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Neuroimaging and Genetic Risk for Alzheimer's Disease and Addiction-Related Degenerative Brain Disorders

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Abstract

Neuroimaging offers a powerful means to assess the trajectory of brain degeneration in a variety of disorders, including Alzheimer's disease (AD). Here we describe how multimodal imaging can be used to study the changing brain during the different stages of AD. We integrate findings from a range of studies using magnetic resonance imaging (MRI), positron emission tomography (PET), functional MRI (fMRI) and **diffusion weighted imaging (DWI)**. Neuroimaging reveals how risk genes for degenerative disorders affect the brain, including several recently discovered genetic variants that may disrupt brain connectivity. We review some recent neuroimaging studies of genetic polymorphisms associated with increased risk for late-onset Alzheimer's disease (LOAD). Some genetic variants that increase risk for drug addiction may overlap with those associated with degenerative brain disorders. These common associations offer new insight into mechanisms underlying neurodegeneration and addictive behaviors, and may offer new leads for treating them before severe and irreversible neurological symptoms appear.

Keywords

Alzheimer's disease; imaging genetics; multi-modal imaging; neurodegeneration; addiction

Introduction

Alzheimer's disease (AD) is a progressive, degenerative brain disease affecting around 1 in 8 people (13%) aged 65 or older (Alzheimer's Association, 2011). AD has alarming consequences for society: the number of AD patients is expected to triple by 2050, increasing health care costs by an estimated 85% (Bruner & Jacobs, 2013). A century after the first reports of AD, we still do not fully understand what causes it, nor what is needed to treat it successfully (Hua et al., 2008; Braskie et al., 2012; Bruner & Jacobs, 2013).

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In AD, many cognitive domains progressively decline, including memory (Filippi et al., 2012). This cognitive decline is promoted by a combination of age-related brain changes and by progressive deposition of beta-amyloid and tau proteins in the brain. The beta-amyloid aggregate can induce inflammation and neurotoxicity (Wang et al., 2012) while tau proteins can lead to neuronal atrophy and finally, cell death (Fasulo et al., 2002). As neurons are lost, the brain's gray matter shows widespread atrophy, visible on a structural T1-weighted MRI scan (also referred to as structural MRI). At the same time, the white matter volume is reduced, reflecting loss of myelin and axons in the neural fiber tracts (Braak & Braak, 1996).

Many neuroimaging studies have assessed brain degeneration in AD by scanning patients and healthy elderly controls, and, in many cases, people with early or late mild cognitive impairment (MCI) - an intermediate state with heightened risk of developing AD. Changes in cognitive performance correlate with characteristic patterns of change in brain structure and function, making it possible to characterize typical patterns of disease progression based on *in vivo* scans. With high-resolution **structural MRI**, we can quantify brain atrophy; software tools can map the profile of cortical gray matter thinning, and volume loss in subcortical structures. PET scans can reveal the pattern of plaques and tangles in the living brain, based on using specialized radiotracer ligands, sensitive to amyloid or tau proteins (Wong et al., 2010; Teng et al., 2011; Mathis et. al 2012; Wolk et al., 2012). A progressive breakdown of the brain's fiber networks may also contribute to cognitive decline in AD. In the most common approach for assessing the white matter, "FLAIR" or T2-weighted MRI scans are used to evaluate the volume or distribution of white matter hyperintensities – a radiological sign of stroke or cerebrovascular disease. More recently, newer methods, such as diffusion-weighted imaging (DWI) and resting-state functional MRI (fMRI), have emerged to assess brain connectivity. These methods reveal how anatomical and functional networks reorganize and break down in degenerative diseases (Delbeuck et al., 2003; Buckner et al., 2005; Gili et al., 2011; Wegrzyn et al., 2012; Daianu et al., 2012; Daianu et al., in press).

Over half of our risk for developing AD is due to genetic factors, with heritability estimates in the range of 58-74% (Bergem et al., 1997; Gatz et al., 1997; Braskie et al., 2011a). Many specific genetic markers have been discovered that are associated with Alzheimer's disease risk (Naj et al., 2011). Historically, these genetic discoveries have been made through genome-wide association scans, or linkage studies, in groups of patients and cognitively healthy controls. Association studies, in particular, are designed to identify common genetic variants that are over- or under- represented in diseased populations.

Case-control **genome-wide association studies (GWAS)** have revealed a large number of genetic variants that have now been consistently associated with AD, and have held up in meta-analyses of a large number of studies worldwide (Nussbaum, 2013). These studies typically use widely-agreed GWAS practices that include quality control of genotyping, testing for population stratification and imputation – merging data collected using different genotyping platforms with different sets of variants (Nussbaum, 2013); these approaches help to avoid false positive and false negative associations, and improve the design of the case-control association studies. As with other GWAS studies of complex diseases, large

sample sizes are needed to ensure adequate power to detect genetic associations. Successful studies often require tens of thousands or even upwards of a hundred thousand subjects (Rietveld et al., 2013, Speliotes et al., 2010), which can be difficult to amass for more costly phenotypes. Therefore, one alternative approach to discover genetic variants that affect disease risk is to use the endophenotype approach (Gottesman and Gould, 2003); endophenotypes are indicators of brain structure or function that index genetic liability for disease (Glahn et al., 2007). For example, one can use neuroimaging biomarkers as quantitative traits to search the genome for variants that affect them (Glahn et al., 2007); this is one key line of work in the promising field of *imaging genetics*. Imaging genetics may also offer a better understanding of the pathways and mechanisms involved in the dynamic interplay of genes, brain, and environment to shape variability in behavior and disease risk (Munoz et al., 2010). A logical and effective initial screen would be to determine which brain measures serve as good endophenotypes based on the heritability of the trait and how it associates with disease (see Glahn et al., (2012) for an endophenotype ranking method). While much work is still being conducted in the field, improved endophenotypes can be discovered by first identifying novel biomarkers for disease and secondly using these and existing biomarkers for genetic discoveries.

