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Staging Alzheimer's Disease Progression with Multimodality Neuroimaging

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Abstract

Rapid developments in medical neuroimaging have made it possible to reconstruct the trajectory of Alzheimer's disease (AD) as it spreads through the living brain. The current review focuses on the progressive signature of brain changes throughout the different stages of AD. We integrate recent findings on changes in cortical gray matter volume, white matter fiber tracts, neuropathological alterations, and brain metabolism assessed with molecular positron emission tomography (PET). Neurofibrillary tangles accumulate first in transentorhinal and cholinergic brain areas, and 4-D maps of cortical volume changes show early progressive temporo-parietal cortical thinning. Findings from diffusion tensor imaging (DTI) for assessment fiber tract integrity show cortical disconnection in corresponding brain networks. Importantly, the developmental trajectory of brain changes is not uniform and may be modulated by several factors such as onset of disease mechanisms, risk-associated and protective genes, converging comorbidity, and

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individual brain reserve. There is a general agreement between in vivo brain maps of cortical atrophy and amyloid pathology assessed through PET, reminiscent of post mortem histopathology studies that paved the way in the staging of AD. The association between in vivo and post mortem findings will clarify the temporal dynamics of pathophysiological alterations in the development of preclinical AD. This will be important in designing effective treatments that target specific underlying disease AD mechanisms.

Keywords

Alzheimer's disease; AD; mild cognitive impairment; MCI; pre-dementia; pre-clinical; pre-symptomatic; biological markers; neuroimaging; multimodal; neuropathology; neuroanatomy; computational; MRI; fMRI; DTI; VBM; DBM; tractography; drug development; clinical trials; CSF; staging; progression; diagnosis; classification; early detection; prediction; biological activity; ADNI; EADNI; regulatory authorities; FDA; EMEA

1. Introduction

AD is a complex and chronic non-linear progressive neurodegenerative disorder, and is the most common cause of dementia among the elderly. At some point of disease progression, the extent of neuronal loss and dysfunction increases; cortical and subcortical brain regions are gradually and subsequently more severely affected at different stages of AD severity. Multiple lines of research indicate that neuronal degeneration in AD is not random but shows a characteristic anatomical sequence as the pathology advances over several decades. Establishing an accurate dynamic map of this sequence is vital for understanding and mapping the complex endophenotype of AD, providing a basis for successfully evaluating treatments designed to resist or prevent disease progression.

New models of the degenerative sequence have recently been developed based on new technologies that track AD pathology as it spreads through the living brain. These dynamic maps reveal the anatomical substrate of the trajectory of cognitive dysfunction, and can help to predict the course of cognitive decline and the onset of psychiatric symptoms including depression, aggression, psychosis and agitation that may occur at different stages of AD. Better modeling of disease progression in individual subjects will provide significant advantages in predicting when a cognitive ability may break down and when social or behavioral abnormalities may result. Biomarker based staging models (Jack *et al.*, 2010) will further allow to evaluate treatment effects of novel drugs in clinical trials on the basis of a drug's effect on slowing down or halting the transition among different stages in the development of neuronal degeneration. Successfully establishing the multimodal AD biomarker signature during the course of AD will further support the development of surrogate biomarkers that are vitally needed as outcomes for clinical trials of disease modifying drug candidates (for reviews see (Hampel *et al.*, 2010a; Hampel *et al.*, 2010b).

The first evidence that AD progresses in stages came from post-mortem examinations of clinically stratified samples, establishing a sequence of early pathological changes in the transentorhinal and entorhinal cortex that spread subsequently to the hippocampus and adjacent allocortical areas and finally neocortical areas (Braak and Braak, 1991). The cortical changes are paralleled by a somatotopic degeneration of cholinergic neurons in the *nucleus basalis* of Meynert, which accounts for the documented, but limited, efficacy of cholinergic drugs in treating the illness in its early clinical stages (Mesulam, 2004). The earliest neurofibrillary changes have been found in the transentorhinal region, but also the dorsal raphe nuclei (Grinberg *et al.*, 2009) and basal nucleus of Meynert (NbM) (Sassin *et al.*, 2000), and by using cytoarchitectonic maps from a post mortem brain specimen in MRI

space (Teipel *et al.*, 2005; Zaborszky *et al.*, 2008) and three independent studies showed significant atrophy of gray matter in cholinergic neurons of the *nucleus basalis* of Meynert in predementia stages of AD (Grothe *et al.*, 2010; Teipel *et al.*, 2005; Teipel *et al.*, 2010b). Taken together these findings point to a possible multilocal onset of the neurodegenerative stage of the disease.

A growing number of neuroimaging studies have assessed the path of neuronal degeneration of AD, making it possible to relate regional topological maps of cortical degeneration to changes in brain function and specific cognitive abilities across different stages of AD. Novel MRI processing algorithms can now reconstruct the profile of thinning in cortical gray matter, and the presence of cortical plaque and tangle pathology (Sowell *et al.*, 2003). These methods have visualized complex spatial patterns of correlated brain changes and mapped these along the time axis of AD development (Lerch *et al.*, 2005). Efforts are also underway to interlink MRI- and PET-based findings with the post-mortem staging model of AD core pathology and neuronal loss.

