Cognitive decline and brain pathology in aging – need for a dimensional, lifespan and systems vulnerability view

Running head: Lifespan changes in brain and cognition

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Abstract

Changes in brain structure and activity as well as cognitive function are commonly seen in aging. However, it is not known when aging of brain and cognition starts, and how much of the changes observed in seemingly healthy older adults that can be ascribed to incipient neurodegenerative disease. Recent research has yielded evidence that the borders between development and aging sometimes can be fuzzy, as can the borders between dementing disease and normal age changes. In this review, we argue that many factors affecting cognitive decline and dementia represents quantitative rather than qualitative differences in characteristics that commonly exist in the population. Further, factors known to affect brain and cognition in aging will often do so through a life-long accumulation of impact, and does not need to be specific to aging. And finally, a host of environmental and genetic factors and their interplay determine optimal aging, leaving room for potential for environmental interventions to affect the outcome of the aging process. Together, we argue that these factors call for a dimensional rather than categorical, lifespan rather than aging, and multidimensional systems-vulnerability rather than simple "hypothetical biomarker" model of age-associated cognitive decline and dementia. This has implications for how we should view lifespan trajectories of change in brain and cognitive function, and how we can study, prevent, diagnose and treat age-associated cognitive deficits.

Introduction

Psychological and behavioral adjustment of the individual throughout life is the result of a dynamic interaction between endogenous and exogenous influences, and is profoundly linked to neural substrates undergoing change. Cognitive functioning relates to structural and functional brain characteristics both in healthy aging and in aging-related disorders, e.g. mild cognitive impairment (MCI) and dementing disorders, both of probable Alzheimer type (AD) and others, such as vascular dementia. Several brain areas have been implicated, and the exact neural foundations vary according to the nature of pathology. However, there also appear to be similarities across clinical conditions and healthy aging, with structural differences and decline repeatedly having been identified in medial temporal, parietal and prefrontal areas, including, but not limited to, hippocampal, entorhinal, parahippocampal, restrosplenial, posterior and anterior cingulate, medial and lateral prefrontal cortices. These areas are central in the default mode network (DMN), crucial to navigation in time and space, including episodic memory and imagery, which appear disturbed in a number of conditions involving cognitive decline. In addition, there may likely be cerebral cortical differences specific to distinct types of cognitive deficits and disease. Moreover, current data point to vulnerabilities of the individual not exclusively being “turned on” in aging, but rather accumulating across the lifespan, as a result of continuous interactions between endogenous and exogenous factors.

In this review, we assemble current empirical investigations to show that many features contributing to determine cognitive decline and dementing disease are likely 1) Not unique to pathology, but rather represent quantitative differences along a continuum, characteristics that are also present in broader populations in aging, 2) Not unique to aging, but rather represent features which have been

present to some degree in early, perhaps even fetal life, and 3) Not necessarily resistant to influence from and interactions with a host of environmental factors.

Together, we argue that these factors call for a dimensional rather than categorical, lifespan rather than aging, and multidimensional systems-vulnerability rather than simple "hypothetical biomarker" (Jack et al., 2013; Jack et al., 2010) model of age-associated cognitive decline and dementia. We argue that a neurobiological relationship between lighter symptoms of cognitive problems and dementing disorder is more evident than often emphasized. This has implications for the view of lifespan trajectories of change in brain and cognition, and how to study, prevent, diagnose and treat age-associated cognitive deficits.

Continuous influences across the lifespan

Recent literature makes clear that a number of cognitive and brain features observed in aging can in fact be predicted by early life characteristics, exerting continuous influences across the lifespan. The most obvious example of this might be observed for cognitive abilities, for which cohort data spanning several decades now exist. For instance, remarkable predictive validity of intelligence tests at age 11 for cognitive performance at age 90 years has been observed (Deary, Pattie, & Starr, 2013). Moreover, it has become clear that a number of other typical outcome measures in studies of aging, in fact may also be predicted by events and mechanisms exerting their influence very early in life, even at the embryonic stage. Yet, currently, a coherent lifespan perspective is largely lacking in aging and AD research. When investigating predictors of brain volumes in aging and neurodegenerative disease, it is our opinion that too little attention is given to the fact that one is studying an organ that reaches above 80% of adult volume in infancy, and virtually maximal size (>95%) before school age (Dekaban, 1978). It follows from this state of affairs that a strong, and possibly the greatest, predictor

of neuroanatomical characteristics in aging is found at a very early stage of life. For instance, birth weight has been found to predict neuroanatomical volumes and cortical surface area in later childhood, adolescence and early adulthood (Walhovd et al., 2012). Moreover, genetic variants found to be associated with brain and cognition in aging and AD, have recently been observed to exert major influences also in children. A prominent example may be variants of the fat mass- and obesity (FTO) –associated gene. For this gene, commonly occurring variation has been associated with reduced brain volumes sin healthy aging (Ho et al., 2010) as well as risk of AD (Reitz et al., 2012). Recently, it was shown that that FTO-variance was associated with smaller brain volumes also in adolescents (Melka et al., 2013), meaning that the reductions observed in aging may be present throughout life, also at the embryonic stage. Likewise, APOE ε4 carriers were recently found to show reduced temporal lobe volumes at birth (Knickmeyer et al., 2013), as discussed further below. In sum, current data point to many risk factors associated with aging and neurodegenerative disease being there from the beginning. They may represent stable risk factors, and sometimes have accumulative consequences throughout the lifespan. If we were able to take these early influences into account in a more precise way, we might be more successful at identifying whatever other, and important, even if potentially modest, influences exist in aging.