Another less explored approach is to understand how brain differences are associated with carrying genetic variants that are associated with multiple disorders, as our group did in (Roussotte et al., 2013). The patterns of brain tissue loss and atrophy are quite similar, at least at the gross anatomical level, in people who abuse drugs and in AD patients, as Figure 1 illustrates. In recent years, it was found that some genes that affect our risk for neurodegeneration are also implicated in risk for substance abuse (as discussed below). This discovery led some investigators to challenge the more traditional assumption (supported by a range of studies, e.g., Thompson et al., 2004) that brain atrophy in drug addicts only results from chronic exposure to drugs of abuse. A provocative hypothesis is that those at genetic risk for addiction may also harbor latent processes that contribute to neurodegeneration later in life, whether or not those people do abuse drugs.

Several neurotransmitter transporters and receptors are now known to be involved in the etiology or pathophysiology of both degenerative brain disorders such as Alzheimer's disease and substance abuse disorders. Examples include the delta opioid receptors. These receptors involved in drug addiction are coded by the *OPRD1* gene, which also harbors several single-nucleotide polymorphisms (common genetic variants) that are associated with risk for substance abuse disorders (Levrin et al, 2012). Delta opioid receptors also play important roles in learning and memory, and are down-regulated in specific regions of the brain in Alzheimer's disease (Thathiah & De Strooper, 2011). In a mouse model of AD, administration of a selective DOR antagonist improved spatial learning and reference memory, and reduced amyloid plaque burden (Teng et al., 2010). Similarly, *in vivo* knock-down of the DOR reduced amyloid- β_{40} accumulation in the hippocampus of an AD mouse model (Teng et al., 2010).

There are other examples of neurotransmitter transporters and receptors involved in the etiology of both Alzheimer's disease and drug addiction, including SLC1 glutamate transporters. These include excitatory amino-acid transporters (EAATs), whose role is to

terminate the excitatory signal by re-uptake of glutamate from the neuronal synapse into neuroglia and neurons. Dysfunction of EAATs can cause abnormal excitatory synaptic transmission and excitotoxicity, and they have been implicated in the etiology of Alzheimer's disease and drug dependence (Nakagawa & Kaneko, 2013). Another instance is the human sigma-1 receptor (S1R), which was once thought to be a type of opioid receptor, but is now considered to belong to a separate class of receptors. S1R activity and dysfunction is implicated in several diseases of the central nervous system including Alzheimer's disease and drug abuse (Ortega-Roldan et al., 2013). These receptors play important roles in plasticity underlying reinforcement and addictive processes (Maurice & Su, 2011). Moreover, S1R receptor ligands show some neuroprotective activity against amyloid toxicity (Marrazzo et al., 2005). Understanding commonalities in the genetic and neuroanatomical pathways of these genetically modulated disorders may help shed light on the pathogenesis of neurological disease and drug addiction.

In this review, we describe a range of biomarkers of Alzheimer's disease, including newer methods that examine and quantify structural brain connectivity. We show how these new biomarkers (brain measures) can be used to discover genetic markers that associate with neuroanatomical variations, and then their role in disease risk can also be evaluated. Next, we review the role that neuroimaging has played in mapping out effects of specific AD-associated genes on the brain, highlighting brain regions where risk gene carriers may first begin to show signs of derailment. Finally, we discuss some neurodegenerative risk genes related to addiction, how they affect brain structure, and how this line of research may help us understand the neurodegenerative process and the genes that put us all at risk.

Multi-modal Neuroimaging for the study of Alzheimer's Disease

AD was called a "disconnection syndrome" by Geschwind (1965) as patients often show neuropsychological deficits that suggest a worsening anatomical and functional disconnection between brain regions (Wernicke, 1874/1977; Lichtheim, 2006). Evidence for this disconnection is evident from a variety of structural and functional imaging methods including **structural MRI**, fMRI, DWI, PET, **electrophysiology (EEG) and more**. In **structural MRI studies**, AD patients have widespread cortical atrophy, severe tissue loss in the hippocampus and medial temporal lobes (often by 10-20%) and expansion of the ventricular and sulcal cerebrospinal fluid spaces (Ewers et al., 2011). To better understand degenerative brain changes, combined structural and functional information is helpful, as well as other multi-modal analyses. Multi-modal imaging can confirm links between brain changes and other blood or CSF biomarkers (Braskie et al., 2010). Neuroimaging can also be used to help predict disease progression in individuals or groups of subjects (Zhang et al., 2012), study treatments effects on the brain (Schmidt et al., 2008) and how genetic and anatomical variations relate to brain function (Wang et al., 2012).

The cumulative effects of neural shrinkage and cell death, as well as intracortical myelin reduction and neuropil loss can be measured with cortical thickness mapping methods and high-resolution 3D volumetric MRI (Duyckaerts & Dickson, 2003). One of the more sophisticated techniques, *cortical pattern matching* (Thompson et al., 2003), relies on aligning cortical sulci and gyri identified by hand to a reference template. Subsequently,

statistical modeling can reveal the 3D pattern of group differences in cortical thickness, or cognitive differences – such as memory decline or apathy – that statistically relate to some of the changes. Cortical thinning is arguably a reflection, although not a perfect one, of how beta-amyloid burden and tau pathology spread in the living brain, as well as vascular and other forms of pathology that contribute to dementia. In one study, healthy elderly subjects and people with MCI and AD were scanned with both MRI and a novel PET molecular probes sensitive to amyloid-beta, neurofibrillary tangle pathology, or both (Braskie et al., 2010). As seen in Figure 2b, AD pathology is generally low or undetectable in controls and higher in those with impaired cognition; the trajectory of pathology, seen here in scans of the living brain (Fig. 2b), is fairly consistent with the known trajectory of neurofibrillary tangle accumulation (Braak & Braak, 1995; Braak & Braak, 1996). Amyloid PET changes are correlated with subclinical cognitive decline in normal controls (Braskie et al., 2010) and some have argued that they may be detected earlier in the disease process than cortical thinning (Jack et al., 2010a; Fjell et al., 2012). Nonetheless, the pattern of brain alterations detected on MRI and amyloid PET is anatomically similar, despite a possible lag between the detection of changes in each modality (Fig. 2).

