The Roots of Alzheimer's Disease: Are High-Expanding Cortical Areas Preferentially Targeted?

Anders M Fjell[a,b,1], Inge K Amlien[a], Markus H Sneve[a], Håkon Grydeland[a], Christian K Tamnes[a], Tristan A Chaplin[c,d,e], Marcello G. P. Rosa[c,d,e], Kristine B Walhovd[a,b], for The Alzheimer's Disease Neuroimaging Initiative*

[a] Research Group for Lifespan Changes in Brain and Cognition, Department of Psychology, University of Oslo, 0373, Norway

[b]Department of Physical medicine and rehabilitation, Unit of neuropsychology, Oslo University Hospital, 0424, Norway

[c]Department of Physiology, Monash University, Clayton, Victoria, 3800, Australia

[d]Monash Vision Group, Monash University, Clayton, Victoria, 3800, Australia

[e]ARC Centre of Excellence for Integrative Brain Function

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[1] Address correspondence to:

Anders M Fjell, Dept of Psychology, Pb. 1094 Blindern, 0317 Oslo, Norway, Phone: +47 22 84 51 29

Fax: +47 22 84 50 01, e-mail: andersmf@psykologi.uio.no

Abstract

Alzheimer's disease (AD) is regarded a human-specific condition, and it has been suggested that brain regions highly expanded in humans compared to other primates are selectively targeted. We calculated shared and unique variance in the distribution of AD atrophy accounted for by cortical expansion between macaque and human, affiliation to the default mode network (DMN), ontogenetic development and normal aging. Cortical expansion was moderately related to atrophy, but a critical discrepancy was seen in the medial temporo-parietal episodic memory network. Identification of "hotspots" and "coldspots" of expansion across several primate species did not yield compelling evidence for the hypothesis that highly expanded regions are specifically targeted. Controlling for distribution of atrophy in aging substantially attenuated the expansion-AD relationship. A path model showed that all variables explained unique variance in AD atrophy, but were generally mediated through aging. This supports a systems vulnerability model, where critical networks are subject to various negative impacts, aging in particular, rather than being selectively targeted in AD. An alternative approach is suggested, focused on the interplay of the phylogenetically old and preserved medial temporal lobe areas with more highly expanded association cortices governed by different principles of plasticity and stability.

Keywords: aging; Alzheimer's disease; cerebral cortex; evolution; default mode network

Alzheimer's disease (AD) is associated with heterogeneous brain atrophy, with accelerated atrophy in the temporal lobe in initial phases, spreading to medial parietal and then most of the cortex in later stages (McDonald et al., 2009). Fundamental to the understanding of disease progression is knowledge about the basic factors governing the distribution of atrophy. Several complementary theories or principles have been proposed. First, AD exists almost exclusively in humans, being very uncommon in other primates (Finch and Austad, 2012, Bufill et al., 2013). On this basis, it has been suggested that human-specific adaptations during evolution of the brain could be the cause of age-related neurodegenerative diseases, and specifically AD (Neill, 1995, Rapoport and Nelson, 2011, Buckner, 2012, Neill, 2012, Bufill et al., 2013). Especially, high-expanding regions of the human cortex have been hypothesized to be preferentially targeted (Rapoport and Nelson, 2011). However, the extent to which prime target areas of AD, including medial temporal lobes (MTL), are relatively more expanded in the human cortex compared to the cortices of other primates is debatable (Van Essen and Dierker, 2007).Critically, the degree of correspondence between cortical expansion from monkeys to humans and distribution of atrophy in AD has not been formally quantified.

Further, it has previously been suggested that what we now conceptualize as the default mode network (DMN) is supported by cortical areas that are particularly enlarged in humans, relative to other primates (Andreasen et al., 1995). Intriguingly, several have pointed to an overlap between DMN and distribution of amyloid plaques (Sperling et al., 2009), and speculated that this may be causally related to overall high levels of DMN activity (Jagust and Mormino, 2011, Buckner, 2012), thereby creating a link between evolutionary change, DMN activity and AD. Parts of the DMN, especially the medial parietal area, are characterized by hypometabolism (Gusnard et al., 2001), disturbed task-induced deactivations (Lustig et al., 2003) and reduced functional connectivity (Greicius et al., 2004) in AD. Hence, DMN function yields a complementary account to the selective cortical expansion hypothesis of distribution of atrophy in AD.

A third view is based on ontogenetic development, according to which brain regions with the most protracted development tend to be more vulnerable to degeneration in AD (Rapoport and Nelson, 2011, Buckner, 2012, Bufill et al., 2013) as well as in aging (Tamnes et al., 2013). For instance, according to this view, the posterior-to-anterior gradient of cortical maturation will be expected to be reversed in aging-related decline. This is often referred to as the theory of retrogenesis, in which degenerative mechanisms are thought to reverse the order of acquisition in normal development (Reisberg et al., 2002, Ewers et al., 2011). Several causes for this phenomenon have been proposed, including similarities in the sequence of myelin acquisition in development and the pattern of myelin loss, cell loss and neurometabolic change in AD (Reisberg et al., 2002). Interestingly, similarities between cortical development and the degree of cortical expansion in monkeys versus humans have also been demonstrated, with high-expanding regions with more complex cellular architecture showing more complex and protracted developmental trajectories (Rosa and Tweedale, 2005, Shaw et al., 2008, Hill et al., 2010). Accordingly, regions that are selectively larger in humans than in other primates, and that show relatively late maturation, may be more vulnerable to AD pathology.

An alternative view to a disease-specific model where high-expanding regions in humans are preferentially targeted in AD is a systems vulnerability model. According to such a view, brain systems affected in AD may also be vulnerable to a range of insults and conditions, including normal aging (Jagust, 2013). Thus, a link between differential cortical expansion and AD can be interpreted in terms of general vulnerability of brain networks, where AD may represent one extreme case of negative impact. If so, one would expect that high-expanding brain regions are as preferentially targeted in normal aging in the absence of neurodegenerative disease, and that the relationship between expansion and AD to a substantial degree would be mediated by brain changes in normal

aging. The same line of reasoning applies to the relationship between the DMN system breakdown, expansion and AD vs. aging.

Lack of formal quantification and comparison of the explanatory power of each of these theories is hampering progress in understanding distribution of atrophy in AD. On this background, we had three major aims: (1) To contrast rate of atrophy in AD between “hotspots” and “coldspots” of expansion of the cerebral cortex across primates of different sizes. We hypothesize that rate of atrophy in AD will not strictly follow degree of expansion, with especially the MTL with its known vulnerability to AD as a candidate for deviation. (2) To test to what extent the possible accelerated atrophy in AD in high-expanding regions can be explained by atrophy that also occurs in normal aging. This contrasts the principle of high-expanding areas being selectively targeted in AD vs. being more generally sensitive to negative impacts, in accordance with a systems-vulnerability view. (3) To test whether and how the affiliation of a cortical region to the DMN, degree of cortical expansion, aging and development are interrelated or independent in accounting for regional distribution of AD atrophy. These questions directly address the degree of specificity in the vulnerability of critical brain systems in AD.

