Hypothesis

Integrated Phylogeny of the Human Brain and Pathobiology of Alzheimer's Disease: A Unifying Hypothesis

Authors: Saak V. Ovsepian[1], Valerie B. O'Leary[3], Cyril Hoschl[1,2], and Laszlo Zaborszky[4]

Affiliations: Department of Experimental Neurobiology, National Institute of Mental Health, Topolová 748, 250 67 Klecany, Czech Republic (1); Department of Psychiatry and Medical Psychology, Third Faculty of Medicine, Charles University, Ruská 87, 100 00 Prague 10, Czech Republic (2); Department of Medical Genetics, Third Faculty of Medicine, Charles University, Ruská 87, 100 00, Praha 10, Czech Republic (3); Center for Molecular and Behavioral Neuroscience, Rutgers, the State University of New Jersey, Newark, NJ, USA (4).

Correspondence: saak.ovsepian@gmail.com

Abstract

The disproportionate evolutionary expansion of human cerebral cortex with reinforcement of cholinergic innervations warranted the rise in functional and metabolic load of conserved basal forebrain (BF) cholinergic system. Given that acetylcholine (ACh) regulates the properties of microtubule-associated protein (MAP) tau and promotes non-amyloidogenic processing of amyloid precursor protein (APP), the growing neocortex increased demands for ACh, while the emerging role of BF cholinergic projections in Aβ clearance entailed greater exposure of source neurons and their innervation fields to amyloid pathology and tau toxicity. The higher exposure of evolutionary most recent cortical areas to amyloid pathology of Alzheimer's disease (AD) with synaptic deficit and atrophy, therefore, might involve reduced homeostatic and protective effects of BF cholinergic projections, in addition to fall-outs of inherent processes of expanding association areas. This unifying model, thus, views amyloid pathology and loss of cholinergic cells as a quid pro quo of the allometric evolution of the human brain, which in combination with increase in life expectancy overwhelm the BF mechanisms and initiate the disease process.

Keywords: brain evolution; cholinergic neurons; p75 NTR; amyloid deposition; cortical expansion; default mode networks; Alzheimer's disease

Introduction

In 1884 Croonian Lectures on the Evolution and Dissolution of the Nervous System, Hughlings Jackson asserted that 'on account of the great preponderance of the highest centers in man, he differs so greatly from lower animals.. we can have a combination.. (of diseases) .. never actually experienced' [1], implying that some neurological and psychiatric conditions can be viewed from an evolutionary perspective as human-specific. Amongst the largely or exclusively human-specific brain diseases, frontal dementia, schizophrenia, and Alzheimer's disease (AD) are most frequently discussed [2-4]. The AD-like neuro-behavioural symptoms and associated pathological changes are very rare in other animals, including in our closest evolutionary relative primates, whereas in humans they are common in old age. The sporadic form of the disease typically sets on after 65 years of age and its prevalence doubles every five years. In developed countries in over 85-year-old populations, the occurrence of AD ranges from 20 to 40% [5, 6].

In support of H. Jackson's thesis, many recent studies have viewed the disproportionate enlargement of the evolutionary most progressive and dynamic cortical areas as a key for the prevalence of AD in humans [7-9]. Clinically, the disease manifests via an irreversible decline in higher mental faculties, including executive and cognitive functions, working and declarative memory, language, computation skills, judgment and social intelligence. While present in many linages, these functions have advanced radically in humans in parallel with the expansion of association cortical networks, which reach maturity during adolescence and contribute towards a dramatic increase in the human brain size and its higher susceptibility to AD in later life. Indeed, during the recent past four million years of evolution, the ~400 cm^3 brain of human ancestors has transformed into the ~ 1465 cm^3 brain of the modern *Homo sapiens*, primarily owing to the enlargement of cortical structures, and more specifically, the association areas [10-12] (Figure 1). Although the evolution of association cortex in human ancestors has been largely

allometric, the process involved major reorganization of connected subcortical structures, in accordance with the model of integrated phylogeny [12-14]. As a result of this process, basal forebrain (BF) cholinergic nuclei became more specialized and compartmentalized in primates, and especially in humans [15-17]. Changes in BF nuclei, however, have been relatively modest, as compared to major expansion of association cortex with reinforcement of cholinergic innervations [15, 18-22]. Such asymmetric upgrades of these deeply integrated systems, therefore, entailed a selective pressure for elaboration of basalo-cortical projections, to ensure acetylcholine supply to expanding innervation fields, resulting in a rise in functional and metabolic load of source neurons.