A number of recent studies have shown that the use of multi-modal imaging for AD or MCI classification offered improved performance compared to studies that used single-modality imaging (Fan et al., 2008, Hinrichs et al., 2011, Vemuri et al., 2009, Walhovd et al., 2010 and Zhang et al., 2012). This is not surprising, as biomarkers from distinct modalities can provide complementary information that is sensitive to AD. Zhang et al. developed a multi-modal multi-task learning method using baseline MRI, FDG-PET, and cerebrospinal fluid data (CSF) in AD, MCI and healthy subjects to estimate a continuous clinical variable from multi-modal neuroimaging data (imaging-based regression), rather than predicting categorical variables as in classification. This method may help to evaluate the stage of AD pathology as a “disease burden score” and predict future progression. Using it, the authors successfully estimated clinical scores (MMSE, ADAS-Cog) and the correct diagnostic classification when distinguishing both AD vs. controls and MCI vs. controls, and predicted 2-year changes in the scores and diagnostic classifications in people who converted from MCI to AD as well as non-converters.

To study the effects of medication on the brain in AD, the multi-modal approach can reveal numerous treatment effects, including changes in brain structure, function and metabolism – which cannot be mapped with a single modality (unless of course MRI, fMRI and MRS are considered submodalities of MRI; Schmidt et al., 2008). Schmidt et al. used structural MRI, PET and chemical shift imaging (CSI) in a longitudinal study in patients with moderate AD and found a reduction in total brain volume, hippocampal volume and in glucose metabolism after 52 weeks of the administration of memantine. However, their CSI results were not conclusive due to patient-related artifacts. Based on this study and others, there is a clear need to understand factors that affect long-term changes in various imaging measures. We also need to assess the variability and reproducibility of methods used in treatment trials for both MCI and AD (Schmidt et al., 2008).

Genetic data can also be integrated with other multimodality imaging data, using machine learning methods to generate new disease-sensitive biomarkers of AD (Wang et al., 2012).

Wang et al. (2012) studied the statistical dependencies among neuroimaging measures, cognitive scores and disease status – which are often ignored in traditional association studies (Wang et al., 2012). Wang et al. found that voxel-based morphometry (VBM) and FreeSurfer measures from structural MRI were associated with disease status and cognitive scores, and glucose metabolism from PET as well as the *APOE ε4* SNP were also found to have strong links to disease status and cognitive measures. These results led to fairly accurate predictions of both disease status and cognitive function and helped elucidate biological pathways from gene to brain structure, function, cognition and disease (Wang et al., 2012).

Recent advances in multimodal imaging provide exciting new opportunities to understanding brain structure and function and how genetic variations affect them. Furthermore, multi-modal imaging may also help explain why there appear to be similarities at the systems level between detrimental effects of drug abuse and alterations that occur with AD (Thompson et al., 2004).

Brain Connectivity and Risk Genes

Diffusion weighted imaging (DWI) has recently been added to several large studies of AD, including the Alzheimer's Disease Neuroimaging Initiative (ADNI), (Jack et al., 2010b). The benefit of adding **DWI** to the more standard imaging approaches is to better monitor aspects of white matter deterioration that are not detectable with standard anatomical MRI. Some recent studies using ADNI DWI data (including our own) have employed network analyses, based on graph theory, to better understand the pattern of connections, their properties, and how the disease disrupts them.

Connectivity analyses typically consider the connections among a large number of brain regions as a *graph* consisting of *nodes* (e.g., cortical regions) linked by *edges* (which may represent densities of fibers inferred based on whole-brain tractography). These topological networks may be used to understand how neural pathways break down with disease; they have only recently been studied in AD (Buckner et al., 2009; Daianu et al., 2012; Toga et al., 2013; Daianu et al., in press).

Early reports suggest that the brain's anatomical “core” structure is highly disrupted in AD relative to normal aging. Some analyses focus on the most highly connected regions in the brain, which are severely affected in AD. Some methods define the brain's “core” anatomical network by “thresholding” the fiber density connectivity matrices so that only a subset (e.g., 50%) of the network's nodes (cortical regions) remain connected. This method identifies “core” regions of the network that are most highly connected. In one of our studies (Daianu et al., 2012), the effect of retaining only highly connected nodes in the network led to a loss of all core connections in the left hemisphere network in AD (Fig. 2). Furthermore, AD patients had lower fiber density than controls for the connections between the following brain regions: the *pars triangularis* and caudal middle frontal regions, the precentral gyrus and the caudal middle frontal gyrus, the rostral middle frontal gyrus and the *pars opercularis*, and the superior parietal area and lingual gyrus. On average, AD patients also had a lower proportion of fibers emanating to and from the fusiform gyrus, precuneus and

rostral anterior cingulate gyrus and higher proportion of fibers in the supra-marginal region (as a fraction of the total number of fibers detected in the brain), relative to controls (Fig. 2) (Daianu et al., in press).

Little is known about which genetic factors account for inter-subject differences in brain connectivity, but a recent study by Jahanshad and colleagues discovered a connectome-wide, genome-wide significant association between a genetic variant in F-spondin (*SPON1*) and connectivity in 59 brain regions (all connectome-wide connections pre-screen to include only those with a detectable genetic influence in a twin study). This same genetic variant was associated with dementia severity in the ADNI cohort (Jahanshad et al., 2013a). The effect of the genetic variant was also replicated in an independent subsample at the same nodes of the brain's connectivity network. *SPON1* encodes F-spondin, a developmentally regulated protein that is attached to the extracellular matrix. *SPON1* is induced in neuronal injury and interacts with receptors for **Apolipoprotein E** (*APOE4*) – a robust AD genetic risk factor. Also, *SPON1* modulates amyloid-beta protein cleavage (Ho & Sudhof, 2004) and binds to cholesterol (Barrett et al., 2012), an important component of myelin. Intriguingly, the overexpression of *SPON1* in mice improves memory performance and reduces amyloid-beta levels (Hafez et al., 2012). Therefore, the *SPON1* variant may have a protective impact on dementia regardless of the *APOE* risk genotype; the same protective variant was associated with stronger white matter fiber connections. In an independent sample (ADNI) the clinical dementia rating (CDR) was found to be lower in carriers of the protective variant of *SPON1* (Jahanshad et al., 2013a; where a higher CDR indicates increased levels of impairment). Additionally, another variant within the same *SPON1* gene was found to play a role in cognitive decline (Sherva et al., 2013).