In the present work, we take advantage of well validated cortical expansion maps between macaque and humans (Bardet et al., 2007, Hill et al., 2010), across several primate species (Chaplin et al., 2013) and from children to adults (Fjell et al., 2013b), as well as longitudinal atrophy maps from healthy older adults and AD patients from the Alzheimer’s Disease Neuroimaging Initiative (ADNI) (Fjell et al., 2013a), and of intrinsic connectivity maps based on 1000 participants (Yeo et al., 2011). These different datasets were re-analyzed and combined in a joint model. Comparing cortical expansion across primate species with grossly different brain sizes is most appropriately referred to

as allometric scaling. Here, cortical expansion from other primates to humans is used as a proxy for cortical areas more or less unique to the human brain.

Materials and methods

An overview of the different analysis steps taken is presented in Table 1.

[Insert Table 1 about here]

Atrophy and DMN maps

Samples were drawn from ADNI (www.adni-info.org), and are identical to those in (Fjell et al., 2013a). Participants were 55-91 years of age at baseline. Healthy controls scored 24-30 on Mini-Mental State Examination (MMSE) (Folstein et al., 1975), Clinical Dementia Rating (CDR) (Morris, 1993) of 0, and were non-depressed. 132 healthy older adults with no conversion to mild cognitive impairment over at least 3 year were available (60-90 years, mean 75.4, SD = 5.1, 63 females/ 69 males), as were 122 AD patients with no change of diagnostic status over the three year interval (55-89 years, mean 74.4, SD = 7.6, 57 females/ 65 males). From this group, a subsample (n = 37) of very low AD-risk was created based on normal levels of CSF Aβ1-42 (> 192 pg/ml, corresponding to an established criterion from the ADNI, see (Shaw et al., 2009)) and homozygoticy for apolipoprotein (APOE) ε3. This biomarker defined very low-risk subsample was used in an additional test of common effect of aging and AD in the final path analysis (see below). All participants had one-year longitudinal MRI passing internal quality control. 1.5 T scanners were used (see http://adni.loni.ucla.edu/research/protocols/mri-protocols/), and percentage volumetric change over one year was calculated for each point on the cortical surface with no anatomical constraints using Quarc (Holland et al., 2011, Holland et al., 2012). DMN connectivity maps were drawn from

FreeSurfer version 5.3 (http://surfer.nmr.mgh.harvard.edu/), based on resting-state data from 1000 subjects (Yeo et al., 2011) and thresholded by a vertex-wise confidence of .15.

Expansion maps

Cortical expansion maps between the macaque monkey and 12 young adult humans (Van Essen and Dierker, 2007, Hill et al., 2010), and between marmoset and capuchin and marmoset and macaque (Chaplin et al., 2013), were used for the calculations. Maps were originally created by surface-based registration methods, computed based on a combination of functional and structural homologies, described in detail elsewhere (Orban et al., 2004, Van Essen and Dierker, 2007, Hill et al., 2010, Van Essen et al., 2012, Chaplin et al., 2013). Only the right hemispheres were available. Computation of expansion maps for human development is described in (Fjell et al., 2013b), based on a sample of 331 healthy children 4-20 years by use of a surface-based smoothing spline approach (Fjell et al., 2010) applied to FreeSurfer generated cortical surface maps (Dale et al., 1999, Fischl et al., 1999a, Fischl et al., 1999b).

Statistics

All maps were Z-transformed to remove scaling differences (mean = 0, SD = 1). The maps were correlated vertex-by-vertex by Pearson correlations to yield a global measure of anatomical overlap (with the medial wall masked out before analyses). Significance was decided by permutation testing (10 000 permutations), and p-values were Bonferroni corrected for multiple comparisons. Partial correlations were run to control for the effect of aging. Regions of correlation vs. anti-correlation between AD atrophy and cortical expansion were identified by thresholding the Z-transformed atrophy and macaque to human expansion maps. Regions of correlation were characterized by $Z > .05$ or $Z < -.05$ for both cortical expansion and AD, and areas of anti-correlation by combinations of $Z > .05$ with $Z < -.05$. A similar procedure was used for DMN vs. AD atrophy. “Hotspots” and “coldspots”

of differential cortical expansion were identified by thresholding average expansion across all included species at $z > 1$ (hotspots) or $z < -1$ (coldspots). These regions were then used to extract rate of atrophy for all AD patients, tested against mean cortical atrophy by one sample t-tests. Next, atrophy in AD and aging, as well as cortical expansion, were correlated with the confidence value of each vertex of belonging to the DMN network, thresholded at .15. To show the distribution of variance across the different variables, a path model was constructed and the significance of each path was decided by permutation testing. This model was also run with the biomarker defined low risk subsample of healthy elderly.

Results

Cortical expansion

The degree to which the surface model of the macaque cortex had to be expanded to reach the size of the surface model of human cortex, i.e. cortical expansion, as well as annual percentage volume change in AD and normal aging, were calculated for 163842 points on the brain surface and related by Pearson correlations (Figure 1). All reported correlations were significant at $p < .05$ (two-tailed, corrected for multiple comparisons) as evidenced by permutation testing. Expansion correlated with regional distribution of atrophy in AD ($r = .35$) and normal aging ($r = .34$). Scatterplot (Figure 2) of the relationship between expansion and atrophy in 34 cortical regions revealed great variability, with some showing high expansion and atrophy, e.g. lateral temporal regions, while others deviated from this trend, e.g. MTL regions. Atrophy in AD and aging showed a stronger correlation ($r = .74$). The AD-expansion correlation dropped significantly to partial $r = .15$ when atrophy in aging was controlled for.

[Insert Figure 1 and Figure 2 about here]

Color-coded conjunction maps of correlations and anti-correlations between AD and differential cortical expansion were computed by thresholding the Z-transformed maps as described above (Figure 2). High expansion and high rate of atrophy could be seen in the entire lateral temporal cortex, extending into the temporo-parietal junction (TPJ) and inferior parietal cortices. Low expansion and low rate of atrophy in AD characterized the central sulcus, cuneus, calcarine sulcus and adjacent extrastriate cortex and the lingual gyrus. Anti-correlations were seen in the medial temporal lobe (MTL), including entorhinal, parahippocampal and fusiform cortices, as well as posterior cingulate/ retrosplenial cortices extending towards the precuneus and supplementary motor cortex, which have marked decline both in AD and in normal aging despite relatively low cortical expansion in the comparison between macaque and human.

Next, expansion maps across several Simian primate species (see (Chaplin et al., 2013)) were compared, showing a conserved pattern of differential cortical expansion (Figure 3). MTL showed the same relative preservation across species that was seen between macaque and human. “Hotspots” and “coldspots” of expansion were identified by thresholding the average expansion map across all species at $z > 1$ (hotspots) or $z < -1$ (coldspots) (Figure 4). Two previously identified major hotspots were situated in the TPJ extending somewhat anteriorly into the lateral temporal cortex (H1 in Figure 4), and in the lateral middle and inferior prefrontal cortex (H2) (Chaplin et al., 2013). Two adjacent coldspots were identified in the MTL extending inferiorly to the fusiform gyrus (C1) and in the medial occipital lobe (C2). In AD, H1 (2.41%) and C1 (2.22%) showed more decline than the mean cortical atrophy of 1.62% ($H1\ t = 4.60$; $C1\ t = 5.13$, $df = 121$, $p < .0001$), as evidenced by a one-sample t-test. C2 (0.57%) showed less decline than the mean ($t = 12.96$, $p < .0001$) while H2 (1.57%) did not differ from mean atrophy ($t = 0.34$, n.s.).