The current review discusses new insights from neuroimaging at several levels of analysis including cortical functional changes, molecular imaging, and structural volumetric assessments, as well as post-mortem MRI validations. We integrate these findings to provide a unified perspective on the spatio-temporal evolution of AD. We relate the characteristic sequence of neuropathology in AD to different factors influencing neuronal vulnerability in cortical networks, including specific developmental, metabolic and morphological characteristics of neurons. The level of axonal myelination also influences a neuron's vulnerability to AD pathology, as does the glial environment. Those axonal projections that have the most protracted maturational time-course, and develop in the later ontogenetic stages, such as the medial temporal lobe and prefrontal cortex, tend to show increased vulnerability in AD (Bartzokis *et al.*, 2004; Reisberg *et al.*, 2002; Reisberg *et al.*, 1999b). AD pathology may progress along neuroanatomical connections of cortical networks, and genetic and epigenetic variability in brain development may play a role. Although AD pathology has a characteristic pattern of progression, prior studies have used different techniques to observe different aspects of the disease process. Here we integrate the wealth of reported neuroimaging findings derived from different acquisition, processing and analysis modalities and methods to provide a unified model of AD neurodegeneration.

2. Cortical atrophy in the development of AD

As AD progresses, prominent brain changes are observed on structural MRI, including widespread cortical atrophy, profound tissue loss in the hippocampus and medial temporal lobes, and expansions of the ventricular and sulcal cerebrospinal fluid (CSF) spaces. Cortical gray matter atrophy is detectable through high resolution 3D MR imaging, and is believed to be a reasonable proxy for neuronal loss (Smith, 2002), although it likely reflects the combined effects of neuronal shrinkage and death, neuropil loss, and intracortical myelin reduction (Duyckaerts and Dickson, 2003).

Techniques developed in the last decade have enabled researchers to quantify gray matter atrophy in 3-dimensional detail, across the cortex, mapping its profile with exquisite accuracy (Ashburner *et al.*, 2003). Some of the most sophisticated methods rely on alignment of cortical features such as gyral/sulcal landmarks identified by hand, or with computer vision approaches. This is then followed by statistically-guided detection of subtle brain changes associated with prognosis, treatment, or other factors of interest. One such technique, termed *cortical pattern matching* (Thompson *et al.*, 2003) allows accurate registration of cortical sulci and gyri in different subjects to a reference template, following manual tracing of 39 sulcal lines as landmarks on each 3D rendered brain. Measures of

cortical atrophy from hundreds of subjects may then be integrated or compared across groups. Although time consuming, this technique has mapped the dynamic progression of atrophy through the cortex in patients scanned repeatedly as their disease progresses from moderate to severe AD (Thompson *et al.*, 2003; Frisoni *et al.*, 2009). A similar travelling development of advancing pathology is seen in the hippocampus (Apostolova *et al.*, 2010a).

On average, patients with moderate AD have gray matter reductions, relative to matched healthy controls, of 15% or more in the medial temporal, posterior cingulate, temporal, and temporoparietal cortices. Gray matter loss also progresses at a rate of 3–4% per year in most of these regions (Thompson *et al.*, 2003). Similar cross-sectional results have been obtained with more automated voxel-based mapping techniques, revealing systematic patterns of gray matter volume loss (Baron *et al.*, 2001; Chetelat *et al.*, 2002; Chetelat *et al.*, 2005; Frisoni, 2000; Karas *et al.*, 2004) and reductions in cortical thickness at specific clinically-defined stages of disease progression (Lerch *et al.*, 2005). Sowell *et al.* (Sowell *et al.*, 2003) applied a cortical pattern matching technique, which combines cortical thickness data from many subjects, to compute the mean anatomical trajectory of gray matter thinning over the human lifespan, in healthy normal subjects. Gray matter thickness was computed at each cortical point, in 176 scans of subjects aged 7 to 87. The frontal cortex underwent rapid thinning in late adolescence, perhaps reflecting dendritic pruning and progressive myelination within the cortex, but it was only late in life that a downswing in temporal gray matter occurred. Supporting the validity of these cortical measures, there was a close regional correspondence between population-based maps of cortical thickness created from *in vivo* MRI (Sowell *et al.*, 2003) and the 1929 *post mortem* data of von Economo (Von Economo, 1929).

More recent work has found that this thinning of the frontal and language cortex is related to distinct changes in cognitive skills (Lu *et al.*, 2009), and frontal cortical thickness predicts amygdala reactivity on fMRI (Foland-Ross *et al.*, 2010). A related study by Gogtay *et al.* (Gogtay *et al.*, 2004) created a time-lapse map of cortical development from ages 4 to 22, and showed that the earliest maturing cortex is least vulnerable to aging and AD. This phenomenon (Figure 1) is sometimes referred to as *retrogenesis* (Reisberg *et al.*, 1999a); it suggests that the most heavily myelinated cortex is relatively resistant to AD pathology. Greater myelination may protect neurons against metabolic stress during the maintenance of the action potential along axons (Arendt *et al.*, 1998). As is visually evident in the time-lapse maps, the maturational sequence in childhood proceeds in a pattern opposite to the classical neurodegenerative sequence in AD (Gogtay and Thompson, 2009).