While connectivity measures have been shown to associate with known AD risk genes including *APOE4* (Brown et al., 2011; Jahanshad et al., 2012a), recent findings from connectome-wide genome-wide association studies (Jahanshad et al., 2013a; Thompson et al., 2013a,b) suggest that diffusion-based connectome measures help in discovering genetic factors that affect the wiring and degeneration of the brain.

Late-Onset Alzheimer's Disease Risk Genes and Neuroimaging Measures

Early-onset familial AD (fAD) is relatively rare, and represents about 5% of AD cases [reviewed in: (Tanzi, 2012)]. fAD follows an autosomal dominant, highly penetrant mode of inheritance. Rare mutations in the presenilin 1 and presenilin 2 genes (*PSEN1* and *PSEN2*), and in the amyloid precursor protein gene (*APP*) lead to a much higher risk of developing early-onset familial AD. In recent years, we have learned a great deal about how fAD affects the brain. Patterns of structural atrophy are more widespread in fAD, without the strong predilection for medial temporal lobes as in late-onset AD (Frisoni et al., 2007; Benzinger et al., 2013; Cash et al., 2013). By contrast, the more common, late-onset form of AD – known as LOAD or sporadic AD – is moderately heritable. Many common genetic polymorphisms have been identified that are associated with increased risk for LOAD (Braskie et al., 2011a provide an in-depth review). Here, as a brief overview, we will discuss 10 of these genetic variants that have been consistently associated not only with increased risk for developing LOAD, but also with specific brain measures in neuroimaging studies (Table 1). For many

of these variants, differences in brain structure are observable not only in AD patients, but also in asymptomatic carriers of risk alleles, including groups of young and healthy carriers. In this review, we summarize some key findings (for a more in-depth review of all neuroimaging genetics studies in one large-scale initiative, ADNI, please refer to Shen et al., 2013, *this volume*).

Common variants in the apolipoprotein E (*APOE* ϵ 2/3/4) gene confer the highest known odds ratio for developing LOAD. On average, around 25% of the world's population has at least one copy of the ϵ 4 risk allele **and each copy of this risk allele** is associated with around threefold increased odds of developing AD (Bertram et al., 2007). There are ethnic differences among carriers of the ϵ 4 allele. The association between the ϵ 4 allele and AD appears stronger in Asian and Caucasian populations than in individuals of African or Hispanic descent (Farrer et al., 1997). Even so, brain structure and function are altered in AD patients and controls who carry *APOE* ϵ 4. Temporal lobe atrophy rates are faster in AD patients with a greater number of ϵ 4 alleles (Lehtovirta et al., 1995; Filippini et al., 2009), and medial temporal lobe volumes are reduced in healthy middle-aged and elderly *APOE* ϵ 4 carriers (Barbora et al., 2000; den Heijer et al., 2002; Wishart et al., 2006). Recently, a study showed reduced hippocampal volume in healthy young *APOE* ϵ 4 carriers, especially in the right hemisphere, suggesting that possession of the *APOE* ϵ 4 allele may lead to greater risk for brain atrophy even in healthy young subjects in their 20s and 30s, long before the **average** age of onset of AD (O'Dwyer et al., 2012).

Another common risk gene for LOAD is clusterin (*CLU*), whose risk allele is carried by 88% of Caucasians (Harold et al., 2009; Lambert et al., 2009). Intriguingly, the more prevalent form of this disease risk gene confers greater risk; in a sense, the **less commonly carried version of *CLU*** may be considered a protective form of the gene. Our group recently showed that the risk variant in *CLU* is associated with differences in white matter microstructure, even in healthy young adults (Braskie et al., 2011b). Each copy of the risk allele is associated with lower white matter integrity in multiple brain regions, including several areas known to degenerate in AD. This distinct profile of lower white matter integrity is observable in healthy individuals in their early 20s, and may therefore help predict vulnerability for AD later in life - a topic in need of further exploration. Consistent with the possibility of lower white matter integrity, the same risk variant has been associated with faster cognitive decline in asymptomatic and presymptomatic elderly individuals (Thambisetty et al., 2013).

The erythrocyte complement receptor 1 (*CRI*) is another risk gene for which a commonly-carried variant is associated with risk for developing LOAD (Lambert et al., 2009; Naj et al., 2011). A risk allele in *CRI* is significantly associated with AD in both Caucasians and Chinese populations (Jin et al., 2012). As with *APOE* and *CLU*, young healthy risk allele carriers, as a group, appear to show structural brain abnormalities long before possible AD symptoms appear. Carriers of the *CRI* risk allele have lower gray matter volumes in the entorhinal cortex, one of the core structures for AD pathology (Bralten et al., 2011). An intragenic functional copy number variation in *CRI* may explain the association between *CRI* and AD (Van Cauwenberghe et al., 2013).

The growth factor receptor-bound protein 2-associated protein, or *GAB2*, encodes the growth factor receptor bound protein 2-associated protein. *GAB2* is well characterized as a risk gene for the development of LOAD, with a moderate effect on disease risk (Reiman et al., 2007; Chapuis et al., 2008). In a recent study, our group found *GAB2* was significantly associated with alterations in brain structure (Hibar et al., 2011). In a follow-up study, we investigated *GAB2*'s effects on brain structure in healthy young adults (Hibar et al., 2012). In line with expectation, subjects with fewer mutations (or minor alleles) in the *GAB2* gene had greater tissue volumes in the parietal lobe, while participants with less common alleles in *GAB2* showed CSF space expansion in the temporal lobe sulci (Hibar et al., 2012). The mechanism by which the *GAB2* gene affects neurodegeneration is quite well understood. The normally functioning *GAB2* protein suppresses the phosphorylation of tau protein, whose accumulation results in neurofibrillary tangles promoting AD (Reiman et al., 2007). We do not yet know how changes in the efficiency of the *GAB2* protein might lead to morphological differences in young adult brains. Even so, morphological differences associated with an AD risk gene such as *GAB2* appear to be detectable in healthy young adults. This may indicate an early vulnerability to LOAD, long before the onset of Alzheimer's disease. However, long term longitudinal studies would be needed to determine whether the carriers with greater brain abnormalities are at heightened risk of AD, beyond what might be predicted from their genotype alone.