Cross-sectional vs. longitudinal studies for detection of life-span trajectories

Changes in cognitive function or brain activity or structures cannot be definitely determined based on cross-sectional data alone (Raz & Lindenberger, 2010), as cross-sectional studies are potentially vulnerable to cohort-effects and selection bias. In some cases, cross-sectional estimates diverge substantially (Raz et al., 2005), or even oppose, longitudinal observations (Nyberg et al., 2010; Raz & Lindenberger, 2011). Some evidence suggests that cross-sectional studies may underestimate the extent of regional brain shrinkage in some regions (Raz et al., 2005). Different procedures can be undertaken to reduce the possible influence of cohort effects. For instance, in studies of brain

structure, it is common practice to correct the data for intracranial volume (ICV). The main determinant of ICV is the lifetime maximum size of the brain, and ICV-corrections thus have the potential to reduce impact of cohort effects (Walhovd et al., 2011b).

Although a longitudinal design often is preferable, some of the inherent problems of mapping life-span trajectories associated with cross-sectional examinations are not easily resolved with longitudinal data. Longitudinal examinations of brain activity or structure over decades are not feasible. Adding to this are methodological problems such as attrition and selective recruitment. The much higher costs associated with longitudinal vs. cross-sectional studies in terms of effort and financing have caused many longitudinal studies to be limited in age-span, sample size and number of follow-ups, especially when it comes to brain imaging. To some degree, combined cross-sectional and longitudinal designs can alleviate the concerns raised above. An ideal approach to reproduce the dynamic process of change would be longitudinal studies with high density of measures and assessment of multiple time windows across the life span (Raz et al., 2010; Raz & Lindenberger, 2011). As of yet, we know of no studies including brain imaging data using such a design from childhood and into old age.

Are AD-susceptibility genes related to general life-long influences?

Heritability for sporadic late onset AD is estimated to be 60-80%, motivating an intense search for genetic variants that confer risk for AD for more than three decades (Bertram, McQueen, Mullin, Blacker, & Tanzi, 2007; Gatz et al., 2006). AD is a genetically complex disorder in which many different genes, each with small estimated effect, is likely to underlie the heritability (Bertram et al., 2007). There are as of October 2013 695 genes and 2973 polymorphisms registered in the Alzgene database (www.alzgene.org) and the number is steadily increasing as new large-scale genome-wide association scans are conducted. The top 10 association list includes *APOE, BIN1, CLU, ABCA7, CR1,*

PICALM, MS4A6A, CD33, MS4A4E, CD2AP – all of which, with the exception of *APOE*, have odds ratios (OR) that barely deviates from 1 (i.e. deviation = 0.1-0.2). One other likely AD susceptibility gene, *TREM2*, is reported to have OR between 3 and 5 (R. Guerreiro et al., 2013; Jonsson et al., 2013), but prevalence of the risk allele is very low (~0.5% or less, depending on the population studied), limiting its usefulness as population level predictor. The most prominent exception to low penetrance in AD genetics is the apolipoprotein E gene (*APOE*) which due to a high OR (~4) and high frequency of the risk variant ε4 (~25%) has a large impact on the prevalence of AD in populations (Bertram et al., 2008; Corder et al., 1993; Genin et al., 2011; Raber, Huang, & Ashford, 2004; Strittmatter et al., 1993) Furthermore, brain and cognition correlates of the *APOE* genetic variants, the specificity of the effects they exert to pathology or old age, and the patterns of interaction with non-genetic factors, have been intensely studied. Similar information is very scarce for the other risk genes.

Effects of Apolipoprotein E on cognition

In the human central nervous system apolipoprotein E (apoE) plays a key role in transport and metabolism of plasma cholesterol and triglycerides, and is involved in synaptogenesis, as well as maintenance and repair of neurons (Mahley, Weisgraber, & Huang, 2006; Mauch et al., 2001) The *APOE* ε4 allele causes a dose-dependent increase in risk of developing AD (Corder et al., 1993; Strittmatter et al., 1993). It decreases the age of diagnosis (Raber et al., 2004), and is the strongest known genetic risk factor for AD – ε4 homozygosity confers about 14 times increase in lifetime risk compared to ε3 homozygosity, but in an age-dependent manner, with a maximum relative risk of 35 in the age group 60-69 (Genin et al., 2011). The basis of this association is poorly understood owing to the complexity of the underlying pathophysiological mechanisms (Holtzman, Herz, & Bu, 2012; Mahley et al., 2006; Verghese, Castellano, & Holtzman, 2011). Mahley et al. (Mahley et al., 2006) present two major hypotheses on the relation between *APOE* and neurodegeneration. In the amyloid