The progression of cortical atrophy is also tightly linked with progressive decline in specific cognitive domains (Thompson *et al.*, 2007). Performance on the Mini-Mental State Examination (Folstein *et al.*, 1975), a widely used global measure of cognition in AD, is strongly correlated with gray matter integrity in the entorhinal, parahippocampal, precuneus, superior parietal, and subgenual cingulate/orbitofrontal cortices (Apostolova *et al.*, 2006). More selective correlations have also been discovered, suggesting that specific cognitive domains may be differentially affected by AD-related atrophy in specific cortical regions. For instance, cortical atrophy in the anterior cingulate and supplementary motor cortices was associated with apathy in patients with AD (Apostolova *et al.*, 2007). Furthermore, linear regression models, fitted at each location on the cortex, detected associations between the degree of language impairment and increasing atrophy of the left temporal and parietal cortices – regions critically involved in language production and comprehension (Apostolova *et al.*, 2008). Although cognitive decline in multiple domains is typical in AD, studies of brain development in childhood also suggest that motor and language performance is selectively linked with cortical morphometry in the regions subserving those tasks (Lu *et al.*, 2007).

Brain tissue loss in early AD has been investigated longitudinally and cross-sectionally in several studies that are highly consistent in their anatomical patterns (Bakkour *et al.*, 2008; Dickerson and Sperling, 2008; Whitwell *et al.*, 2007; Whitwell *et al.*, 2008). As such, 3D maps of cortical thickness or gray matter density have become widely accepted as a structural correlate of functional decline in AD, and have been related to other neuroimaging measures of cortical pathology, such as functional MRI (fMRI) activation (Dickerson and Sperling, 2008), metabolism (Apostolova *et al.*, 2009) or molecular pathology at the group level (Braskie *et al.*, 2008).

3. Tracking pathology with PET

PET scanning has long been used to reveal reductions in cerebral blood flow and metabolism in AD, and is valuable for the differential diagnosis of dementia in individual patients (see (Silverman and Thompson, 2006) for a review). Hypometabolism of the posterior cingulate cortex, for example, is observed early in AD using fluoro-deoxyglucose (FDG) PET scanning, even when no atrophy is detectable on MRI (Mosconi *et al.*, 2004). As AD progresses, there is widespread decreased cerebral metabolism and perfusion in posterior cingulate and association cortices, but the basal ganglia and thalamus, cerebellum, and primary sensorimotor cortices are largely spared until later stages of the disease (Apostolova *et al.*, 2010b). More recently, there has been renewed interest in tracking AD with PET, using new molecular probes sensitive to amyloid-beta ($A\beta$) or neurofibrillary tangle pathology, or both types of pathology (Braskie *et al.*, 2008; Klunk *et al.*, 2004; Mintun *et al.*, 2006; Small *et al.*, 2006). To better understand how $A\beta$ load spreads in the living brain, Braskie *et al.* (Braskie *et al.*, 2008) applied cortical pattern matching to 23 subjects (10 controls, 6 subjects with amnesic mild cognitive impairment (MCI), 7 AD) scanned with both MRI and a recently developed PET ligand sensitive to plaque and tangle pathology ($[^{18}F]FDDNP$ (Small *et al.*, 2006)). Figure 2 shows two frames from an animation sequence that shows the degree of amyloid burden, for different levels of cognitive impairment. The advance of pathology largely follows the known trajectory of neurofibrillary tangle accumulation (Braak and Braak, 1995). Related work by Mintun *et al.* (Mintun *et al.*, 2006) and Rowe *et al.* (Rowe *et al.*, 2007) using an amyloid-sensitive tracer termed *Pittsburgh Compound B* ($[^{11}C]PIB$) shows frontal lobe labeling early in the degenerative sequence. The PIB deposition pattern is consistent with the Braak trajectory for amyloid deposition, which, unlike tangle deposition, shows early increases in the basal neocortex, particularly in frontal and temporal lobes and primarily in poorly myelinated regions such as the perirhinal cortex. These PET changes may occur at a much earlier stage of the disease than cortical thinning – amyloid PET appears to detect abnormal brain changes earlier than gray matter measures, and is also correlated with subclinical cognitive decline even in normal subjects (Braskie *et al.*, 2008; Small *et al.*, 2007). PET measures of cerebral plaque and tangle burden may also be used to predict a person's Mini-Mental State Exam score, with reasonable accuracy (Protas *et al.*, 2010). The ability of $[^{11}C]PIB$ to detect specific insoluble A-beta fractions was confirmed in an autoradiographic study on human brain specimens showing specific binding in temporal, parietal and frontal lobe gray matter in AD brains compared to controls (Svedberg *et al.*, 2008). Despite these findings, $[^{11}C]PIB$ did not show significant progression of amyloid binding over 2 years follow up in AD patients (Engler *et al.*, 2006). It is still unresolved whether this reflects a ceiling effect of amyloid binding in clinically manifest AD or an artefact from the lack of a dynamic quantification model of $[^{11}C]PIB$ binding that controls for perfusion effects.