As discussed in this study, the radical expansion of the association fields with conserved BF seem to play a key role in selective vulnerability of human brain to amyloid β (Aβ) depositions and related pathological alterations of AD. Indeed, unlike the vast majority of sporadic AD cases exhibiting complex and characteristic amyloid plaques and neurofibrillary tangles with widespread loss of synapses and neurodegeneration, combination of these changes are extremely rare in the brain of other mammals, including non-human primates [23, 24]. To date, Aβ deposits have been described in few occasions in camels, polar bears, dogs, and cats, with human-like neuritic plaques and vascular deposits also present [25-28]. In all these animals, the amyloid pathology and neurodegeneration occurs spontaneously, unlike laboratory rodents. In aged dogs, for instance, while extracellular Aβ (oligomers and fibrils) deposits have been demonstrated, dog brain rarely contains neurofibrillary tangles [29]. Aged dogs also display signs of vasculopathies with degeneration of cholinergic neurons of the BF, with later not correlating with the extent of Aβ cortical load [29, 30]. Research by Raghanti and co-workers have demonstrated several pathological hallmarks of AD in aged chimpanzee, which include parenchymal and vascular amyloid deposits [31-34]. Authors also report AD-like changes in microglia phenotypes with increased activation, which unlike human AD cases did

not correlate with tau lesions [33]. Likewise, although chimpanzee exhibit regional neuronal loss with aging, they appear protected from the cell death found in AD [31]. Overall, in non-human primates as well as in other animals, the intensity of amyloid pathology with neurofibrillary tangles and knock-on effects are considerably lower as compared to human AD. These and a growing number of similar studies have led recently to the notion that AD-like signs while can manifest in aging primates and other mammals, only humans develop the fully blown neuropathological and clinical AD.

In developing the thesis of AD as a human-specific condition, Rapoport and others noted that one of the corollary criteria for qualifying it as such is that the pathology affects the evolutionary most recent and rapidly expanding cortical structures, which arose during primate and especially human speciation [7, 8, 35]. While comparative evidence supports the selective vulnerability of specific cortical areas and functions to the disease, the underlying mechanisms of such effects remain controversial. Proposed mechanistic models view pathological alterations in AD cortex exclusively as a fall-out of intrinsic cortical mechanisms [2, 7, 36], discounting the potential contribution of subcortical effects. Given the well-recognized early onset deficiency of acetylcholine (ACh) with loss of cortical cholinergic innervations in AD, none of the models can be considered as complete, but warrant conciliatory revision. Throughout this study, we provide a unifying outlook at the AD evolution that integrates established and more recently emerging facets of the neurobiology of the BF cholinergic system along with their potential contribution to the greater susceptibility of association cortex to the disease.

Differential susceptibility of cortical regions to AD pathology

There is overwhelming data from functional brain imaging and autopsy studies suggesting differential vulnerability of various cortical regions to neuropathological changes of AD. In the

majority of reports, the onset of the cortical pathology with early amyloid-related impairments have been mapped to the temporal areas, spreading over the medial parietal, prefrontal, posterior parietal association areas, orbitofrontal cortex, and cingulate gyrus [37-40]. From there, at more advanced stages of the disease, the pathology propagates further over the primary sensory and motor areas as well as subcortical structures. Such hierarchy provided a basis for the neuropathological staging of AD proposed by Braak and co-workers [37]. Mapping and correlational of cortical regions affected by AD with networks of resting-state activity, or so-called default mode network (i.e. DMN), has shown a high degree of spatial correspondence [41, 42] (Figure 2). The latter has been interpreted as an evidence for a mechanistic link between neuronal activity and amyloid load with neurotoxicity [41, 43, 44]. Importantly, DMNs also overlap with the evolutionary youngest and most dynamic cortical regions. Despite growing data supporting the association between neuronal activity with release of Aβ peptide from neurons, a major gap remains in understanding specific mechanisms of the higher susceptibility of the evolutionary most progressive cortical structures to the disease [36]. The dependence of APP processing and Aβ production on synaptic activity might contribute to the higher amyloid load [45-48] given the above average basal activity in DMN circuits [42, 49]. Anatomical evidence shows that dramatic evolutionary enlargement of the temporal association, prefrontal, and parietal areas was related with reorganization of intrinsic connectivity, to process complex and multimodal information related to sensory inputs and intrinsic activity. Accordingly, pyramidal cells in human association areas show more elaborate synaptic architecture with complex connections, as compared to those in other cortical regions in humans and non-human primates [40, 50, 51].

The fundamental link between the level of neuronal activity and the rate of metabolism with production of toxic by-products is also in agreement with early-onset neurodegeneration and atrophy in association cortex, given the reliance of neurons on aerobic metabolism, with

related risks for oxidative damage [52, 53]. Accordingly, the decrease in glucose metabolism (hypo-metabolism) revealed by numerous neuroimaging studies has been reported from the early stage of AD, with affected cortical areas faithfully overlapping with the most active cortical regions [49, 54, 55]. Moreover, it was shown that the association circuits with above-average activity maintain large number of juvenile neurons, displaying higher structural plasticity with incomplete myelination [2, 56-58]. The latter is expected to contribute to greater energy demands with higher risks for oxidative stress and toxicity. Indeed, during development, parts of the prefrontal cortex and parietal association areas display the slowest myelination, with a large fraction of axons maintained in a non-myelinated state in adulthood. The combination of higher activity levels of juvenile neurons with low levels of myelination, hence, maintain the energy expenditure and associated risk of oxidative damage at an above average level [58]. Also, the high concentration of iron in immature oligodendrocytes, which is released upon their damage, would promote the Aβ oligomerization with plaque formation.