hypothesis ε4 is suggested to interact with Aβ to inhibit clearance and/or stimulate deposition of Aβ (Huang, Weisgraber, Mucke, & Mahley, 2004), enhance Aβ production (Aubert et al., 2005), and increase lysosomal leakage and apoptotic cell death (Ji et al., 2006). In the neuronal repair hypothesis ε4 is thought to lead to deficient neuronal health through enhanced neuron-specific proteolysis where neurotoxic fragments of the apoE protein is translocated into the cytosol where they lead to cytoskeletal disruption and mitochondrial dysfunction (Mahley et al., 2006). Thus, according to the neuronal repair hypothesis apoE may be related to neuronal health throughout the life span, and may therefore have identifiable physiological phenotypes that are distinct from those caused by pathological processes late in life, such as those suggested by the amyloid hypothesis. *APOE* ε4 interacts strongly with specific age-associated pathogenic factors, most significantly with amyloid accumulation (Liu, Kanekiyo, Xu, & Bu, 2013). Amyloid accumulation is absent or infrequent below the age of 50, and remains relatively low even in ε4 carriers until the early 60s (Morris et al., 2010). Therefore, in studies including participants that are middle-aged or younger, amyloid burden is unlikely to bias the results. A large number of studies with non-demented and healthy old participants, healthy middle-aged and young adults, and increasingly also children, indicates that *APOE* genotype affects the structure and function of the normal brain, through roles in neurodevelopment, maintenance and repair.

A large meta-analysis found evidence for memory deficits in ε4 carriers (Wisdom, Callahan, & Hawkins, 2011), but the effects size was modest (OR ~1.2 for episodic memory, and < 1.2 for other cognitive domains). Many of the studies analyzed may have involved middle-aged and old persons at different stages of prodromal AD, thus challenging the notion that there are measureable cognitive effects of ε4 in healthy samples, at least as assessed with standard psychometric batteries. In a recent structural equation model study Yu et al. (Yu, Boyle, Leurgans, Schneider, & Bennett, 2014) tested whether they could identify direct effects of ε4 on decline in performance on two cognitive

components, episodic memory or nonepisodic cognition as constructed from psychometric battery of tests, or whether ε4 effects were mediated by pathogenic factors such as amyloid β loads, tau tangle densities, presence of cortical Lewy bodies, or macro- or micro infarcts. The results showed that there were no direct effects of ε4 on decline on either episodic memory or nonepisodic cognition after accounting for these pathogenic factors. Studies focusing on tailor-made attention and working memory tasks with middle-aged participants have reported significantly poorer performance for ε4 carriers (Espeseth et al., 2006; Greenwood, Lambert, Sunderland, & Parasuraman, 2005; Negash et al., 2009; Reinvang, Winjevoll, Rootwelt, & Espeseth, 2010; Rosen, Bergeson, Putnam, Harwell, & Sunderland, 2002). These findings are promising but effects sizes are relatively modest (ORs ~1.5). In children and young adults both adverse and protective effects have been reported. Han & Bondi (Han & Bondi, 2008), among others, have suggested that the relation between ε4 and cognitive performance across the life span can be characterized as an example of antagonistic pleiotropy – that ε4 may have different effects on fitness across the life span. A meta-analysis including 20 studies in which participants were between 5 and 35 years of age found no support for this hypothesis as no effect sizes reliably differed form zero (Ihle, Bunce, & Kliegel, 2012). However, it is still possible that ε4 may have protective effects in children under adverse environmental circumstances, such as in Brazilian shanty town children who showed less diarrhea and accompanying impairments in cognitive development (Oria, Costa, Lima, Patrick, & Guerrant, 2009; Oria et al., 2005), and better cognitive responses to micronutrient supplementation (Mitter et al., 2012).

Effects of Apolipoprotein E on brain structure and activity

MRI and PET studies provide stronger support for effects of ε4 in non-demented individuals. FDG-PET studies with young adults (i.e. in their 20s and 30s) have shown reduced cerebral glucose metabolism for ε4 carriers in posterior cingulate, parietal, temporal, and prefrontal cortex (Reiman et al., 2004).

Effects were in the same regions found for AD patients and older ε4 carriers, but were quantitatively smaller (Reiman et al., 2001; Reiman et al., 1996).