[Insert Figure 3 and Figure 4 about here]

Default Mode Network (DMN) vulnerability

AD correlated .27, aging .19 and cortical expansion .15 with the DMN network (Yeo et al., 2011) ($p < .05$, corrected) (Figure 5). More detailed inspections revealed overlap between DMN and AD in parts of lateral temporal cortex and around TPJ and in the medial parietal (precuneus) and posterior cingulate/ retrosplenial cortex (Figure 2), while high atrophy regions outside DMN was seen in the rest of the lateral and medial/ inferior temporal cortex. MTL had lower probabilities of being part of the DMN according to this parcellation scheme, although by use of a lower confidence threshold for inclusion, some vertices in the parahippocampal gyrus, mainly in the left hemisphere, would have been included in the DMN (Yeo et al., 2011). Interestingly, within DMN, cortical expansion and AD correlated in the lateral temporal cortex and TPJ, but were anti-correlated in posterior cingulate/ retrosplenial cortex.

[Insert Figure 5 about here]

Path modeling

Using all variables as predictors and AD atrophy as dependent in a multiple regression yielded $R^2 = .57$. A path model (SPSS Amos version 21) was constructed to disentangle variance across all variables (Figure 6). Cortical expansion between macaque and human was the single exogenous variable, AD was the endogenous variable, with DMN affiliation, development and aging as mediating variables. Paths were drawn from cortical expansion to all variables and from all variables to AD. Additional paths were drawn from DMN to aging and development and from development to aging. All paths were significant ($p < .05$, corrected). Aging was related to AD by partial $\beta = .67$, compared to .12 for DMN and .10 for cortical expansion. Expansion was further related to aging by $\beta = .30$ and to DMN by $\beta = .15$. DMN was related to aging by $\beta = .12$. The indirect contribution from

expansion to AD through aging was .20. DMN had an indirect contribution through aging of .08. Developmental expansion was related to cortical expansion (β = .11), DMN (β = .13), aging (β = .18) and to a smaller degree directly to AD atrophy (β = .04). The indirect contribution from development to AD through aging was .12.

[Insert Figure 6 about here]

As a final test, the estimations were re-run with the biomarker defined low risk group of elderly included instead of the full sample of elderly. The general results upheld, but with a moderate reduction in the relationship between cortical expansion and aging (from β = .30 to β = .19) and aging and AD (from β = .67 to β = .56), and an increase in the relationship between cortical expansion and AD (β = .10 to β = .19).

Discussion

Atrophy as a function of cortical expansion

Different rates of cortical expansion between the macaque and human brains explained 12.2% of the distribution of atrophy in AD. One hotspot of expansion, TPJ and parts of lateral temporal cortex, showed highly elevated rates of atrophy in AD. Conversely, medial parts of the occipital cortex showed low expansion and resistance to atrophy. However, the results also revealed deeply problematic aspects with the view that high-expanding regions are specifically targeted in AD. MTL is the earliest and most heavily affected region in AD (Price and Morris, 1999, McDonald et al., 2009) but show relatively low rates of expansion between macaque and human (Bardet et al., 2007, Hill et al., 2010) and across several simian species (Chaplin et al., 2013). This “coldspot” of expansion showed accelerated atrophy, with the MTL and medial parietal memory network showing marked anti-correlation between degree of expansion vs. AD. Rodent models are frequently used to study

learning, memory and spatial navigation (Colgin et al., 2008), because the MTL system is evolutionary preserved, with similarities in organization and function across many species. It has also been shown that a part of the retrosplenial cortex in primates, the prostriate cortex, has evolutionary old histological characteristics, with some very primitive visual response properties (Yu et al., 2012).

These low-expanding and AD-vulnerable regions overlapped well with the Papez' circuit, which is important for normal episodic memory function. The fact that such cognitive functions are reduced due to degeneration of low expanding brain regions and networks prompts the question of to what degree they really represent human-specific adaptations. Since storage and transmission of knowledge in preliterate societies should depend highly on individual brain capacity, evolution of a human-specific memory capacity, with corresponding expansion of relevant cortical regions, could be plausible (Bufill and Carbonell, 2004). In accordance with such an account, there are aspects of human memory vulnerable to AD (Addis et al., 2009) that may not be shared with other primate species, such as episodic simulation and long-term foresight - mental time travels ((Tulving, 1983), but see (Schwartz and Evans, 2001)). A prime candidate for supporting such functions is the DMN, likely involved in aspects of complex cognition such as episodic simulations (Addis et al., 2009), self-projection (Buckner and Carroll, 2007), and mental time travels (Ostby et al., 2012). These are functions that may possess qualities that could be human-specific ((Tulving, 1983, Suddendorf, 2013), but see (Schwartz and Evans, 2001, Corballis, 2013)). However, DMN-like activity develops quickly during the first year of infancy (Gao et al., 2013), likely prior to establishment of more stable, extensive and prolonged episodic memory and mental time travel abilities, and has been observed in a number of species, including non-human primates (Rilling et al., 2007, Barks et al., 2013, Belcher et al., 2013), rats (Lu et al., 2012) and mice (Sforazzini et al., 2013). A meta-analysis of fMRI data in monkeys showed consistent task-related deactivation within a network including medial prefrontal and medial and lateral parietal cortex, thus very similar to the human DMN (Mantini et al., 2011),

indicating that DMN may not be exclusive to humans. There is even evidence that DMN in chimpanzees, like in humans, plays a role in social cognition (Barks et al., 2013). A recent study of humans and monkeys identified two human-specific resting state networks, which did not include DMN (Mantini et al., 2013). Although it is very difficult to make inferences from brain activity to cognitive function, especially across species and particularly during uncontrolled task-free conditions, comparative data do not support the view that the DMN reflects the brain's most human and complex parts. This also means that the function of the DMN not necessarily represents human-specific cognition. Of course we do not know if the DMN has the same function across species, and there could be microstructural differences that lead to differences in DMN function.

Regardless of whether certain aspects of episodic memory differ between humans and other primates (Corballis, 2013, Suddendorf, 2013), it is not evident that these aspects are the most vulnerable early in AD. Spatial navigation is an early AD symptom related to episodic memory (Bellassen et al., 2012, Lithfous et al., 2013), also dependent on the MTL system, which can hardly be said to be a human-specific cognitive adaptation. The basis of spatial navigation is rooted in grid cells in the entorhinal cortex (Fyhn et al., 2004), which is the first region to harbor increased amounts of neurofibrillary tangles and other AD-pathology (Braak and Braak, 1991, Van Hoesen et al., 1991), although likely not β-amyloid in the initial phases (see below). Together with the occipital cortex, MTL was the major "coldspot" region in the expansion of the cerebral cortex, with a high degree of relative preservation across several primate species. Thus, even though we can not exclude the possibility that certain human-specific cognitive functions may be impaired in AD, there seems to be no clear connection between the early cognitive symptoms and brain pathology on the one hand, and cortical expansion across primate species and human-specific higher-order cognitive functions on the other.

