicted it better [61]. Because brain structure typically changes before cognitive ability [12], the same study performed earlier before cognitive changes were evident may have shown different results.

DISEASE PROGRESSION

Understanding the progression of AD beginning in its presymptomatic phases is an essential goal for AD research for at least three reasons. First, determining in what order measurable biomarkers change helps clarify which factors help cause the disease and which may be incidental. Second, identifying the earliest biomarkers of change can be used to focus treatment efforts on those who do not yet have massive loss of brain tissue. Third, gaining a

better understanding of the disease progression provides insight into the effects of treatment efforts or lifestyle factors at each disease stage. Several recent papers have used multiple types of biomarkers to assess the sequence of changes in early MCI and AD. In one study of amnestic MCI patients, hippocampal atrophy led to atrophy of the cingulum bundle and uncinate fasciculus, which was followed by glucose hypometabolism of the cingulate and subgenual cortices [127]. Another study assessed longitudinal amyloid deposition (using PIB PET scans) and ventricular expansion (using MRI) over 1 year. Ventricular expansion rates increased with worsening diagnosis and correlated with cognitive test scores, but amyloid deposition rates were similar among diagnostic groups. This suggests that amyloid deposition occurs at a constant slow rate, and that clinical symptoms relate to neurodegeneration rather than to amyloid deposition [38]. Other researchers found that low levels of CSF $A\beta_{42}$ was correlated with brain and hippocampal atrophy rates and with the rate of ventricular expansion in cognitively normal older adults [128], demonstrating that the change in CSF $A\beta_{42}$ precedes and can predict brain atrophy, even before AD symptoms are evident. Cross-sectionally, CSF $A\beta_{42}$ correlated with whole brain volumes in nondemented subjects, but in AD, CSF tau and phosphorylated tau were higher in those with smaller brains; this suggests that Aβ toxicity may precede both clinical symptoms and changes in tau [129]. Other longitudinal studies focused on one imaging modality. Research showed that three years before an AD diagnosis, amnestic MCI patients showed brain loss largely in the medial temporal lobe (particularly anterior hippocampus, entorhinal cortex, and amygdala) compared with controls. By one year prior to diagnosis, this atrophy had spread to include the middle temporal gyrus and more posterior medial temporal lobe, as well as parts of the parietal lobe. By the time the patients progressed to AD, the temporal and parietal atrophy was more severe, and substantial frontal lobe atrophy had occurred as well [130]. This spread of atrophy roughly mirrors the pattern of neurofibrillary tangle progression noted by others [131], and is evidenced in cross-sectional research in which the temporal and parietal cortices, which are affected earlier [132], are also more severely atrophied compared with other cortical regions in AD versus MCI [133]. In MCI and AD patients, increased hippocampal volume loss rates over a one-year period were associated with lower CSF $A\beta_{42}$ [134], and the atrophy rates increased with worsening diagnosis and cognitive decline [135]. Similarly, temporal lobe atrophy rates in MCI were associated with greater cognitive decline [136], and AD patients with higher CSF phosphorylated tau/$A\beta_{42}$ ratios also had faster atrophy rates [136]. Others have found that hippocampal volumes are smaller in those with amnestic versus multi-domain MCI [137], and are good predictors of clinical diagnosis [138]. Together, these findings suggest that temporal lobe and hippocampal atrophy are excellent biomarkers for clinical and pathological aspects of AD, and that such atrophy may be an early sign of AD processes in asymptomatic older adults. In AD and MCI, it may serve as the most sensitive outcome measure for clinical trials [139].

Familial early onset AD (FAD), caused by rare autosomal dominant genetic mutations, also has offered insights into disease progression in recent years. The benefit of such studiesis that it is possible to determine, even in asymptomatic adults, who will develop AD, and approximately when. This precludes the need for lengthy prospective or retrospective studies to examine presymptomatic AD brain changes. Additionally, smaller initial sample sizes can be used because all of the mutation carriers will eventually develop AD as opposed

to a much smaller fraction of older adults who are simply “at-risk” for AD based on environmental or genetic risk factors. Approximately 5.5 years prior to AD diagnosis, presymptomatic FAD mutation carriers had greater hippocampal atrophy rates than non-carriers, and smaller baseline hippocampi 3 years before diagnosis [140]. Additionally, FAD mutation carriers had lower white matter integrity in the columns of the fornix, even presymptomatically [141]. It is unclear to what extent FAD brain changes serve as a good model for late-onset AD, presymptomatically or otherwise. Expansion of such research to directly compare the two will be useful, because it may facilitate better treatments for those who are presymptomatic. It may also offer insights into general AD triggers and features of disease progression regardless of the specific genetic risk.