Another interesting line of work concerns genes involved in iron regulation, a mechanism disrupted in many neurodegenerative disorders including AD (Ke et al., 2003). Hemochromatosis, for example, is the most common genetic disorder in the world, and involves an inability of the body to regulate iron levels. Genetic studies of those affected found that the human hemochromatosis protein is encoded by the *HFE* gene, in which common variants explain a large part of the risk for hemochromatosis (see Thompson and Jahanshad, 2012; Jahanshad et al., 2013b, for a review).

The *HFE* protein regulates iron absorption by modulating the interaction of the transferrin with its receptor. The H63D polymorphism in the *HFE* gene is well-known for its association with iron overload (Aguilar-Martinez et al., 2001). Patients with AD who carried the H63D polymorphism had increased plasma iron and transferrin levels, but this pattern was not found in healthy control subjects with the variant (Giambattistelli et al., 2012). A meta-analysis found that the H63D polymorphism may actually be *protective* against AD (Lin et al., 2012). In a recent investigation, our group found that the *HFE* H63D polymorphism influences both serum transferrin levels and white matter microstructure in the external capsule in young healthy adults (Jahanshad et al., 2012b). This finding links blood serum-related genomic variation to brain structure, and suggests that iron may be beneficial (e.g., for myelination) at a young age; however, the effect of the variant on brain integrity in old age has yet to be studied, and it is possible the same variant has a detrimental effect later in life, and may exacerbate disease risk. The role of other metal ions in neurodegeneration is a key target of study, as many of the molecular pathways regulating them are fairly well-understood (Jahanshad et al., 2013b).

Another gene associated with susceptibility for LOAD codes for the phosphatidylinositol binding clathrin assembly protein (*PICALM*) (Harold et al., 2009). This gene likely

contributes to the pathogenesis of AD via its effect on amyloid beta metabolism (Xiao et al., 2012) and also through its association with neurofibrillary tangles and the development of tau pathology (Ando et al., 2013). A recent study integrating **structural MRI** measures and genome-wide common variant data reported that a variant in the *PICALM* gene was most strongly associated with entorhinal cortical thickness (Furney et al., 2011). The *PICALM* variant identified earlier in the large case-control studies (Harold et al., 2009) was associated with less atrophy in the entorhinal cortex, suggesting a protective effect against neurodegenerative diseases (Furney et al., 2011).

A recently discovered rare variant in *TREM2*, which encodes the Triggering receptor expressed on myeloid cells 2 protein, almost triples the lifetime risk of AD (Benitez et al., 2013; Guerreiro et al., 2013; Jonsson et al., 2013). If the odds ratio for this variant holds up in future studies and meta-analyses, it is the variant with the second strongest known effect (in terms of odds ratio) on the risk of late-onset AD, following *APOE4*. A missense mutation in *TREM2* is associated with a significantly higher risk of Alzheimer's disease in diverse human populations (Benitez et al., 2013; Guerreiro et al., 2013; Jonsson et al., 2013). Our group recently reported that elderly *TREM2* mutation carriers in the ADNI cohort appear to lose temporal lobe brain tissue around twice as fast as elderly individuals who lack the mutation (Rajagopalan et al., in press). The risk allele was associated with smaller hippocampal volumes, higher levels of cerebrospinal fluid biomarkers of neurodegeneration, and poorer cognitive performance (Rajagopalan et al., in press). Given the anti-inflammatory role of *TREM2* in the brain, the mutation may lead to an increased predisposition to AD through impaired containment of inflammatory processes (Jonsson et al., 2013), possibly leading to a dysfunction in the microglial phagocytosis pathway (Neumann & Daly, 2013). This may lead to the inability of the brain to clear amyloid plaques (Jones, 2013). If these findings regarding *TREM2* are corroborated in future studies, the selective enrollment of carriers (or *post hoc* stratification by *TREM2* status) may empower clinical trials, by selecting a population more likely to decline.

Another gene associated with increased risk for LOAD is *MTHFR*, which encodes the methylenetetrahydrofolate reductase enzyme. Some common variants in this gene are associated with reduced enzyme activity and result in increased serum homocysteine levels (Mansoori et al., 2012). A moderate elevation of plasma homocysteine is considered a potential risk factor for AD. Homocysteine has garnered significant interest recently, as vitamin B supplementation can lower homocysteine levels, and some studies report that such supplements may reduce the rate of brain atrophy (Douaud et al., 2013). The involvement of *MTHFR* in the pathogenesis of AD is somewhat controversial. Some *MTHFR* polymorphisms may confer greater susceptibility for developing AD in Asian populations, but not in Caucasians (Zhang et al., 2010; Hua et al., 2011). Even so, our group recently reported an association between a common *MTHFR* variant and brain structure in elderly Caucasian individuals with mild cognitive impairment (Rajagopalan et al., 2012a). Carriers of the *MTHFR* risk allele had significant brain volume deficits in the white matter locally at baseline. These subjects also showed accelerated brain atrophy at 1-year follow-up. These brain volume deficits were replicated in an independent elderly cohort with mild cognitive impairment (Rajagopalan et al., 2012a). An earlier report also confirmed a link between

brain atrophy and homocysteine levels in the ADNI cohort, with higher levels appearing to have an adverse effect (Rajagopalan et al., 2011).