Specificity of atrophy: aging vs. AD

Despite discrepancy in the critical medial DMN and MTL regions, there were also some overlaps between cortical expansion and AD atrophy. A further aim of this study was to test whether high-expanding regions with accelerated atrophy were preferentially targeted in AD compared to aging. The expansion-atrophy relationship was similar in magnitude in aging and AD. Partialling out the effect of aging caused the relationship between cortical expansion and AD to drop from 12.2% to 2.25% shared variance. This suggests that rather than being specifically targeted by AD, some high expanding areas may represent regions of high vulnerability to different conditions, aging in particular, in line with a systems vulnerability view (Jagust, 2013). The hotspot region in the TPJ/ lateral temporal cortex showed accelerated decline in AD, but was heavily affected by aging as well. To the extent that high-expanding regions are specifically targeted in AD, we would not expect to see the same pattern of decline in normal aging. The same general pattern was upheld when only the healthy elderly negative for amyloid and homozygote for APOE ε3 were included, although the relationships naturally were somewhat attenuated.

A common denominator for low-expanding regions that are vulnerable to AD and normal aging could be high levels of unique types of plasticity (Cotman et al., 1993, Neill, 1995, Mesulam, 1999, Neill, 2012). MTL and DMN play special roles in memory, with high demands for life-long plasticity (Aimone et al., 2010, Lazarov et al., 2010). MTL also harbors the only area of adult human neurogenesis besides the olfactory bulb, the dentate gyrus (Eriksson et al., 1998, Lotsch et al., 2013). This state of affairs is markedly different in a number of other species, including other primates, where new neurons may be added throughout life in areas of the neocortex ((Gould et al., 2001, Bernier et al., 2002), but see (Rakic, 2002)). Evolution must progress with a delicate balance of plasticity and stability, and appears to have favored stability over plasticity in humans (Rakic, 2002, 2004, Bhardwaj et al., 2006). Hence, although the human MTL is not very different from other primate species in

terms of anatomy, function (Clark and Squire, 2013) or neurogenesis (Rakic, 2002), what is special about the human MTL may rather be its role as an evolutionary old and plastic area within an otherwise much more developed and expanded neocortex.

Altered neurogenesis in the hippocampus has been proposed as an early critical event in AD (Mu and Gage, 2011), and lesions in the limbic system could have consequences for association cortices function due to reciprocally interconnections (Mesulam, 1999). Of note, many of the structures on the surface of the basal forebrain and within MTL that comprise olfactory cortex are also sites of initial pathology (Price et al., 1991, Wang et al., 2010), and along with episodic memory and navigation (Drago et al., 2011), olfactory function (Stamps et al., 2013) is among the first to decline in AD. The downside of being lone areas involved in, or surrounding or tightly interconnected to areas being involved in, this type of plasticity in the human brain may be increased vulnerability, with accumulation of negative impacts through life (see below). Different mechanisms related to neuroplasticity are then manifested in other cortical regions. For instance, dendritic spines may represent a primary site of structural plasticity throughout the cortex, and spine density and plasticity is reduced in aging (Jacobs et al., 1997, Esiri, 2007, Freeman et al., 2008, Bloss et al., 2011, Benavides-Piccione et al., 2012). Importantly, while tangle accumulation starts in MTL, spreading to isocortical association areas in later AD stages (Braak and Braak, 1991), medial parietal and prefrontal DMN regions are characterized by increased concentrations of β-amyloid in initial phases (Sperling et al., 2009). Thus, the two hallmark histopathological criteria for AD originate in regions characterized by different mechanisms of plasticity, that are relatively preserved during evolution while showing high rates of atrophy.

The cost of maintained plasticity may be increased vulnerability to factors which can trigger cognitive decline (Bufill et al., 2013). Perturbation of neuroplasticity has been proposed as a fundamental

principle that could potentially account for the clinical and neuropathological features of AD, and that amyloid depositions and neurofibrillary tangles are manifestations of the same underlying phenomenon (Mesulam, 1999). The potential for neuroplasticity is higher in the limbic system than in other parts of the cerebral cortex, which increases its vulnerability to neurofibrillary degeneration. A consequence of this view may be that late-onset AD is the manifestation of a failure to keep up with the "*increasingly more burdensome work of plasticity*" (Mesulam, 1999).

Interestingly, this calls for a life-span perspective on aging and AD, in that the same regions are sensitive even to prenatal factors. For instance, recent research demonstrated effects of normal variation in neonatal characteristics such as birth weight on MTL (Walhovd et al., 2012) and DMN structures (Raznahan et al., 2012). Thus, rather than regarding such networks as specifically targeted in AD, a life-span systems vulnerability view may explain dysfunction of these systems across a range of insults and conditions. Effects of APOE4, the major risk allele for sporadic AD (Corder et al., 1993), have been found on gray matter volume in MTL in neonates (Knickmeyer et al., 2013) and in the entorhinal cortex and the hippocampus in children and adolescents (Shaw et al., 2007). The likely existence of life-long gene × environment interactive negative influences indicates that antagonistic pleiotropy is not the only explanation for brain degeneration in aging-related dementias such as AD. The possibility of extreme sensitivity to initial conditions, and developmental contributions to emergence of pathology due to allostatic load (Lenroot and Giedd, 2011), may fit better with a systems vulnerability account for aging-related degeneration.

Common and shared effects

The final aim of the study was to test the distribution of variance between DMN, degree of differential cortical expansion between species, development, aging and AD. Atrophy was higher within the DMN, and DMN showed on average more expansion than non-DMN regions. Interestingly,

DMN and cortical expansion were mainly independent predictors of AD. Although there was a small indirect contribution to AD atrophy from cortical expansion through DMN, the proposed link between DMN and expansion in explaining AD-vulnerability was not strong. DMN and cortical expansion also contributed to explain AD atrophy indirectly through the influence of age. The indirect contribution from expansion to AD through aging was .20, compared to the direct contribution of .10. This suggests that expansion and DMN affiliation explain the anatomical distribution of atrophy in AD to a substantial extent through their influence on atrophy in aging. The same was true for developmental expansion, which as expected was related to cortical expansion between macaque and human (Hill et al., 2010, Fjell et al., 2013b), with a direct relationship to AD of .04 and an indirect relationship through aging of.12.