Based on an MRI study, thinner entorhinal cortices were reported for adolescent ε4 carriers (Shaw et al., 2007). Many of the participants underwent multiple scans and the neuroanatomical effects of *APOE* genotype seemed to be fixed over the age-range examined. In a recent structural MRI study of 269 neonates, Knickmeyer et al. (Knickmeyer et al., 2013) observed decreased gray matter volume in the temporal lobes, including the hippocampus, and increased parietal lobe volumes in ε4 heterozygous babies compared to ε3 homozygotes. Dean III et al. (Dean et al., 2014) tested ε4-related differences in white matter myelin water fractions (MWF) and gray matter volumes (GMV) in 162 healthy infants aged 2 to 25 months and found reduced MWF and GMV in precuneus, posterior/middle cingulate, lateral temporal, and medial occipitotemporal regions for ε4 carriers. Alexander et al. (Alexander et al., 2012) found a pattern of gray matter reduction in ε4 carriers (N=14, age 26-45) involving bilateral frontal, anterior cingulate, parietal, and lateral temporal cortices with correlated volume increases in the hippocampal region. In a study of morphometric variation in middle-aged and older-age individuals, Espeseth et al. (Espeseth et al., 2008) found that middle-aged ε4 carriers had a thicker cortex than non-carriers in several frontal and temporal areas in both hemispheres, but showed a steeper estimated age-related decline in adjacent areas. Upon comparison of the ε4-specific negative age-correlations with previously published patterns of thinning in normal aging and AD, they concluded that ε4 may function to accelerate thinning in areas found to decline in normal aging (medial prefrontal and pericentral cortex), but also to initiate thinning in areas associated with AD and amyloid β aggregation (occipitotemporal and basal temporal cortex). A follow up study by Espeseth et al. (Espeseth et al., 2012) showed that cortical thickness in the selected regions was associated with attention performance and amplitude of attention-related ERP (event-related potential) components.

Trachtenberg et al. (Trachtenberg et al., 2012) recently performed an analysis on resting-state networks (RSNs), including medial and lateral visual, sensorimotor, auditory, DMN, an "executive control network", right and left frontoparietal networks, and anterior and posterior hippocampal networks in 77 healthy subjects aged 32-55 years. *APOE* genotype affected the anterior and posterior hippocampal networks, the auditory network, and the left frontoparietal network. Intriguingly, functional integration was similar in ε2 and ε4 carriers, but both groups differed significantly from ε3 homozygotes. The authors concluded that in healthy adults, *APOE* genotype affects the differentiation of functional brain networks independently of the *APOE*-related increased risk of AD, and may instead reflect a functional role of different apoE isoforms during neurodevelopment. The observations of alterations in patterns of functional connectivity in ε4 carriers may be indicative of changes in white matter microstructural integrity. Several DTI studies have documented decreased diffusion anisotropy in ε4 carriers (Heise, Filippini, Ebmeier, & Mackay, 2011; Honea, Vidoni, Harsha, & Burns, 2009; Persson et al., 2006) possibly indicating less coherent fiber architecture or altered microstructural integrity. Heise et al. (Heise et al., 2011) compared younger (age 20-35) with older (age 50-78) subjects, but concluded that there was no evidence of age group by *APOE* interactions on any of the DTI measures. Westlye et al. (Westlye, Reinvang, Rootwelt, & Espeseth, 2012) studied a healthy sample (N=203) with a wide age distribution (21-70 years) and showed an age-independent increase in radial diffusivity in ε4 carriers. As previously reported by Trachtenberg et al. (Trachtenberg et al., 2012) on RSNs, similar changes were observed in ε2 carriers. ε2 has been reported to have a protective effect with regards to the development of AD (Corder et al., 1993). Thus, when effects on the brain's functional and structural connectivity is similar for ε2 and ε4, and is present from young adulthood, this may suggest that effect of *APOE* genotype on white matter microstructure and RSNs is independent of its effect on AD risk.

Several studies reviewed above converge on a significant impact of *APOE* on brain morphology. The evidence further suggests that the effects may already be present at birth, and that *APOE* may also modulate the rate of brain aging. In a recent review of effect of *APOE* genotype in aging and early AD (Reinvang, Espeseth, & Westlye, 2013), we concluded that these results are not strongly influenced by presence of amyloid β, either because it has been explicitly controlled for or because of the relatively young age of participants. The findings reviewed indicate that ε4 is a vulnerability factor and not a pathogenic factor at ages where cerebral diseases or injuries are infrequent. This is not to deny that pathogenic factors that interact with *APOE* genotype may have an impact in younger groups, but their frequency or intensity is not sufficient to result in an interaction of *APOE* genotype with age, suggesting that the unique genotypic effects on the various biological and brain phenotypes are relatively invariant with age in healthy subjects. However, the frequency of cerebral injuries are likely to increase with age even in non-demented samples, and when these cannot be identified and controlled for, one may observe increased effects of ε4 with age. Reduced effects of ε4 in high age have also been observed, both in healthy (Espeseth et al., 2006; Espeseth et al., 2010; Small, Rosnick, Fratiglioni, & Backman, 2004) and AD (Chang et al., 2013; Farrer et al., 1997) samples, potentially due to sampling error. Our conclusion differs from those of earlier reviews and meta-analyses (Cherbuin, Leach, Christensen, & Anstey, 2007; Wisdom et al., 2011), possibly because these studies comprised mainly older participants who may have been pre-symptomatic and had unknown amyloid status. It also differs from a strict version of the cascade model of Jack et al. (Jack et al., 2013; Jack et al., 2010). Amyloid β is clearly a highly significant pathological factor at initial stages of disease but there is also a high degree of diversity of *APOE*-related pathological mechanisms, affecting the rate and biomarker profile of clinical development. Furthermore, subtle MR and cognitive markers are detectable early in the development of the pathophysiological process that renders ε4 carriers vulnerable to MCI and AD, but they are not only watered-down versions of the changes seen in clinical AD, such as hippocampal atrophy and memory deficit. The conclusion is