Whether each imaging modality can detect changes depends on the population studied, the sample sizes, and details of signal reconstruction, partial volume correction, and registration. As such, it is difficult to make absolute statements about how the binding of various PET ligands (FDDNP versus PIB, or others) relate chronologically to each other and to cortical

thinning and *post mortem* histology, unless all measures are compared head-to-head in the same subjects, which is logistically challenging. Initial studies show a dissociation between local [^{11}C]PIB binding (high in frontal lobes) and cortical atrophy (high in temporal lobes) (Jack *et al.*, 2008). This raises questions about the functional relevance of amyloid deposition for regional neuronal loss in AD. A combined [^{11}C]PIB/structural MR study, however, has shown that, despite the relatively low amount of amyloid deposition in the medial temporal lobe, amyloid deposition at a more global level in the brain is strongly related to atrophy of the hippocampus (Apostolova *et al.*, 2010; Frisoni *et al.*, 2009). It is still unknown whether this amyloid related atrophy in the medial temporal lobe is due to specific amyloid fragments being deposited in the medial temporal lobe or to local lower resilience of the neuronal tissue. Even so, in normal elderly subjects amyloid-sensitive PET signals correlate with cognitive performance and brain atrophy in cortical areas that deteriorate earliest in AD (Bourgeat *et al.*, 2010; Chételat *et al.*, 2010; Mormino *et al.*, 2009). Amyloid PET may therefore be useful for early detection of prodromal AD before symptoms are prominent.

4. Progressive degeneration along anatomical fiber connections

Neuronal activity in different brain regions does not occur independently, and is organized in non-randomly interconnected neuronal networks. According to the retrogenesis model mentioned above, ontologically late-myelinating brain regions such as the prefrontal and other association cortices, and basal and parahippocampal cortices that develop until the 5th decade during life (Bartzokis, 2004), show the highest susceptibility to neuropathological insult (Bartzokis *et al.*, 2006).

DTI can be used to map microstructural white matter integrity (Basser and Jones, 2002; Mori and van Zijl, 2002), and their changes with aging over the lifespan and in neurodegenerative diseases (Kochunov *et al.*, 2010). In agreement with the retrogenesis hypothesis, studies showed that region specific decline in fractional anisotropy (FA), a measure of fiber tract integrity, is primarily present in intra-cortical late-myelinating white matter in brain regions such as inferior longitudinal fasciculus, prefrontal cortex white matter, and temporo-parietal brain regions, but relative preservation in early myelinating white matter such as (extra-) pyramidal pathways and sensorimotor cortex and cerebellar peduncle in patients with AD (Chua *et al.*, 2009; Stricker *et al.*, 2009; Teipel *et al.*, 2007a). While there is significant variability among DTI studies on MCI and AD (Sexton *et al.*, 2010), a large number of studies report decreased fiber integrity within the parahippocampus, hippocampus, posterior cingulum, and splenium already at the stage of MCI (Chua *et al.*, 2009; Takahashi *et al.*, 2002; Zhang *et al.*, 2007; Zhuang *et al.*, 2010). These brain regions are part of the Papez circuit underlying episodic memory and show correlated changes in AD (Avants *et al.*, 2010; Teipel *et al.*, 2007b; Teipel *et al.*, 2007c). Thus, in addition to retrogenesis it is also possible that the distribution of early fiber projection follows that of anatomical and functional connectivity. Possible mechanism of propagating white matter degeneration within neuronal networks include Wallerian neurodegeneration or backward degeneration in which neuronal grey matter atrophy is followed by axonal degeneration (Coleman, 2005), and first DTI studies have now begun to differentiate different mechanisms underlying fiber tract changes (Di Paola *et al.*, 2010; Pievani *et al.*, 2010; Stricker *et al.*, 2009). First longitudinal studies on DTI changes suggest a high temporal rate of fiber tract deterioration along association fiber tracts in aging and MCI (Barrick *et al.*, 2010; Teipel *et al.*, 2010c), and longitudinal studies in joint assessment with functional and structural studies, using elegant advanced methods such as joint multimodal independent component analysis (Calhoun *et al.*, 2009), will be needed to confirm cross-sectionally observed association between functional and structural network changes (Koch *et al.*, 2010; Teipel *et al.*, 2010a). Recent studies have begun to integrate

different neuroimaging modalities for diagnostic purposes in AD, e.g. including modalities such as MRI and FDG-PET (Hinrichs *et al.*, 2011). functional MRI and structural MRI (Fan *et al.*, 2008), or DTI and DBM (Friesen *et al.*, 2010). The spatial pattern of DTI derived indices of fiber tract integrity and the spatial distribution of atrophic changes are only partially overlapping and may complement each other in defining AD specific patterns of brain changes (Figure 6). It remains to be determined exactly which spatial patterns of brain changes across different modalities provide additive information to improve the prediction of AD at the early stages of the disease.