Limitations and conclusion

The human brain is not a direct result of evolutionary adaptation of living primates, as humans and other primates have extinct common ancestors. As pointed out by Rakic (2009), comparative anatomical and DNA sequencing data indicate that macaques and humans belong to different branches on the phylogenetic tree (Rakic, 2009), and as such, one cannot draw inferences about evolution directly from cortical differences between them. Thus, inter-species comparisons can only be used to test hypotheses about aspects of the brain that are more or less human-specific, or at least, more or less different between humans and other living primate species. This way, inter-species comparisons can be very useful in informing us about the anatomical correspondence between AD atrophy and degree of “human uniqueness” in regional cortical size. Further, during hominid evolution, cortical adaptations in addition to expansion have certainly occurred (Geschwind and Rakic, 2013), e.g. related to gene expression (Bufill et al., 2013), microstructural changes (Chen et al., 2013) and network reorganization (Buckner and Krienen, 2013). Given that AD appears to be a unique human disease, we would expect overlap between disease mechanisms and unique aspects

of the human brain at some levels. The present results indicate that a simple expansion-vulnerability model of cortical atrophy may not be warranted, instead favoring an approach focusing on why regions well-preserved across several primates seem to be critical in the chain of pathology. As speculated, it may be worth closing in on the interplay between phylogenetically old and preserved mechanisms of plasticity, as seen for example in the dentate gyrus, and high-expanding association cortices.

Another issue of discussion is the delineation of DMN. It has been suggested to fractionate DMN into an MTL and a dorsal medial prefrontal subsystem including TPJ and lateral temporal cortices, with posterior cingulate and anterior medial prefrontal cortex as hubs (Andrews-Hanna et al., 2010). Following this scheme, the MTL system would be preserved across primates and characterized by high degree of atrophy. The prefrontal would be more expanded, with some regions less (medial prefrontal) and others more (lateral temporal) prone to atrophy. Thus, the DMN is not easily characterized as a unitary system in terms of either expansion or AD atrophy.

The data also demonstrate that aging is the major factor explaining the anatomical distribution of atrophy in AD. Differential degree of cortical expansion, affiliation to DMN and developmental timing all contribute to explain the regional distribution of AD atrophy to a substantial extent through their influence on aging. Thus, a systems vulnerability approach to AD, with the aim of trying to understand why certain brain regions and neural networks are vulnerable to different detrimental influences accumulating through life (Jagust, 2013), may be a more promising approach than focusing on the effect of the disease in isolation. What is now needed are proper mechanistic models to explain the observed correlations between expansion and vulnerability across aging and AD on a molecular neurobiological level.

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Figure Legends

Figure 1 Regional distribution of atrophy and cortical expansion

Panel A: Mean annual atrophy in terms of volume reduction in AD, z-transformed to remove scaling effects. Panel B: z-transformed cortical expansion between from macaque and human. Panel C: z-transformed maps of atrophy in terms of volume reductions in normal aging. For all panels, red-yellow indicates higher than mean annual atrophy, while blue-cyan indicates lower than mean atrophy. Scales go from 2 (red-yellow) to -2 (blue-cyan). The brains are semi-inflated to allow better visualization of effects within sulci.

Figure 2 AD atrophy, cortical expansion and DMN

Panel A: Mean AD atrophy and expansion (z-scores) were quantified within 34 cortical regions of interest to illustrate variability across regions. The x-axis denotes degree of cortical expansion from relatively lower (blue-cyan axis color) to higher (red-yellow axis color). The transition point between blue and red axis color denotes mean expansion across the surface. The y-axis denotes percentage annual cortical volume decline in the AD patients. The color of the dots indicates from which gross region of the brain they are taken. Although there is a correlation between how much cortical expansion is seen within a region and the amount of AD atrophy, there are also regions not following this tendency, e.g. the medial temporal regions characterized by relatively low degree of expansion but high levels of atrophy in AD. Panel B: The Z-transformed cortical expansion and AD atrophy maps from Figure 1 were thresholded at $0.5 < Z < -0.5$. Areas of correlation were characterized by $Z > .05$ (green) or $Z < -0.5$ (yellow) for both cortical expansion and AD, while areas of anti-correlation (pink) were characterized by combinations of $Z > 0.5$ with $Z < -0.5$. The medial surface is slightly tilted to allow inspection of inferior temporal and fusiform cortex. Panel C: A similar procedure was used to show areas of high atrophy within DMN (green), low atrophy outside DMN (yellow) and high atrophy outside DMN (pink).

Figure 3 A conserved pattern of differential expansion across primate species

Cortical expansion (Z-scores) from comparisons between cortical area of smaller vs. larger brained Simian primates. From left to right are shown marmoset vs. capuchin, marmoset vs. macaque and macaque vs. humans, as well as the mean expansion across all species. General patterns of high and relatively low expansion are well preserved across species. The medial temporal cortex (lower panel) showed high degree of preservation across all comparisons (thresholded by $z < -1$).

Figure 4 Hotspots and coldspots of cortical expansion

Upper panel: The average expansion maps across marmoset, capuchin, macaque and human were thresholded at $z > 1$ or $z < -1$ to reveal regions of consistently high ("hotspots" – green-yellow) and consistently low ("coldspots"- blue-pink) cortical expansion through across primates. Lower panel: Mean atrophy in AD was quantified within the two hotspot regions (H1 & H2) and the two coldspot regions (C1 & C2). H1 and C1 showed elevated rate of atrophy, while C2 showed reduced decline.

Figure 5 Default mode network (DMN) and cortical expansion

Upper panel: Delineation of the DMN based on (Yeo et al., 2011). Colors denote the probability for each vertex being a part of the DMN. The scale goes from .15 (red) to 1 (yellow). Lower panel: Atrophy and expansion from the maps in Figure 1 were extracted for vertices inside vs. outside DMN and plotted in terms of z-scores. Atrophy and expansion are larger for DMN vertices than vertices outside DMN. All contrasts were significant ($p < .05$, corrected).