Variants in the *TOMM40*, which codes for the translocase of the outer mitochondrial membrane 40 homolog protein, was recently associated with an increased risk of developing LOAD at an earlier age (Roses et al., 2010). Downregulation of *TOMM40* expression has been found in the blood of AD subjects compared to healthy controls in Asian populations (Lee et al., 2012). A study of middle-aged subjects with *APOE* $\epsilon 3/\epsilon 3$ genotype showed that carriers of a risk allele in *TOMM40* had poorer cognitive performance than non-carriers. A dose-dependent increase in the risk variant was also associated with decreased gray matter volumes in regions of the brain that are affected early on in LOAD, such as the medial ventral precuneus (Johnson et al., 2011). In addition, there are poly-T “repeats” in the *TOMM40* gene, and some studies have begun to relate the length of the expansion to AD risk and to brain measures (Babakchian et al., 2011). Nonetheless, the involvement of *TOMM40* in the pathogenesis of AD is somewhat controversial, mainly because *TOMM40* is in strong linkage disequilibrium with *APOE*. Several authors have tried to tease apart an *APOE*-independent role for *TOMM40* in the risk for developing AD and the age of onset (Guerreiro & Hardy, 2012; Rajagopalan et al., 2012b).

In a genome-wide association study of temporal lobe degeneration, our group identified a risk variant for lower temporal lobe volume in the *GRIN2B* gene, which encodes the *N*-methyl-*D*-aspartate (NMDA) glutamate receptor NR2B subunit. This risk variant was significantly over-represented in subjects with AD and mild cognitive impairment than in healthy elderly controls, and was also associated with poorer performance on the Mini Mental Status Exam (MMSE) (Stein et al., 2010). The NR2B subunit of the NMDA receptor is involved in learning and memory, structural plasticity of the brain, and in characteristic features of AD and neurodegeneration. NMDA receptors are an evolving target for the treatment of dementia. The genetic association of *GRIN2B* variants with neuroimaging and cognitive phenotypes supports the relevance of these receptors as therapeutic targets in AD.

Neurodegenerative Risk Genes Related to Addiction

The 10 genes described above only begin to paint a picture of how AD related genes exert their effects on the brain. Intriguingly, **as discussed in the introduction**, some genetic variants associated with neurodegeneration may *also increase our risk for substance abuse*. Understanding how these pleiotropic genes influence differences in the brain, would not only shed light on the neuroanatomical pathways altered by the gene, but may allow us to detect which common pathways are affected by both conditions. For instance, the *COL25A1* gene encoding Collagen XXV alpha 1, also known as collagen-like Alzheimer’s amyloid plaque component precursor, is a transmembrane protein specifically expressed in neurons. It co-localizes with amyloid-beta in senile plaques, in the brains of AD patients (Hashimoto et al., 2002; Tong et al., 2010). *COL25A1* may also be associated with substance dependence (Li et al., 2012).

To our knowledge, very few neuroimaging studies have examined how some of the genes affecting both our risk for neurodegeneration and for substance abuse influence brain

structure. We discuss three of them below. Two of these studies examined the *BDNF* gene encoding the brain derived neurotrophic factor. The most studied polymorphism in this gene has been the Val66Met mutation. Several older studies already showed that Val/Val individuals were at greater risk of developing AD (Ventriglia et al., 2002; Harris et al., 2006). A recent imaging genetics study demonstrated that healthy elderly Val/Val individuals had diminished entorhinal cortex thickness, lower white matter tract integrity, and poorer episodic memory performance, providing a compelling picture of the effect of the Val66Met polymorphism on an intermediate phenotype related to AD (Voineskos et al., 2011). Interestingly, *BDNF* also plays important and diverse roles in addiction-related behaviors (reviewed in (Autry & Monteggia, 2012)). Val/Val carriers may also be at higher risk for methamphetamine abuse (Heinzerling & Shoptaw, 2012). In previous work from our group, the *BDNF* polymorphism was a significant but weak predictor of white matter integrity in young adulthood (Chiang et al., 2011) – its predictive value was weaker than that of several other genes so far discussed, including *CLU* and *HFE* (Kohannim et al., 2012).

Another neuroimaging study focused on the *OPRD1* gene encoding delta opioid receptors, **mentioned earlier**. These receptors are involved in neurodegeneration and promote the processing of amyloid-beta precursor protein (APP). Knockdown or antagonization of delta receptors ameliorates amyloid-beta-related pathology and amyloid-beta-dependent behavioral deficits in mice (Teng et al., 2010). In particular, one *OPRD1* polymorphism (rs1042114) changes the evolutionarily conserved phenylalanine to cysteine in the N-terminus of the receptor. In human cell lines, this change in the amino-acid sequence of the delta receptors leads to a detrimental accumulation of one type of APP, which is degraded less efficiently (Sarajarvi et al., 2011). Interestingly, this same variant is strongly associated with opioid dependence (Zhang et al., 2008). Thus the same allele, which seems to promote neurodegeneration (Sarajarvi et al., 2011), also confers a predisposition to drug addiction (Zhang et al., 2008).

In a recent study, our group used imaging genetics tools to investigate the relationship between another *OPRD1* polymorphism implicated in addiction, rs678849 (Crist et al., 2013) and regional brain volumes in two large independent samples in early and late adulthood (Roussotte et al., 2013). The first sample was an elderly cohort including multiple diagnostic groups: AD, MCI, and healthy elderly controls. The second cohort consisted of young healthy adults. We discovered that carriers of this *OPRD1* variant have identifiable differences in brain structure. The brain regions affected differed between the two samples, but the same minor allele (previously implicated in addiction, Christ et al., 2013) in the same gene (which encodes receptors known to be involved in the processing of amyloid-beta precursor protein and neurodegeneration, Teng et al., 2010, Sarajarvi et al., 2011) was associated with reduced volumes in two very different cohorts (Roussotte et al., 2013). Indeed, we detected these brain abnormalities not just in the elderly (Fig. 3), but also in healthy young adults without any history of substance abuse or cognitive impairments (Fig. 4).