5. Moderating factors in the development of AD related brain changes

Neuropathology progresses with a relatively stereotyped sequence of involvement of brain structures (Braak and Braak, 1991), but the onset and progression of clinical symptoms are remarkably variable across patients and are critically affected by the resilience of the individual brain to molecular mechanisms and neuropathology, also referred to as *brain reserve* which has been defined to mean that “individual differences in the brain itself allow some people to cope better than others with brain pathology” (in (Stern, 2009), p.2016). The concept refers to the structural and functional redundancy of brain networks that determines where the threshold is set for a given individual. Brain reserve may result from structural brain properties: persons with higher neuronal or synaptic counts have greater brain reserve and can withstand more pathology before performance is affected. As a result, they develop symptoms later in the biological course of AD, when a larger number of neurons or synapses has been damaged. Functional brain reserve (Caroli *et al.*, 2010 (a)) may result from activation of brain structures or networks not normally used by individuals with intact brains to compensate for brain damage (Galluzzi *et al.*, 2008; Vernooij *et al.*, 2009). Although the concept of brain reserve is largely a hypothetical construct still under experimental testing, some neuroimaging studies provide empirical support (Cohen *et al.*, 2009; Kemppainen *et al.*, 2008). It can be speculated that the breakdown of functional networks correlates with cognitive impairment, where initial hyperactivity of functional brain networks during mild stage of cognitive impairment turns into brain activation deficits at stages of more severe cognitive impairment (Celone *et al.*, 2006), for review see (Bokde *et al.*, 2009)).

Brain reserve is modulated by innate and acquired factors such as education, cognitive and physical stimulation during life, stress and trauma, epigenetic factors, protective and risk genes, such as the ApoE genotype (and e.g. PICALM, Clusterin, complement receptor gene 1), non-AD age-associated changes, and converging comorbidity, such as cerebrovascular, endocrine and metabolic alterations. The ApoE e4 allele (ApoE4) is the strongest known genetic risk factor for late-onset sporadic AD and was found associated with deficits in glucose metabolism in the very same neocortical areas affected by AD, i.e. the temporoparietal and posterior cingulate cortex (Reiman *et al.*, 1996) and with abnormal A β load as measured with PIB and CSF based biomarkers of A β (Reiman *et al.*, 2009; Vemuri *et al.*, 2010). ApoE4 carriers also have abnormally enlarged ventricles (Chou *et al.*, 2008) and faster rates of hippocampal atrophy in MCI and even in AD. A rarer allelic variant, ApoE2, found in around one-sixth of healthy controls, is also known to be protective on brain structural damage (Hua *et al.*, 2008). The notion that A β pathology accumulates in the brain decades before the onset of memory symptoms (Smith, 2002) temptingly leads to the hypothesis that these metabolic deficits are the very earliest signs of AD. However, ApoE-related functional brain alterations have been reported to occur at the much earlier age of 20 to 39 years (Reiman *et al.*, 2004; Scarmeas *et al.*, 2005; Scarmeas *et al.*, 2003), a time when plaque and tangle accumulation is highly unlikely. This and other evidence on the effect of ApoE4 on normal brain structure and function (Filippini *et al.*, 2009) and on the cortical morphology of children and adolescents (Shaw *et al.*, 2007) suggest that early genetically-related developmental brain features may predispose to the development of AD-related

changes in later life and may thus alter the course of AD in a specific way. The modulatory effect of ApoE on brain plasticity impacting the AD endophenotype is suggested by a study that showed greater memory deficits and medial temporal lobe atrophy in ApoE4 carriers in contrast with greater language deficits and frontal atrophy in non-carriers (Wolk *et al.*, 2010).

In a similar vein, alterations in brain function and fiber integrity in late life may be influenced by developmental brain changes occurring as early as in adolescence (Chiang *et al.*, 2010; Thompson *et al.*, 2001). Commonly-carried genetic variants, such as the obesity gene, FTO (Ho *et al.*, 2010c), and the brain derived neurotrophic growth factor gene, BDNF, have been found to influence brain volume and fiber integrity throughout life (Chiang *et al.*, 2009). There is also growing evidence that non-genetic “lifestyle” factors, such as cardiovascular exercise, diet, education, and body mass index are also important in for modulating brain atrophy (Ho *et al.*, 2010a; Ho *et al.*, 2010b), as well as risk for AD and other dementias. One intriguing study assessed 40 surviving participants of the Scottish Mental Survey in the year 1932 who remained free of dementia. Their DTI assessed fiber tract integrity was shown to correlate with cognitive performance on a number of psychometric tests, but controlling for IQ at age 11 years attenuated this association by approximately 85%, indicating that diffusion parameters in old age might be largely influenced by developmental factors at a young age (Deary *et al.*, 2006). This suggests that studies on white matter changes in adult and older persons should be thoroughly re-evaluated, and it opens a window of opportunity for the study of innate factors on age-associated changes in later life.