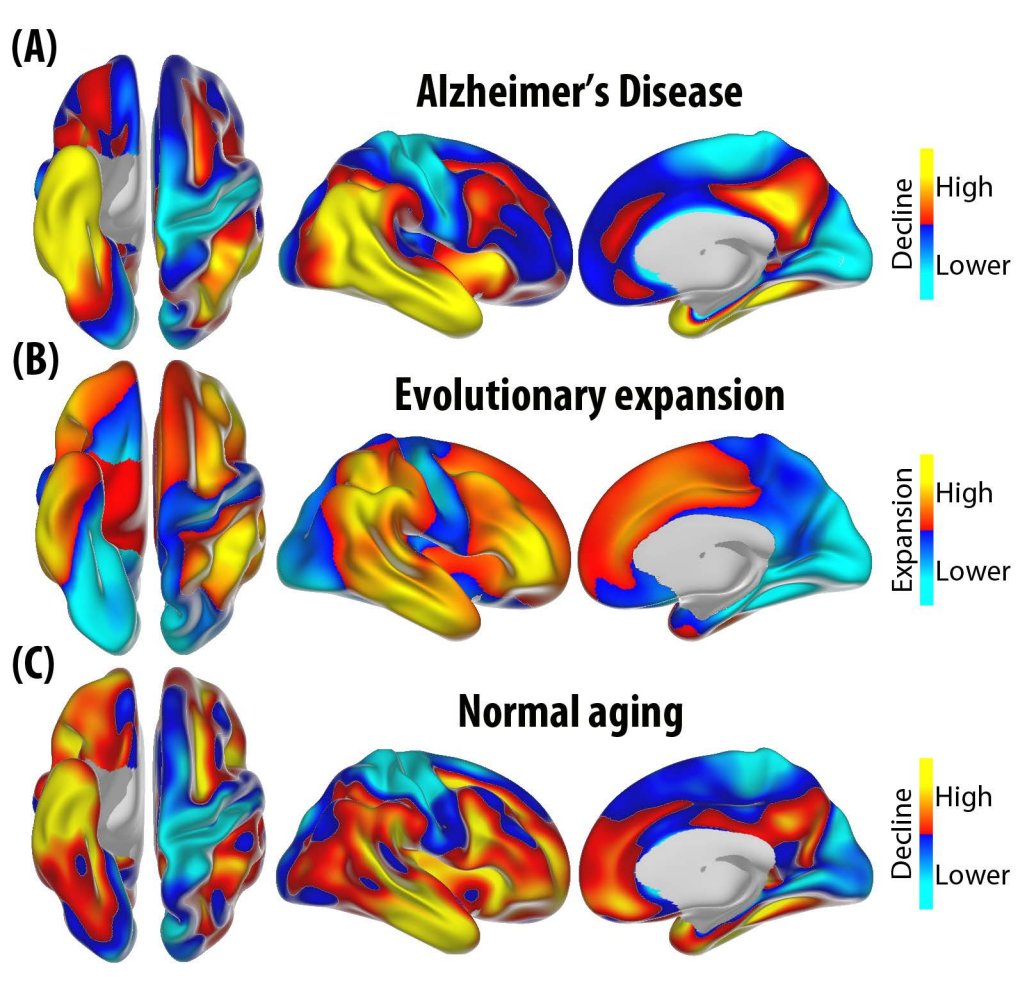
Figure 6 Path model of shared and unique contributions to distribution of AD pathology

A path diagram was constructed to show how the variance was distributed among variables. Arrows show relationships between any two variables in terms of independent (start of line) vs. dependent (end of arrow), colors and thickness of lines correspond to standardized partial path weights.

Input	Processing	Output
	Human atrophy maps	
1-year longitudinal MRI in 122 AD patients	Quarc, surface-based analysis (Holland et al., 2011), Z-transformation	AD atrophy maps (z-scores)
1-year longitudinal MRI in 132 healthy elderly	Quarc, surface-based analysis, Z-transformation	Aging atrophy maps (z-scores)
1-year longitudinal MRI in 37 healthy elderly with very low AD -risk	Quarc, surface-based analysis, Z-transformation	Low-risk aging atrophy maps (z-scores)
	Cortical expansion maps between primates of different size	
MRI of one macaque and 12 young humans	Surface-based registrations, based on inter-species homologies, by CARET (Orban et al., 2004; Van Essen and Dierker, 2007), Z-transformation	Macaque-vs-human expansion maps (z-scores)
MRI of one marmoset, one capuchin, one macaque	Surface-based registrations, based on inter-species homologies by CARET (Chaplin et al., 2013; Van Essen et al., 2012), Z-transformation	Marmoset-vs-capuchin expansion map, marmoset-vs-macaque expansion map (z-scores)
Normalized (0-1) expansion maps of marmoset-vs-capuchin, marmoset-vs-macaque, macaque-vs-human	Average of normalized expansion maps across all species (Chaplin et al., 2013), Z-transformed	Average expansion map across primates (z-scores)
Average expansion map (z-scores)	Thresholded at $1 < Z$ or $Z < -1$	"Hotspots" and "Coldspots" of expansion
	Human developmental expansion	
MRI of 331 healthy children, 4-20 years	FreeSurfer reconstructions and area calculations, surface-based smoothing spline (Fjell et al., 2010), Z-transformation	Estimated mean cortical expansion (z-scores)
	Default mode network	

Resting-state BOLD scans from 1000 healthy participants	Surface-based alignment, clustering approach (Yeo et al., 2011), thresholded at .15 confidence	Thresholded DMN confidence maps

Table 1 Overview of the main analysis and reconstruction steps


(A)
Alzheimer's Disease
Decline
High
Lower
(B)
Evolutionary expansion
Expansion
High
Lower
(C)
Normal aging
Decline
High
Lower

(A)