The association of these addiction-related variants with greater risk for developing degenerative brain disorders (Tong et al., 2010; Sarajarvi et al., 2011), decline in cognitive performance (Voineskos et al., 2011) and differences in brain structure (Voineskos et al.,

2011; Roussotte et al., 2013) are key discoveries. This field of study is in its infancy and further research is needed to follow through with these findings and better characterize how genetic polymorphisms associated with addiction affect brain structure, function, and networks in the brain. Currently, many pharmacological agents targeting neurotransmitter receptors and transporters involved in the etiology or pathophysiology of both AD and drug addiction are being investigated as potential therapeutic agents for treating these brain disorders, including EAATs (Nakagawa & Kaneko, 2013), S1Rs (Guitart et al., 2004), and delta opioid receptors (Pradhan et al, 2011). Further investigations outside the field of macroscopic brain imaging could also reveal possible genetic and biological pathways that may underlie specific mechanisms for these gene-brain associations. Gene therapy has become more common and many clinical trials are being conducted for the management of various brain disorders, including AD and those resulting in part from drug addiction. Effective development of gene therapy requires not only the identification of specific molecular and anatomic targets but also specific brain regions or networks to modulate with genetic intervention (Gelfand & Kaplitt, 2012). Therefore, this line of research may help in devising more targeted and effective treatments for degenerative brain disorders.

Conclusion

The pathology of degenerative brain diseases, specifically AD, may progress along structural and functional connections in brain networks. Common genetic variations may also affect a whole host of biological processes that contribute to atrophy, amyloid processing, and vascular integrity. As we have seen in this brief overview, a variety of brain imaging modalities provide complementary information on how the disease progresses in the brain. To fully understand the effects of AD, discoveries must be integrated from a range of imaging methods, and a variety of processing algorithms and statistical analyses, surveying atrophy, dysfunction, and network breakdown, to name a few. Moreover, there is growing evidence of some overlap between genes that promote neurodegeneration and risk for substance abuse; this offers important new avenues for research. Degenerative disorders are typically diagnosed only after severe brain changes have occurred, so it is vital to discover genetic variants that may influence brain volume or atrophy, as well as addictive behaviors in young and healthy individuals. Understanding these associations is within our reach. It may offer new directions for understanding promoters of brain degeneration, and ultimately intervention, many decades before symptoms appear.

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Figure 1. Similarities in brain tissue loss between stimulant abusers and Alzheimer's patients

Panel A: Brain tissue (gray matter) deficits in methamphetamine abusers, relative to healthy adults, mapped using T1-weighted MRI scans. Frontal and limbic brain regions involved in drug craving, emotion and reward, and hippocampal regions involved in learning and memory, show deficits of up to 5% in gray matter density. Red colors denote brain regions with greatest deficits, blue colors regions that remain relatively intact. [Adapted, with permission of the authors, Thompson et al, 2004 – and publishers].

Panel B: Brain tissue loss in Alzheimer's disease patients, relative to average healthy elderly over time, interpolated and inferred using longitudinal T1-weighted MRI scans. These are frames from a time-lapse film computed from MRI; by contrast with Panel A, the maps in this panel represent p-values (showing the significance of the group difference) between a group of AD patients and controls. Red colors denote brain regions with greatest tissue loss. The deficits in temporo-parietal and hippocampal territory spread into the cingulate and frontal lobes over time, with some apparent similarities with brain tissue deficits associated with drug abuse. [Adapted, with permission of the authors, Thompson et al, 2003 – and publishers].

Figure 2. Cortical thinning and changes in apparent cerebral amyloid and tau burden as AD progresses

(a) In mild AD (*left*), cortical gray matter deficits are most severe in the temporal lobes but tend to progress to the frontal lobes in **moderate AD** (*right*); these maps compare patients to controls and are constructed **using T1-weighted MRI** and a method known as “cortical pattern matching” in a longitudinal dataset. (*b*) The apparent profile of amyloid and tau burden based on PET scans - with the ligand [^{18}F] FDDNP - tends to be low in controls (*left*) and higher in cognitively impaired subjects (*right*).

[Adapted, with permission of the authors – Braskie et al., 2010; Thompson et al., 2003 – and publishers].

Figure 3. Structural “core” of anatomical connectivity in healthy controls and AD subjects, reconstructed using DWI scans of the brain

Set of nodes present in the weighted k -core¹ networks of 28 controls (*top left panel*), and 15 AD subjects (*top right panel*). In healthy controls, the structural core was defined to include at least half of the detectable connected nodes per hemisphere. In AD, the left hemisphere loses its k -core connections (FDR critical p -value = 0.0015). The *bottom panel* shows connections that survived FDR when comparing the k -cores ($k=18$) of AD subjects to controls, using age and sex as covariates, and the scanning site as a random effect. *Figures follow anatomical convention (where the left hemisphere is on the left and the right hemisphere is on the right). [Adapted, with permission of the authors – Daianu et al., in press – and publishers]

¹A “weighted k -core” is a technical term that aims to define the core anatomical network in the brain. It is defined as a set of network nodes (cortical regions) that are highly and mutually interconnected (Hagmann et al., 2008; Sporns et al., 2011).

Figure 4. Effects of the minor allele at the rs678849 locus in the delta opioid receptor gene, on regional brain volumes in the elderly cohort

The intronic *OPRD1* polymorphism rs678849 was significantly associated with regional frontal, temporal, and occipital brain volumes. Negative beta values (*warm colors*) show regions where minor allele carriers had lower tissue volumes. The color bar encodes the average percentage of volume difference relative to the template for the subjects carrying at least one minor allele, versus noncarriers. Tests for associations are adjusted for age and sex; maps are corrected for multiple comparisons with the searchlight false discovery rate (FDR) method. Images are in radiological convention (left side of the brain shown on the right) (Roussotte et al., 2013).

Figure 5. Effects of the minor allele at the rs678849 locus in the delta opioid receptor gene, on regional brain volumes in the young healthy cohort

The same *OPRD1* polymorphism, rs678849, was significantly associated with regional frontal, temporal, and occipital brain volumes. Negative beta values (*warm colors*) show regions where minor allele carriers had lower tissue volumes. The color bar encodes the average percentage of volume difference relative to the template for the subjects carrying at least one minor allele, versus noncarriers. Tests for associations are adjusted for age and sex; maps are corrected for multiple comparisons with the searchlight false discovery rate (FDR) method. Images are in radiological convention (left side of the brain shown on the right) (Roussotte et al., 2013).