consistent with theories of AD development allowing for heterogeneous mechanisms, such as the one proposed by Herrup (Herrup, 2010).

Other genetic predictors of AD

As compared to *APOE*, very few translational studies have so far been reported for the other top ten candidates. Some evidence is available for *CLU*, *CR1*, and *PICALM*, which were shown to be associated with AD in two large genome-wide association studies (GWAS) in 2009 (Harold et al., 2009; Lambert et al., 2009). Bralten et al. (Bralten et al., 2011) investigated *CLU*, *CR1*, and *PICALM* in a MRI study aiming to reveal genetic variant effects on voxel-based morphometry assessed integrity of the entorhinal cortex and hippocampus in two samples (*n* = 430 and *n* =492, respectively) consisting of healthy young individuals aged 18-36 years. They found reduced grey matter volume in the entorhinal cortex for *CR1* rs6656401 A allele carriers in both samples. Erk et al (Erk et al., 2011) showed that healthy young participants (mean age ~31 years) had altered functional coupling of the hippocampus in carriers of the risk variant for *CLU* rs11136000 (C allele) during a fMRI memory task. This effect was independent of *APOE* genotype. In a DTI study with 400 young participants (Mean age = 23.6 years) Braskie et al. (Braskie et al., 2011) found reduced fractional anisotropy (FA) in splenium of the corpus callosum, the fornix, cingulum, and superior and inferior longitudinal fasciculi for C allele carriers of the same *CLU* SNP.

A rare missense mutation in triggering receptor expressed on myeloid cells 2 *(TREM2)* was very recently shown to be associated with AD, but has generated much interest because the effect size appears to be comparable to that of *APOE* (Bertram, Parrado, & Tanzi, 2013; R. Guerreiro & Hardy, 2013; R. Guerreiro et al., 2013; Jonsson et al., 2013; Jonsson & Stefansson, 2013). *TREM2* variants have been reported to be associated with autosomal recessive form of early-onset dementia with bone cysts and consequent fractures (Paloneva et al., 2003), frontotemporal dementia and with

leukodystrophy (R. J. Guerreiro & Hardy, 2012). Jonsson et al (Jonsson et al., 2013) showed that non-demented *TREM2* mutation carriers had reduced performance on the Cognitive Performance Scale. Furthermore, this effect seemed to accelerate with age (increase from age around 80 to late 90s), although this effect was measured on only 53 carriers in total, and no formal gene by age interaction was reported. Since no interaction was reported and the age range was limited to old age, it is not clear whether *TREM2* is most accurately defined as a genetic marker for cognitive performance as such, or for cognitive aging. Furthermore, because of the high age of the participants and evidence of cognitive impairment, it is not clear whether *TREM2* is best categorized as a gene involved in normal or pathological states. Similarly, using tensor-based morphometry, Rajagopalan et al. (Rajagopalan, Hibar, & Thompson, 2013) recently reported effects of rs9394721, a close proxy for the AD risk variant rs75932628, on temporal lobe atrophy over a 24-month period. They reported that *TREM2* mutation carriers lost 1.4 – 3.3% more tissue than noncarriers in a pattern that is similar to the profile of AD. Mutation carriers also had smaller hippocampi, poorer cognitive performance, and elevated levels of p-tau181p. Interestingly, a recent GWAS of cerebrospinal fluid tau levels revealed a marker within the *TREM* region (Cruchaga et al., 2013). However, both the carrier and noncarrier groups consisted of a mixture of healthy non-demented participants, MCI and AD, and no group by genotype interaction was reported, making it difficult to verify whether the effects were specific to, or at least larger, in the AD group.

What do we know about the genetics of AD?