cingulate
frontal
parietal
lateral temporal
occipital
medial temporal

4.0
3.0
2.0
1.0
0.0

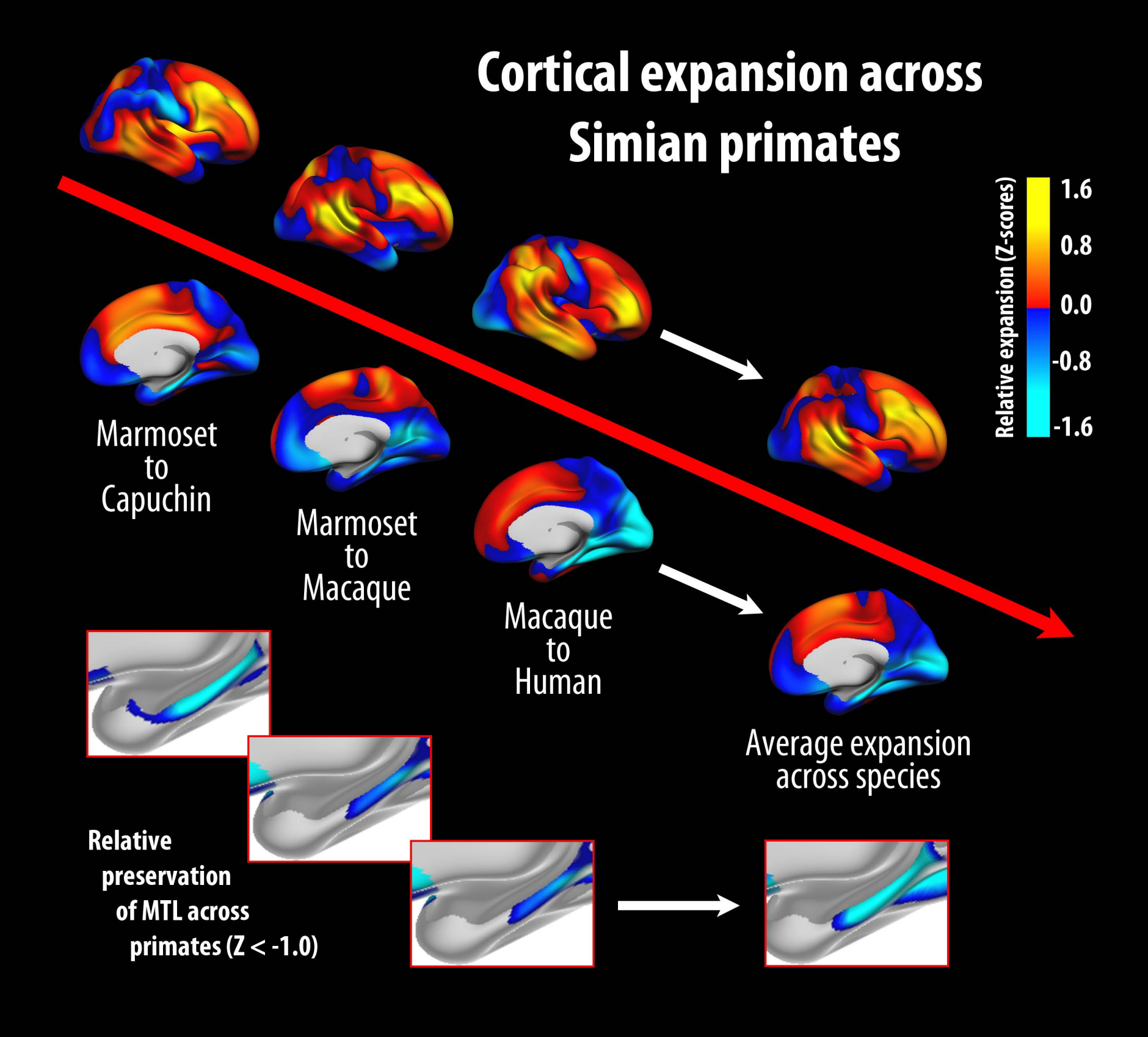
% annual decline

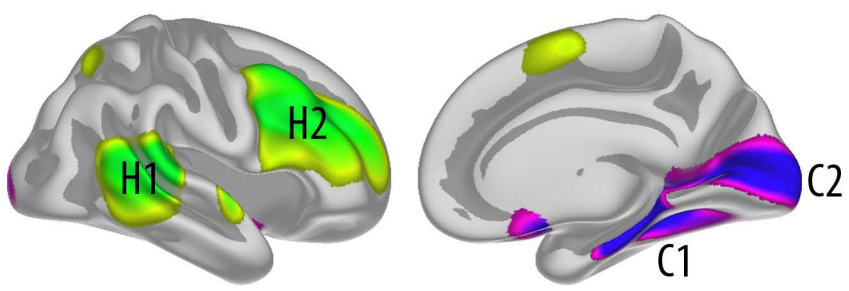
Lower
Higher
Cortical expansion

(B) Expansion vs. Alzheimer

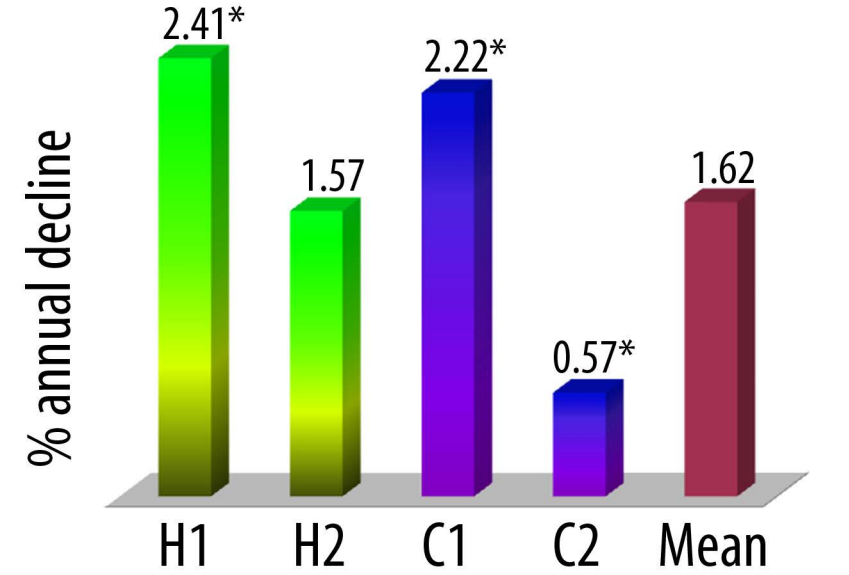
(C) DMN vs. Alzheimer

Both high
Both low
Anti-correlated


Cortical expansion across Simian primates
Relative expansion (Z-scores)
1.6
0.8
0.0
-0.8
-1.6
Marmoset to Capuchin
Marmoset to Macaque
Macaque to Human
Average expansion across species
Relative preservation of MTL across primates (Z < -1.0)