In addition, environmental factors, alone or in interaction with genetic predispositions may influence brain reserve through its effect on cognitive reserve. PET studies have shown more pronounced metabolic impairment or higher amyloid load in AD patients with higher level of education compared to patients with lower education at the same level of cognitive impairment (Kemppainen *et al.*, 2008; Pernecky *et al.*, 2006). These findings suggest that education level as a surrogate marker of cognitive reserve helps subjects to maintain cognitive performance despite a more severe pattern of cortical damage. Similar findings have been shown based on brain atrophy and subcortical white matter microstructure using DTI (Kidron *et al.*, 1997; Teipel *et al.*, 2009). By late adolescence, environmental factors begin to outweigh innate genetic factors in their effects on white matter microstructure (Chiang *et al.*, 2010). The effect of age of disease onset on the disease phenotype has been explored using structural MRI (Frisoni *et al.*, 2007). In general, a lower level of molecular pathology may be sufficient for older persons to show cognitive symptoms, as they have lower functional reserve. In groups of patients with comparable levels of cognitive decline, the average gray matter loss was 19.5% in early-onset AD but only about half as great (11.9%) in late-onset AD, relative to appropriately matched healthy controls. Interestingly, not only was tissue loss more severe in early-versus late-onset AD, but neocortical regions were more affected in early-onset and medial temporal regions in late-onset patients (Frisoni *et al.*, 2007; Frisoni *et al.*, 2005; Grady *et al.*, 1987; Seltzer and Sherwin, 1983). This agrees with neuropsychological studies indicating that neocortical functions (aphasia, apraxia, agnosia) are more affected in early-onset AD and medial temporal functions (verbal and non-verbal learning) in late-onset AD (Grady *et al.*, 1987; Jacobs *et al.*, 1994). The complex interplay between innate and acquired factors can be appreciated in view of the hypothesis that age at onset might be a function of the rate of deposition of the neuropathological AD lesions, which may be affected by ApoE (Lambert *et al.*, 2005; Tiraboschi *et al.*, 2004).

Ongoing large-scale multi-center international study programs, such as the worldwide Alzheimer’s Disease Neuroimaging Initiative (ADNI, <http://www.adni-info.org/>), are now beginning to integrate structural, metabolic, perfusion, and amyloid imaging in a prospective

design along with variables that may mediate the progress of pathology such as genetic variables, reserve capacity and other yet to be discovered factors to capture the complexities of cerebral disease progression in AD.

6. Conclusion

Evidence indicates rapid progress in our understanding of the trajectory of AD in the living brain. The characteristic sequences of AD pathology were first discovered based on post mortem maps of plaque and tangle accumulation; these maps bear a remarkable similarity to the recently re-constructed dynamic maps of cortical atrophy in living patients, scanned sequentially with MRI. The advent of PET ligands sensitive to AD pathology has also allowed the pathological sequence to be tracked at an earlier stage of the illness, perhaps before substantial neuronal loss has set in. In parallel with these neuroimaging developments, there is a continued need to integrate detailed *post mortem* assessments with pre-mortem PET, MRI and diffusion tensor data to establish the cellular and molecular basis of the observed changes. This effort will require large harmonized multicenter datasets such as those being collected in North America, Europe and elsewhere (Frisoni *et al.*, 2008; Mueller *et al.*, 2005) as well as the combined expertise of molecular biologists, neuropathologists, imaging scientists, and computer scientists to develop standard operational procedures to assess disease biomarkers. Several lines of research require future rigorous study. Clinical-pathological correlations are needed to further validate the utility of MRI data as surrogate marker of synaptic and neuronal loss. It should be noted that most studies on disease progression presented here are based on cross-sectional assessment. Conclusions concerning the brain changes derived from cross-sectional studies, however, can be confounded with cohort effects that may result from historic differences in experiences and environmental exposures including famines, changes in educational system, nutrition etc. Such factors may be shared only by specific age groups and could thus potentially influence age-related brain differences. Longitudinal studies are needed to measure brain changes within the same individuals over time, independently of such cohort effects. However, longitudinal studies are expensive, suffer from subject-drop out over time and often span a relatively short period of follow up. Large-scale longitudinal studies with repeated multimodal neuroimaging assessments such as ADNI or Australian Imaging Biomarkers & Lifestyle Flagship Study of Ageing (AIBL, <http://www.aibl.csiro.au/>) are expected to produce data to address these concerns. Mathematical models to assess longitudinal changes have been developed and have begun to be validated (Caroli and Frisoni, 2010). Finally, the clinical relevance of these new technologies has to be assessed in large-scale controlled international multi-center clinical trials examining diagnostic and predictive utility and mapping of treatment effects with different neuroimaging modalities. This is even more important with the ongoing development of new anti-dementia treatments that require easily accessible, cost-effective and non-invasive techniques to diagnose AD in its early stages and to detect beneficial or detrimental effects supported by outcome and surrogate biomarkers of novel treatments with high accuracy and power.