In conclusion, AD is not only polygenic, the genes associated with AD are also pleiotropic. *APOE* is common, exerts a large effect on risk for AD, and a range of other more or less related phenotypes. *APOE* exerts effects over the whole life span, not only in relation to pathological processes, or age-related cognitive decline, and interacts with non-genetic/environmental factors. Less is known about

other AD susceptibility genes such as *CLU, CR1, PICALM,* and *TREM2*, but it seems likely all of them have pleiotropic effects, and variability in at least the three former genes also exerts effects on brain morphometric properties and task-related functional coupling at young ages (at least as early as young adulthood), before significant amyloid β burden. Less is known about gene by environment interactions for these. Thus, it seems reasonable to conclude that extant research on five of the strongest genetic predictors of AD, effects are not specific to pathology, are not specific to old age, and are likely to be modifiable by environmental factors. This pattern of result supports a dimensional, life span, and systems vulnerability view on cognitive decline brain pathology in aging, which we will now discuss in more detail.

A dimensional, systems-vulnerability view of aging vs. dementia: the sample case of Alzheimer's Disease

Incidence of people with AD increases sharply after 60 years (Kawas, Gray, Brookmeyer, Fozard, & Zonderman, 2000), and symptoms of AD and symptoms of "normal aging" are overlapping. Disruption of episodic memory function (Koivisto et al., 1995; Nyberg, Lovden, Riklund, Lindenberger, & Backman, 2012), brain atrophy (Driscoll et al., 2009; Fjell et al., 2009b; Raz et al., 2005) and accumulation of amyloid protein (Morris et al., 2010) are found in AD patients as well as in many presumably healthy elderly. As shown above, several genes related to AD risk seem to impact brain and cognition also in non-demented and early in life. Even though few would argue that AD is not a disease distinct from aging, many researchers have proposed that to understand AD, we must understand its relationship to aging (Herrup, 2010). Although less commonly argued, the statement can also be reversed: Understanding why aging is the major risk factor for AD may help us understand brain aging itself. Thus, a systems vulnerability approach to aging and AD, where we try to understand why certain brain regions and neural networks are vulnerable to different detrimental

influences (W. Jagust, 2013), may be a more promising approach than focusing on specific diseases, conditions or single etiologies (Khachaturian, 2011). This is not uncontroversial, however, as for instance the popular 'dynamic biomarker model' assumes that AD always starts with deficient processing of beta-amyloid (Jack et al., 2013; Jack et al., 2010), while others argue that AD may be driven by factors less related to aging per se, and should be studied separately from normal aging (Nelson et al., 2011). Both these examples go against a systems-vulnerability view of aging and AD.

What is normal aging?

On one hand, there is a discussion of whether AD should be understood with a basis in normal aging. On the other hand, there is also a discussion of what *normal aging is.* Do pure age-related brain changes exist in isolation from the first stages of progressive degenerative conditions? As dementias like AD are associated with increased rates of brain atrophy (Davatzikos, Xu, An, Fan, & Resnick, 2009; Jack et al., 2013; Jack et al., 2010) and subtle cognitive symptoms (Elias et al., 2000) years before diagnosis, cases with undetected disease in presumably normal samples can lead to erroneous inferences about decline in brain structure and function and cognitive abilities in normal aging (Burgmans et al., 2009; Sliwinski & Buschke, 1999). Interestingly, it is also possible that the opposite problem exists – that very high-functioning elderly are over-represented in research samples and thus yield an overly optimistic picture of brain and cognition in higher age (Nyberg et al., 2010).

There are no easy solutions to the problems with undetected dementia and sampling problems described above. However, we believe recent research has made a strong case that changes in brain and cognitive function characterize normal aging - independently of AD, the most common neurodegenerative disease. Even though the overall pattern of brain changes can be used to differentiate normal aging from AD (Driscoll et al., 2009; Fjell, Amlien, et al., 2010; McEvoy et al.,

2009; McEvoy et al., 2011), brain regions affected by AD nevertheless show decline also in normal aging. Entorhinal cortex and the hippocampus are especially vulnerable to AD disease pathology, including neurofibrillary tangles, atrophy and other types of AD-pathology (Braak & Braak, 1985, 1991; Jack et al., 1997; McDonald et al., 2009; Van Hoesen, Hyman, & Damasio, 1991). These regions are among the most vulnerable in normal aging, with accelerating decline from about 60 years (Driscoll et al., 2009; Fjell et al., 2009a, 2009b; Fjell et al., 2012; Pfefferbaum et al., 2013; Raz, Ghisletta, Rodrigue, Kennedy, & Lindenberger, 2010; Walhovd et al., 2011a). This does not mean that atrophy in these regions cannot be used to aid classification of patients and in prediction progression of the disease (Fjell, Walhovd, Fennema-Notestine, McEvoy, Hagler, Holland, Brewer, et al., 2010), but rather that decline is not restricted to degenerative conditions.