Table 1

List of several major Alzheimer's disease risk genes that have been studied using neuroimaging. Here we list a range of studies that have found associations between brain imaging measures and common variants in major Alzheimer's disease risk genes. Note that the prevalence of the risk-associated variant is different for each gene. Some of the AD risk alleles are fairly rare - the one in *TREM2* is carried by only about 1% of the healthy population. Other risk alleles (e.g., for *CLU*) are carried by more than half of the healthy population, meaning that carriers of the rarer form are at lower risk for the disease, if other factors were equal. For other in-depth reviews of neuroimaging studies of common genetic variants, see Thompson et al., 2013b, and Shen et al., 2013 (*this issue*).

Publication	Gene	Reference number, or location, of the common genetic variant (SNP) that is associated with risk for Alzheimer's disease	Minor Allele (i.e., the least prevalent form)	Minor Allele Frequency (MAF) [%]	Imaging Modality	Brain Regions Assessed	Results	Affected Regions	Population
O'Dwyer et al., 2012	<i>APOE</i>	rs7412 and rs429358; for <i>APOE</i> , the genotype E2, E3 or E4 depends on the genetic variants at two locations on the chromosome	T and C, respectively	7.4 and 14.9, respectively ^{*,**} ; around 25% of healthy people, but 40-65% of AD patients, carry at least one <i>APOE4</i> allele	T1-weighted MRI	Hippocampal morphometry	ApoE4 carriers have smaller hippocampal volumes	Greater effects on the right than the left hippocampus	Not stated
Braskie et al., 2011	<i>CLU</i>	rs11136000	T	35 [*] (T-allele); for <i>CLU</i> , the minor allele is associated with lower risk, and the more common allele is associated with higher risk	Diffusion tensor imaging (DTI); tested voxel-wise association with FA	Full white matter FA	Carriers of the <i>CLU-C</i> variant (major allele) had lower white matter integrity	Strongest effects in the splenium, bilateral posterior and anterior corona radiata, bilateral perithalamic tracts, and posterior thalamic radiation, left SLF, ILF/IFO	Caucasian
Bralten et al., 2011	<i>CR1</i>	rs6656401	A	24 [*]	Voxel-based morphometry	Regional gray matter volume	<i>CR1</i> minor allele is negatively associated with local gray matter volume	Lower local gray matter volume in entorhinal cortex and hippocampus	Caucasian

Publication	Gene	Reference number, or location, of the common genetic variant (SNP) that is associated with risk for Alzheimer's disease	Minor Allele (i.e., the least prevalent form)	Minor Allele Frequency (MAF) [%]	Imaging Modality	Brain Regions Assessed	Results	Affected Regions	Population
Hibar et al. 2011, Hibar et al 2012	<i>GAB2</i>	rs7101429	G	13 [*]	T1 weighted MRI / voxelwise gene based test (PCR)	Whole brain voxel based morphometry (VBM)	In the right parietal lobe, <i>GAB2</i> loading is negatively correlated with overall tissue volume; in the temporal lobe sulci, there was a positive correlation between CSF volume and <i>GAB2</i> loading	Significant differences in the right parietal lobe, additional smaller clusters in left parietal, along CSF boundary, and in the temporal lobe	Caucasian
Jahanshad et al., 2011	<i>HFE</i>	rs1799945	G	18 [*]	Diffusion tensor imaging (DTI); tested voxel-wise association with FA	Full white matter FA	<i>HFE</i> minor allele has a negative correlation between transferrin levels and FA measures	Mainly in the external capsule and portions of the genu of the corpus callosum	Caucasian
Furney et al., 2011	<i>PICALM</i>	rs3851179	T	41 [*]	T1-weighted MRI / cortical thickness and volume	Entorhinal cortex	<i>PICALM</i> major allele carriers have thinner entorhinal cortical volume than minor allele carriers	Increased entorhinal cortical thickness in minor allele carriers	Participants in the AddNeuroMed study and ADNI

Publication	Gene	Reference number, or location, of the common genetic variant (SNP) that is associated with risk for Alzheimer's disease	Minor Allele (i.e., the least prevalent form)	Minor Allele Frequency (MAF) [%]	Imaging Modality	Brain Regions Assessed	Results	Affected Regions	Population
Rajagopalan et al., 2013 (in press)	<i>TREM2</i>	Rajagopalan et al. assessed rs9394721, a close proxy for the newly discovered risk variant, rs75932628, in <i>TREM2</i>	A allele for rs7593268; T allele for rs75932628 in the Jonsson et al. paper	Around 1%, but more common in AD patients	T1-weighted MRI	Tensor-based morphometry, focusing on the temporal lobes	Carriers of the (rare) <i>TREM2</i> minor allele have faster rates of brain atrophy	<i>TREM2</i> mutation carriers annually lose brain tissue up to 1.4–3.3% faster than non-carriers, in a pattern that mirrors the profile of AD pathology in the brain	Caucasian participants in the ADNI
Rajagopalan et al., 2012	<i>MTHFR</i>	rs1801133 rs1054523; this is a SNP, but some studies focus on a poly-T repeat in the same gene	A	31*	T1-weighted MRI	Whole brain morphometry	<i>MTHFR</i> -T (major allele) is negatively associated with regional brain volume	Significant volume deficits in the bilateral parietal white matter, periventricular parietal white matter, and posterior parieto-occipital white matter	Caucasian
Johnson et al., 2011	<i>TOMM40</i>		NA	NA	MRI; voxel-based morphometry	Gray matter morphometry	Risk-associated variant in <i>TOMM40</i> is negatively correlated with brain volume	Significant effects seen in the left ventral posterior cingulate and the cuneus	Participants of WRAP
Stein et al., 2010	<i>GRIN2B</i>	rs10845840	T	46*	MRI; voxel-based association testing	Tensor-based morphometry, focusing on the temporal lobes	<i>GRIN2B</i> minor allele has wide ranging effects across the temporal lobe	Strongest effects in the bilateral temporal poles and medial temporal lobes	Caucasian participants in the ADNI

* MAF obtained from the CEU database in <http://hapmap.ncbi.nlm.nih.gov/>

** MAF obtained from <http://www.ncbi.nlm.nih.gov/SNP/>