CONCLUSION

Improvements in brain scans and the toolstoanalyze them offer a wealth of opportunity in the field of AD research, allowing high-throughput analyses and new insights into disease processes. These developments have led to rapid discoveries regarding disease risk factors, how to predict AD onset, and how to monitor its progression. Such insights are essential for planning future studies as they identify sensitive biomarkers that most reliably reflect disease processes, allowing for more focused treatment and prevention efforts with the greatest statistical power to detect their effects.

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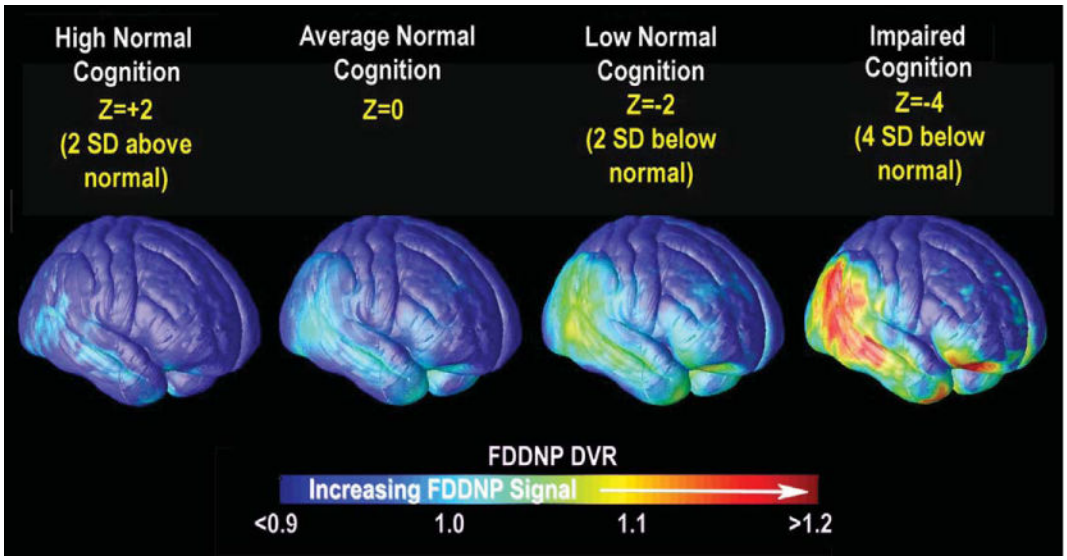

Fig. 1.

Spread of AD pathology mapped with PET. By regressing cortical measures of [^{18}F]FDDNP signal (DVR) against cognitive scores in cross sectional data, we computed the pattern of pathology for subjects who were certain numbers of standard deviations above and below the norm for cognitive performance. Red indicates where greater predicted [^{18}F]FDDNP signal was associated with poorer cognition based on a nonlinear spatially-varying model. Adapted from Braskie et al. [31] with permission from the authors and publishers.