Several lines of evidence support this view. Resnick and colleagues found significant reductions in brain volume in all cortical lobes in very healthy participants who experienced no medical condition or cognitive impairment up to ten years after the initial examination, and argued that the uniformity of tissue loss across individual participants indicated that these were not pathological changes associated with preclinical dementia (Driscoll et al., 2009; Resnick, Pham, Kraut, Zonderman, & Davatzikos, 2003). Fjell et al. demonstrated reductions in the temporal lobe, including the hippocampus and the entorhinal cortex, in groups of elderly with very low probability of having incipient AD (Fjell et al., 2013; Fjell et al., 2012). Subgroups of clinically and cognitively super-stable, as well as groups of elderly who were amyloid negative, negative for APOE ε4 and with only minute change in episodic memory scores, all showed temporal lobe reductions in thickness or volume. Importantly, the brain changes also correlated with changes in scores on tests of episodic memory, indicating that these brain changes, although likely not related to AD-processes, were not completely benign. These results demonstrate that significant entorhinal and hippocampal atrophy can be detected in groups of elderly at very low risk of AD defined by clinical neuropsychological, genetic

and biomarker criteria (Fjell et al., 2013). An independent study also identified small hippocampal volumes in amyloid negative elderly (Knopman et al., 2012). Thus, age-related changes that cannot be ascribed to undetected AD are very likely, even in AD-prone regions. Of course, there is accumulation of other neurodegenerative conditions besides AD in aging. However, the uniformity of the anatomical distribution of atrophy makes it in our view unlikely that these changes are driven mainly by specific, disease-related neurodegenerative processes.

Why are brain regions vulnerable to AD also vulnerable to normal aging?

These findings bring us over to a pertinent and very interesting question: Why are AD-prone areas especially atrophic in normal aging? A popular view is that brain regions characterized by high degree of neuroplasticity are especially vulnerable both to aging and AD (Bufill, Blesa, & Augusti, 2013; Bufill & Carbonell, 2004; Mesulam, 1999; Neill, 1995, 2012; Rapoport & Nelson, 2011). This is in line with a systems vulnerability view. In the aging brain, neuroplasticity, rather than being adaptive, could contribute to neuropathology. While, as argued above, a number of genetic candidates of focus in brain aging may in fact exert their influence also early in the lifespan, some would argue that there are also cases of antagonistic pleiotropy, where evolutionary changes beneficial for survival in youth increase the vulnerability to diseases in aging (but see Ihle et al, 2012, referred above). Data obtained to date show that many genes associated with AD at some levels, including APOE4, are involved in synaptic plasticity (Bufill et al., 2013). Human specific evolutionary changes in neuroplastic potential could therefore have occurred to allow optimal behavioral flexibility, and maladaptive interaction between this human specific evolutionary brain adaptation and age-related changes can be responsible for cognitive decline in aging (Neill, 2012). Brain regions with highly neuroplastic long axonal connections are highly affected in AD, including parts of the entorhinal cortex, hippocampus and association neocortex (Rapoport & Nelson, 2011). Potential for neuroplasticity in elderly, with performance gains and accompanying changes in gray matter density (Boyke, Driemeyer, Gaser,

Buchel, & May, 2008), cortical thickness (Engvig et al., 2010) and white matter microstructure (Engvig et al., 2012), has been shown, demonstrating that humans have a high level of neuroplasticity retained in late life. This neuroplastic system is particularly responsive to environmental and internal factors. Neurons in certain association areas retain juvenile characteristics into adulthood, e.g. increased expression of genes related to synaptic activity and plasticity, incomplete myelination and elevated aerobic metabolism, which likely cause an increase in oxidative stress in these neurons (Bufill et al., 2013). The cost of such maintained plasticity may be increased vulnerability to factors which can trigger cognitive decline (Bufill et al., 2013).

The medial temporal lobes are high-vulnerability areas for the impact of both normal aging and AD. Together with posterior parietal association cortices, e.g. the precuneus, these regions are critical in learning and memory, with high demands for neuroplasticity (Aimone, Deng, & Gage, 2010; Deng, Aimone, & Gage, 2010). For instance, it has been suggested that altered neurogenesis in the hippocampus is an early critical event in AD (Mu & Gage, 2011). Neurogenesis in the adult human brain is restricted (Rakic, 2004) and unlikely to be a main factor in the changes in brain and cognition associated with aging. However, mechanisms such as dendritic spine plasticity (Benavides-Piccione, Fernaud-Espinosa, Robles, Yuste, & Defelipe, 2012; Bloss et al., 2011; Esiri, 2007; Freeman et al., 2008; Jacobs, Driscoll, & Schall, 1997) may be critical in aging, likely of importance for long-term memory (Sanders, Cowansage, Baumgartel, & Mayford, 2012). Thus, it may be that certain brain regions are characterized by increased demands for plasticity throughout life, and that this makes them especially vulnerable to subtle lesions and accumulating pathology. This could be one common denominator for brain atrophy and memory problems in aging and AD.