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List of abbreviations

Aβ	amyloid-beta
AD	Alzheimer's disease
ADNI	Alzheimer's Disease Neuroimaging Initiative
ApoE4	Apolipoprotein ϵ 4
BDNF	brain derived neurotrophic factor
CSF	cerebrospinal fluid
DTI	diffusion tensor imaging
FA	fractional anisotropy
FDG-PET	fluoro-deoxyglucose positron emission tomography
MCI	mild cognitive impairment
MRI	magnetic resonance imaging
MTR	Magnetic transfer ratio
NbM	basal nucleus of Meynert
[^{11}C]PIB	Pittsburgh Compound B

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Validation of the staging model of neuronal atrophy: Combined MRI and histochemical approaches

In vivo MRI volumetric studies in humans have identified the same regions with early atrophy within the hippocampus corresponding to those cytoarchitectural regions (CA1 and subiculum) as those detected by pathology (Frisoni et al., 2008a; Apostolova et al., 2008; Frisoni et al., 2006; Wang et al., 2006).

To date, the resolution of most state-of-the-art MR scanners (typically 0.5 mm to 1 mm) is lower than the resolution of neurohistological and immunohistochemical methods. Therefore, *in vivo* MRI cannot confirm the cellular basis of the frequently described subtle volumetric MRI changes in MCI and early stages of AD. Using stereological methods, the total cell numbers in cytoarchitectural well-defined regions can be accurately estimated without bias resulting from histological distortions. These studies show that Nissl-stained perikarya contribute to less than 10% of the total brain volume, whereas the sum of all nerve cell processes that are not stained by Nissl stains (the so-called neuropil) compose at least 85% of the human gray matter (Blinkov and Glezer, 1968). These findings are critical to interpret the cellular basis of regional atrophy measured using MRI. In order to validate structural imaging findings, several groups have correlated *in vivo* imaging results with post-mortem cytoarchitectonic, histopathologic and biochemical findings. For instance, Zilles and colleagues pioneered an approach to create probabilistic maps of cytoarchitectural areas (i.e. Brodmann areas) in MRI space based on MRI scans of formalin-fixed human brains that were also analyzed histologically (Eickhoff et al., 2005; Toga et al., 2006). Using related methods, other groups have defined the neuropathological substrate of Alzheimer's disease (Bobinski et al., 2000; Bronge et al., 2002) or white matter hyperintensities (Braffman et al., 1988; Mazziotta et al., 2001). Although it is indisputable that these approaches are helpful for the interpretation of MRI findings, the fixation process makes it difficult to determine the morphological substrate of subtle and less specific volume changes as seen in MCI (Challa et al., 2002; Kretschmann et al., 1982; Uylings et al., 1986). As the MR signal depends on tissue water content and temperature, brain fixation is associated with a shift of fluids. This can lead to a potential misinterpretation of *post-mortem* MRI results (Grinberg et al., 2008). In addition, unpredictable swelling and shrinkage during fixation is known to distort the tissue, making it difficult to correlate histology with *in vivo* maps without nonlinear image matching algorithms (Mega et al., 1997) (Figure 3). In fact, a primary goal of post-mortem MRI studies is to test the validity of these algorithms. Therefore, other approaches are required to validate *in vivo* MRI findings based on *post-mortem* data.

The use of *ante-mortem* MRI could be the gold standard, if the interval between MRI and autopsy was short enough to allow for direct comparisons. A recent study found significant correlations between cortical gray matter and hippocampal volume, as well as subcortical white matter lesions determined using ante-mortem MRI followed by histologically determined semi-quantitative ratings of overall plaque and tangle burden, hippocampal sclerosis and cerebrovascular abnormalities (Jagust et al., 2008). However, even in the most recent study the interval between MRI and autopsy was on average 3.3 years in the AD group (Jagust et al., 2008).

An alternative approach may be scanning of *post-mortem* brains *in situ*. This approach avoids tissue deformations and signal changes induced by post-mortem brain fixation. The postmortem MRI scan *in situ* serves as a proxy of the *in vivo* space and can be used as reference to match histological findings to the *in vivo* space based on intra-individual data. This approach has been applied to 18 human brains scanned post-mortem *in situ* prior to histological processing (Grinberg et al., 2008c). *In situ* post-mortem MRI

included MRI, DTI and magnetization transfer ratio (MTR) acquisitions as respective measures of regional volume, neuronal fiber tract integrity and macromolecular structural integrity of brain tissue (Figure 4). Stereological, histochemical and immunohistochemical assessments of serial histological sections are compared with the MRI data (Figures 4 and 5) using a point-to-point tridimensional platform. This latter approach is a promising tool to validate *in vivo* imaging findings, and ongoing research should better verify this potential.