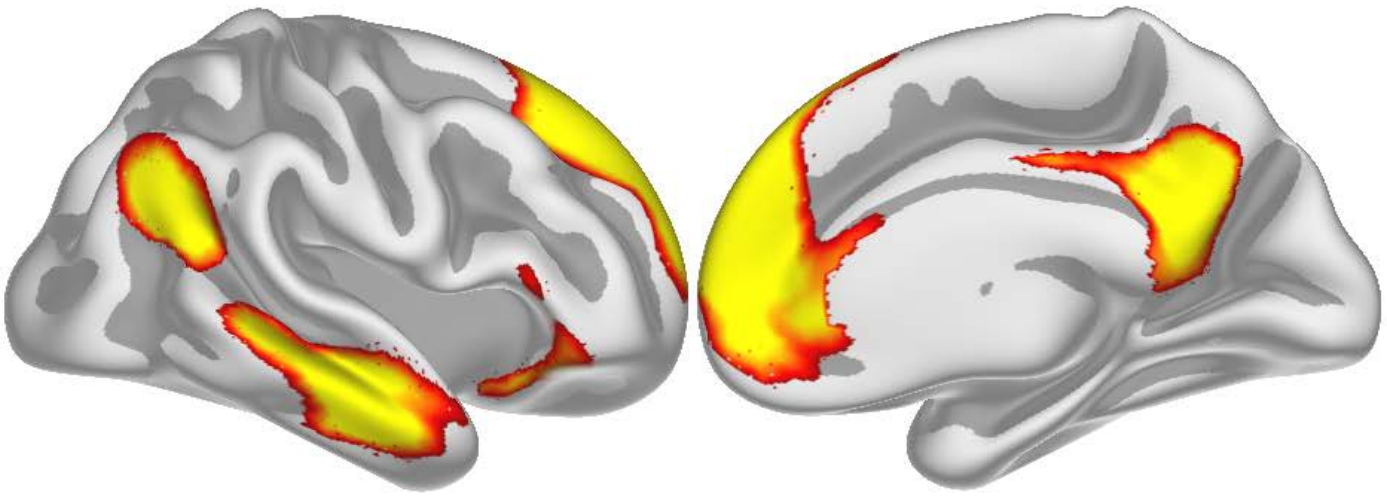


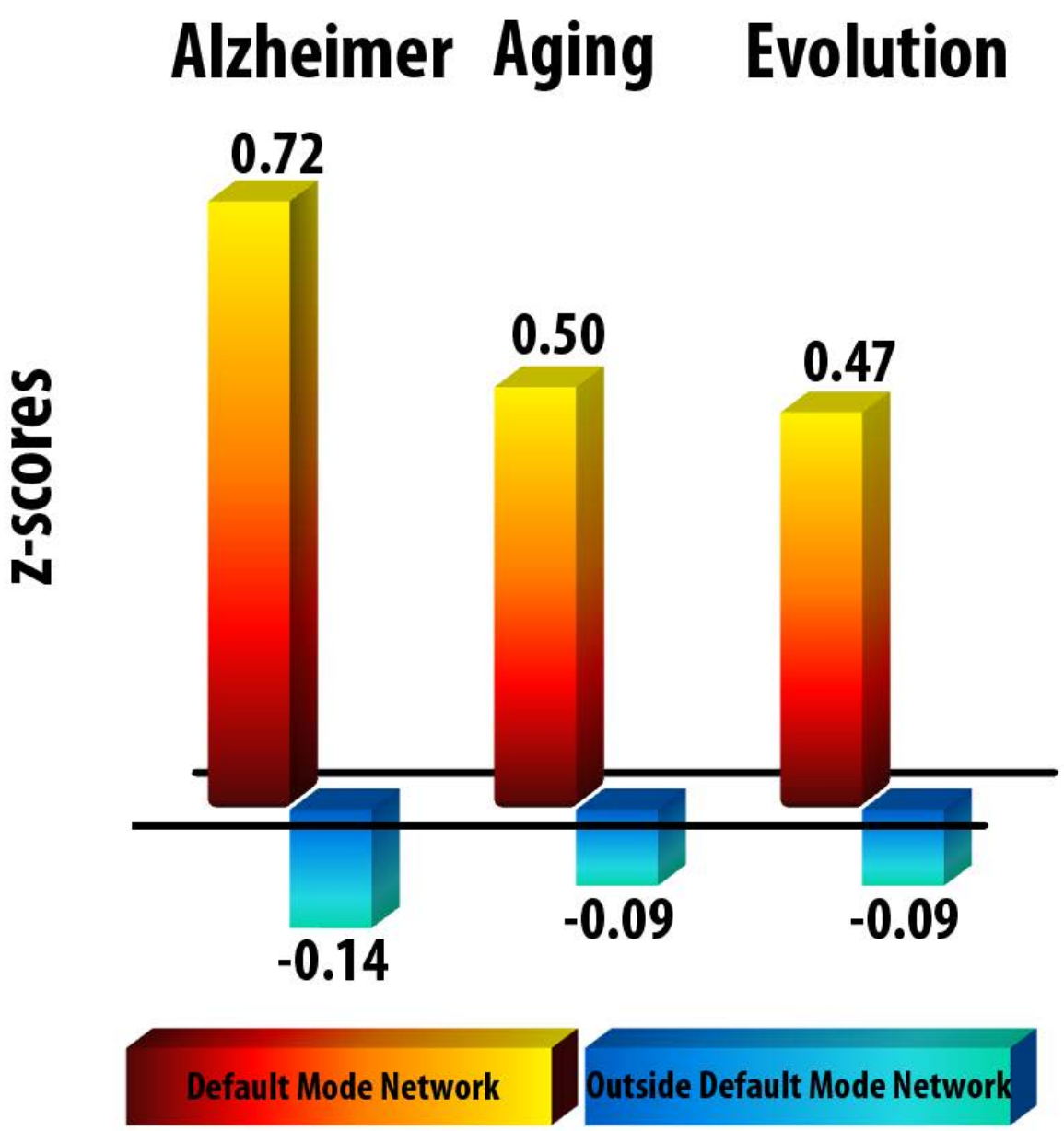
Hotspots of evolution Coldspots of evolution

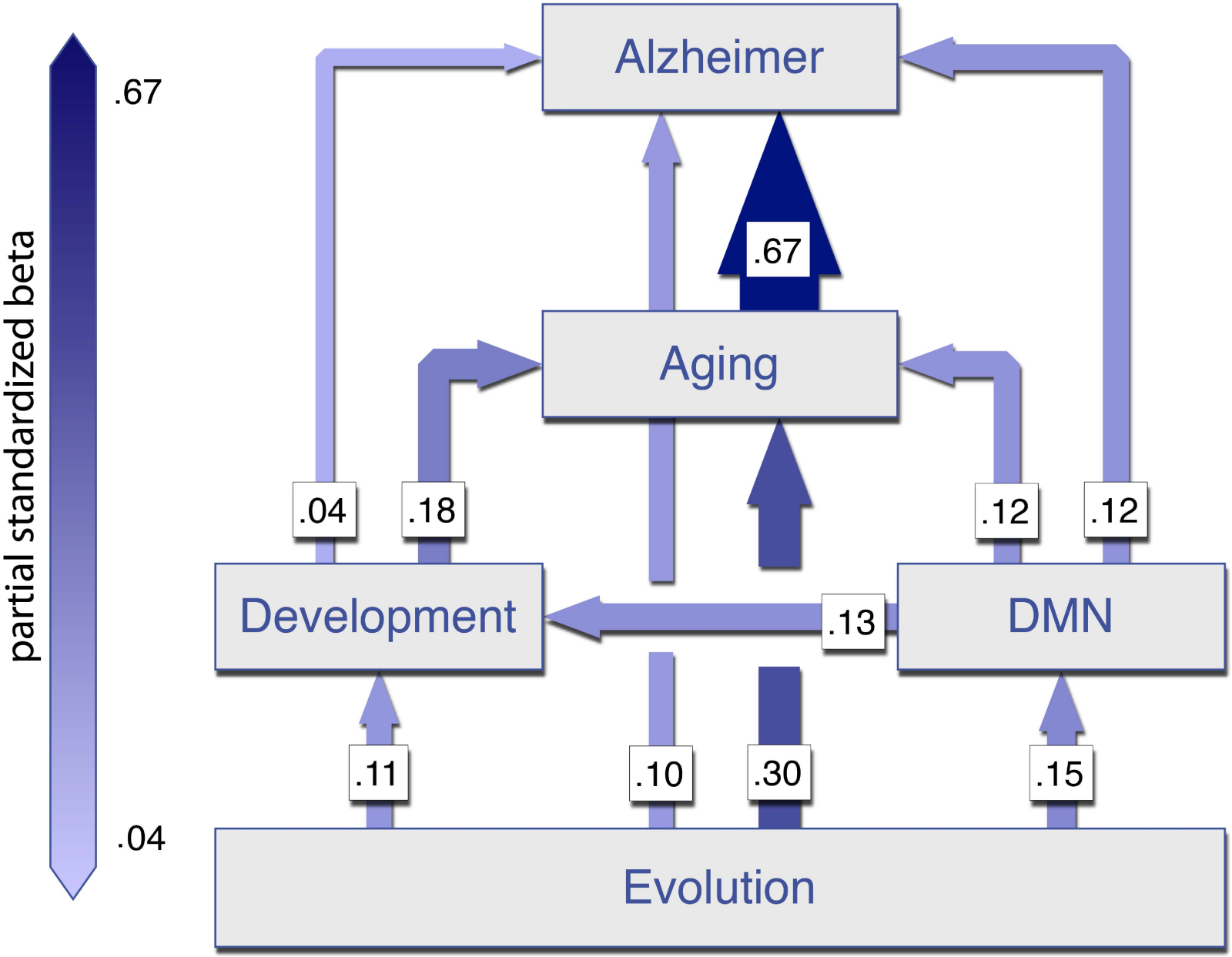


$* p < .05$ compared to mean

Default Mode Network






partial standardized beta
.67
.04
Alzheimer
.67
Aging
.04
.18
.12
.12
Development
.13
DMN
.11
.10
.30
.15
Evolution