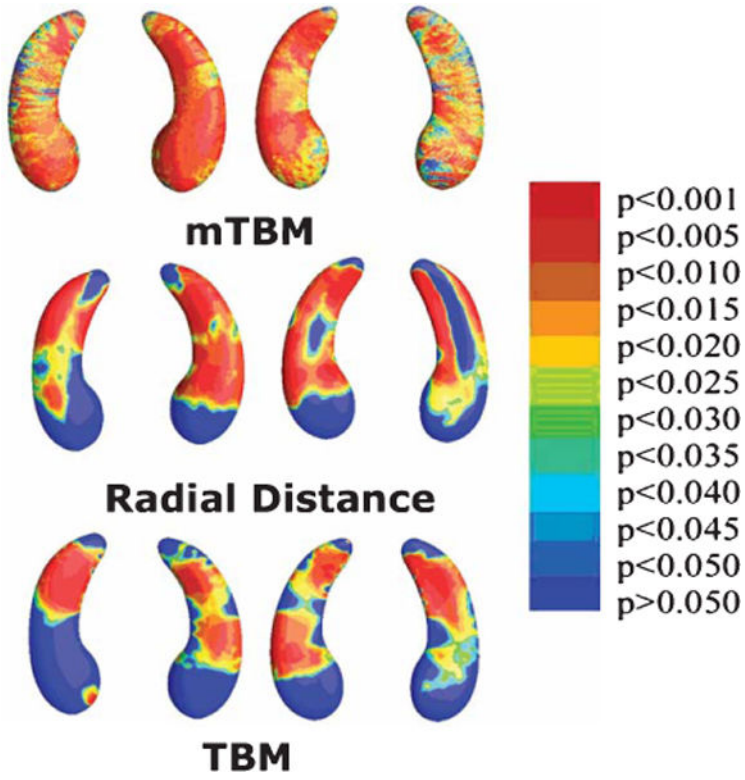

Fig. 2.

Mapping hippocampal correlates of tau proteins in the CSF. Here 3D maps show where alterations of hippocampal shape relate to levels of tau protein, measured in the CSF using lumbar puncture. To create these maps, we use a method called 'multivariate tensor-based morphometry' (mTBM; *top row*), as well as other methods to assess surface morphometry: radial distance maps (*middle row*) and standard TBM (*bottom row*). Non-blue colors show vertices with statistical differences, at the 0.05 level, uncorrected. Relationships were detected most sensitively with mTBM. Clearly, advanced mathematical methods can boost power to pick up associations between brain and CSF biomarkers, offering more detail than traditional measures of hippocampal volume. Adapted from Wang et al. [70] with permission of the authors and publishers.

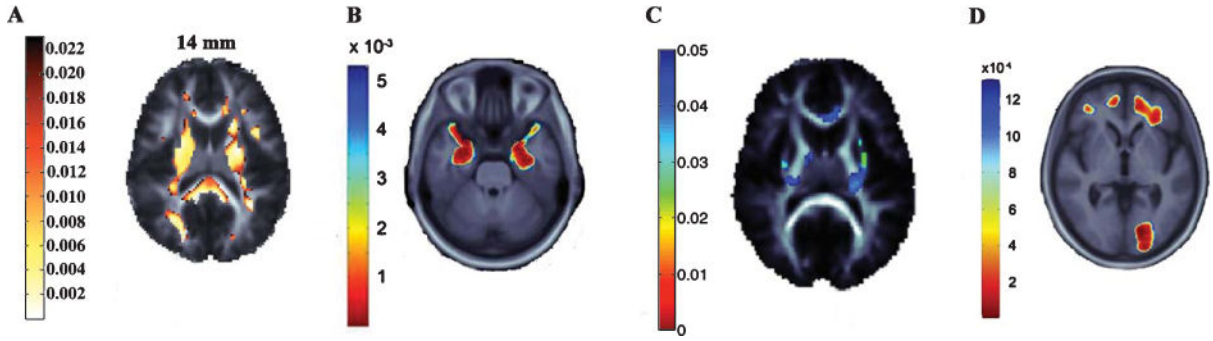

Fig. 3.

Commonly carried genes associated with brain atrophy on MRI and brain integrity on diffusion tensor imaging. Highlighted voxels in each panel represent *p*-values indicating the relationship between a genetic variant and a brain feature. A) The AD risk allele C at rs11136000 in the *CLU* gene was associated with lower diffusion tensor imaging fractional anisotropy (FA), a measure of white matter integrity, in healthy young adults [11]. B) rs10845840 in the *GRIN2B* glutamate receptor gene—important in learning and memory—is associated with medial temporal lobe structure in MCI patients [94]. C) The H63D polymorphism in the *HFE* gene was associated with white matter FA in healthy young adults [13]. D) Regional brain tissue volumes in healthy older adults was lower in those who carried the obesity-associated allele of rs3751812 in the *FTO* gene [99], in line with prior work showing higher brain atrophy in more obese people. Figures are adapted from the referenced publications with the permission of the authors and publishers.