Research Highlights

- Neuroimaging allow for 4D *in vivo* brain maps to stage pathological changes in Alzheimer's disease
- Parallels in progressive grey matter atrophy, hypometabolism and amyloid deposition
- DTI shows retrogenesis of fiber connections in medial temporal brain network of memory
- Progression is modulated by genetic risk factors and life style factors
- Staging model useful to monitor disease progression, evaluate drug-efficacy and diagnose AD

Figure 1. Degenerative sequence of brain changes in AD is the reverse order of the normal developmental sequence

In a process termed *retrogenesis* (e.g., by (Reisberg *et al.*, 1999)), cortical regions that mature earliest in infancy tend to degenerate last in AD. The developmental sequence echoes the phylogenetic sequence in which structures evolved. The most heavily myelinated structures, with least neuronal plasticity, resist AD-related neurodegeneration. Arrows denote the childhood cortical maturation sequence (*left panel* (Gogtay *et al.*, 2004)) and the gray matter atrophy sequence in AD (*right panel* (Thompson *et al.*, 2003)). Images are from time-lapse films compiled from cortical models in subjects scanned longitudinally with MRI.

Figure 2. Progression of AD based on pathology, MRI, and the amyloid-sensitive Probe, [^{18}F] FDDNP PET

Neurofibrillary tangles, one of the molecular hallmarks of AD, tend to spread in the brain in a characteristic advancing trajectory (*top row*; adapted from (Braak and Braak, 1991)). Darker red colours denote areas with greater tangle deposition, based on histologic staining of post mortem material. On MRI, the areas with gray matter deficits in mild AD include primarily the temporal lobe, but in moderate AD these deficits have spread to involve the frontal cortex (*middle row*; adapted from a longitudinal study by (Thompson *et al.*, 2003)). Finally, cerebral amyloid estimated in vivo from the PET ligand FDDNP is low in controls, but higher in those with impaired cognition (*bottom row*; adapted from (Braskie *et al.*, 2008)). The anatomical agreement is striking between these *in vivo* maps and the well-established *post mortem* maps for the staging of AD. In all maps, the sensorimotor cortex shows least disease-related degeneration. [Adapted, with permission of the authors and publishers.]

Figure 3. Effect of Formalin Fixation on the Human Brain

Top row: coronal section perpendicular to AC-PC plane through optic chiasm of *in situ* brain in native space (A) and after transformation in standard space (C); formalin brain in native space (B) and in standard space (D). *Bottom row:* deformation field from *formalin* to *in situ* space projected in standard space (E). The 3 mm by 3 mm red grid indicates the extent of deformation at each 9 mm² location, with the extent and direction of deformation given by the relative deviation from a straight line. The grid is projected on the corresponding coronar slice of the *in situ* MRI scan. Voxel-wise volume effect of deformation from *formalin* to *in situ* space projected into standard space (F). Yellow to red: shrinkage in percent of volume from *in situ* to *formalin*, green to blue: expansion in percent of volumes from *in situ* to *formalin*. Threshold for effects is > 35% in both directions.

Figure 4. Examples of High Quality Post-Mortem MRI *in situ*.

Examples of high-quality post-mortem MRI *in situ*. Good results can be achieved in most MRI modalities. Brain of a 50 years old man scanned 8h after death. (A) Axial T2-weighted image, (B) Corresponding relaxometry map, (C) Corresponding MTR map, (D) Corresponding fractional anisotropy map, (E) Axial Eigen-vector images, blue corresponds to major axis in anatomical superior-inferior orientation, green corresponds to anterior-posterior and red to right-left orientations, (F) Tractography of the uncinate fascicle showing two groups of fibers connecting temporal with frontal regions.

Figure 5. MRI Guided Sampling of Regions of Interest on Histological Sections

(A) T2-weighted image of a brain from an 80 year-old male (A, PMI: 8h). The corresponding unstained brain region mounted in celloidin (B). For neuropathological assessment, the ROI boxed on (A) was cut out, embedded in paraffin, cut in serial 12 μ m sections and submitted to routine as well as special staining and immunohistochemistry. Bielschowski-stained section for assessing axonal integrity (C), Klüver-Barrera stained section for assessing myelin (D), note that (C) and (D) are from the boxed area on (B). GFAP immunostaining of the circled area on (D) for detecting reactive cortical astroglia (E, arrows).

A

B

Figure 6. Combination of DTI and DBM Brain Differences to Diagnose Alzheimer's Disease
 Projection of the spatial pattern of reduced fiber tract integrity as measured by DTI derived indices of FA (yellow) and mean diffusivity (MD, red) as well as brain atrophy as measured by DBM (blue) for the comparison of AD patients vs. elderly healthy controls (A). The combination of both DTI and DBM changes in these brain regions as determined by factor scores in a principal component analysis was used for the diagnostic discrimination of both groups (B). The combination of MD from DTI and DBM components yielded a sensitivity of 0.71% and specificity of 0.95% to separate AD from healthy controls. Reproduced with permission from (Frieze *et al.*, 2010).