Tle role of amyloid in normal aging

The default mode network consists of a set of brain regions vulnerable to both normal aging and AD, especially the medial parietal and posterior cingulate/ retrosplenial, lateral temporal and temporo-parietal cortices. Interestingly, there is anatomical overlap between deposition of amyloid as measured by PiB PET *in vivo* and the default mode network of the brain. Unfortunately, the role played by amyloid in normal aging and in the transition from normal aging to neurodegeneration is very poorly understood. Are amyloid-atrophy correlations in cognitively normal elderly always indicative of undetected, AD-related degeneration, or could amyloid be a part of normal aging as well? Rodent research has demonstrated that synaptic and neural activity increases amyloid-beta levels (Bero et al., 2011; Cirrito et al., 2005). If the same mechanisms exist also in humans, it could be that the level of brain activity itself may be causally related to amyloid deposition (Buckner, 2012; W. J. Jagust & Mormino, 2011). This theory has some interesting implications. For instance, it has been argued that higher education enables people to maintain cognitive function despite high levels of brain pathology, related to the concept of cognitive reserve (Stern, 2006, 2012; Stern, Albert, Tang, & Tsai, 1999). According to the activity-dependent amyloid accumulation view, however, higher education itself could lead to the build-up of amyloid pathology through enhancement of life-long mental activity.

Although the theory of accumulation of amyloid in specific cortical regions as a result of higher levels of cognitive activity has received a lot of recent attention, there are difficulties: First, mental activity in the form of cognitive interventions (Engvig et al., 2010; Zatorre, Fields, & Johansen-Berg, 2012) and accumulated mental activity (Valenzuela, Sachdev, Wen, Chen, & Brodaty, 2008) have positive effects on brain and cognition in elderly, and has been shown to be inversely related to amyloid deposition ((Landau et al., 2012), but see (Members et al., 2010; Vemuri et al., 2012)). Second, even if the overlap between DMN and early Aβ deposition is causally related to the generally high DMN activity (Buckner, 2012; W. J. Jagust & Mormino, 2011), it is yet not obvious whether the life-long

pattern of brain activity is higher in the areas with higher Aβ depositions, e.g. the medial posterior parietal cortex, than in the areas with less, such as the medial temporal lobes or the visual cortex (Mormino et al., 2012; Sojkova et al., 2011). Finally, there is growing agreement that Aβ accumulation in sporadic AD is more related to decreased clearance than increased production (Castellano et al., 2011; DeMattos et al., 2004; Mawuenyega et al., 2010). Thus, it may not be increased Aβ production that is the most relevant factor for amyloid deposition, but rather the ability of the brain to keep the Aβ peptides soluble (Robakis, 2010).

Cognitive reductions in aging – complex causes

In any case, the weak correlations between amyloid level and cognitive function in normal aging suggest that other mechanisms (Hedden, Oh, Younger, & Patel, 2013), such as functional compensation (Cabeza, Anderson, Locantore, & McIntosh, 2002; Grady, 2012; Park & Reuter-Lorenz, 2009), also impact cognitive ability. According to a compensation view, the magnitude of brain insults that can be accommodated without cognitive decline and progression to AD varies significantly between individuals, and a key to understanding why may be individual differences in neural and cognitive plasticity. Thus, it is important to understand the mechanisms that cause some older adults to develop AD and some to maintain cognitive function in spite of accumulated brain amyloid and other possibly detrimental factors. For instance, the relationship between brain atrophy and amyloid load varies substantially between different groups of people (Fjell, Walhovd, Fennema-Notestine, McEvoy, Hagler, Holland, Blennow, et al., 2010). We will argue that a key to understand cognitive function in aging and AD, as well as the AD disease mechanisms themselves, is to systematically investigate individual differences in the relationships between the major cognitive, genetic and biological events in aging and AD. One approach would be to directly focus on the relationship between cognitive and brain plasticity on the one hand, and aging- and AD-related biomarkers, including genetics, on the other. The results of such studies may substantially move the limits of our

understanding of the relationship between cognitive function and brain integrity in normal aging and the earliest phases of AD. The basis of this approach would need to be a systems vulnerability view, where cognitive changes in normal aging and AD at least to some extent have overlapping causes, and where focus is on the interplay between multiple factors and brain regions more than single etiological factors.

Conclusion

In this review, we have tried to show that the factors affecting brain aging often can traced back to early development, and that modifiers of aging may exert their influence through a life-time. For both genetic and environmental factors, this can be true. This is what we refer to as a lifespan perspective. Further, we have tried to show that on a neurobiological level, the borders between normal aging and neurodegenerative conditions such as AD may not always be clear cut, and that many brain and cognitive symptoms are not unique to dementia. This is what we call the dimensional perspective. Finally, cognitive decline in aging and dementia do not have a single etiology, as there is not one single brain region or system that is affected. Rather, different factors impact brain and cognitive function both in health and disease, and a major aim of contemporary research is to understand what make the different brain systems vulnerable to all these different factors. This is what we refer to as a systems-vulnerability view. Agreeing with these perspectives will mean a rejection of the common focus of aging as separated from the rest of the life, a revision of the view that changes in brain and cognitive functions in normal aging and AD do not have overlapping causes, and moving away from the search for single etiological factors, e.g. amyloid accumulation, as the “big evil” in cognitive reductions in dementias and normal aging.

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