Arendt and co-workers proposed that the greater vulnerability of association cortex to AD could also be contributed by the extra rounds of division of neuronal precursors supplying neurons to these regions, with related genetic aberrations [7]. Although general mechanisms of cortical development in mammals are relatively conserved, major variations in cortical size in different linages implies considerable evolutionary adjustments in cell proliferation programs, resulting in the differential supply of neurons. The expanding cortex, thus, requires a supply of extra neurons produced via additional mitotic rounds [59-62]. Generated by asymmetric division, post-mitotic neurons migrate out of the ventricular area, leaving behind dividing progenitors. Analysis of the kinetics of cell division in monkeys and murine models [59, 60] showed that in macaques, the period during which progenitor cells proliferate is 10 times longer than in mice. The extended cell division accounts for the expansion of the cortical sheet, including in primates. Unlike progenitor cells in the ventricular zone of mice undergoing ~11

rounds of division, in macaque, progenitors of cortical neurons divide at least 28 rounds, with these numbers most likely even higher in humans [59, 60, 62-64]. Additional mitotic cycles of progenitors, hence, increases the exposure of newly made neurons to harmful exogenous and endogenous factors, resulting in genetic aberrations, which accumulate in 'sibling' cells derived from the same progenitor, enhancing the rate of molecular errors and exposure to neurodegeneration.

While supported by strong experimental data, the principal shortfall of discussed models is that they attribute the cause of selective susceptibility of association cortex to AD exclusively to cortical processes, disregarding subcortical effects. Also, none of the models explains the early onset ACh deficit with loss of cholinergic innervations - one of the best recognized characteristic of the disease. Finally, all models leave unattended the potential contribution of reduced functional reserve of the BF cholinergic system, due to disproportionate expansion of cortical projection fields.

Integrated Evolution of the Human Brain and AD

There has been a standing debate as to whether the cephalization process in mammals has gone through a mosaic reorganization of selected brain structures or upgrades and restructuring occurred as an integral part of a holistic process [14]. Despite dramatic expansion of association areas in mammalians brain evolution, comparative anatomical evidence infers these changes as part of a broader process [10, 12, 14]. Neuro-anatomical analysis with connectome studies have shown that as the size of the forebrain has increased, largely due to the growth of frontal, occipital, and parietal association areas, other connected structures underwent considerable reorganization [12, 14]. In primates, for instance, the enlargement of the neocortex was paralleled with upgrades in old cortical structures such as the hippocampus and particularly the CA2 and subicular regions with associated entorhinal area [65, 66]. Similar reorganisations

occurred in subcortical formations, including BF cholinergic nuclei, which are known to play a key role in modulating functions and plasticity of the association fields affected most severely by AD [12, 16, 17, 67-70]. In primates and humans, changes in the size and complexity of the medial septum and nucleus basalis Meynert (NBM) show a clear parallel with upgrades of the cerebral cortex [12, 17]. This trend is evident from the relatively early stages of mammalian evolution. In insectivores with the rudimentary cortex, the cholinergic BF is not discernible. In rodents, the cholinergic BF nuclei can be readily distinguished, although they remain somewhat underdeveloped and incompletely demarcated from the adjacent globus pallidus [71, 72]. In macaques and in higher primates, the cholinergic BF is well developed and shows features of a high compartmentalization. In humans, this evolutionary trend leads to condensation of BF cholinergic cells in elaborate nuclei, with NBM reaching its highest organization, comprised of densely packed neurons readily discernible from the overlying globus pallidus [17]. The result is the human NBM - the sole source of cortical cholinergic innervations comprising of ~200 000 neurons within each hemisphere that project their axons free of long collaterals to the cerebral cortex, innervating specific fields [73, 74].

As already noted, the upgrades of BF cholinergic system was far modest as compared to the cortical expansion (Figure 3). Indeed, the radical expansion of the cerebral cortex in humans resulted in a structure ~5000 times larger than that in mice, ~1400 times than that in rats, and ~4 times than that of our closest relative chimpanzee. For comparison, the increase of the number of BF cholinergic cells in humans was only ~100-150 times as compared to mice and rats, respectively, and less than ~40% as compared to chimpanzee [15, 18-21]. Notably, the cortical expansion in primates and humans was associated with reinforcement of cholinergic innervations, with density of cholinergic axons in humans ~4-6 times higher than that in rat and mouse, and ~10-15% higher than that in chimpanzee [15, 21]. In the absence of cortical cholinergic neurons in humans, the disproportionate enlargement of the associative fields with

increasing cholinergic innervations infers a major elaboration of cholinergic axons [18]. Given that the increase in axon size comes with considerable neurobiological challenges [75, 76], it is reasonable to think that the most recent upgrades of basalo-cortical cholinergic projections with cortical expansion might have contributed towards the selective vulnerability of human brain to AD. Indeed, larger axons present major cellular expenditure and maintenance load, as well as challenges for transport of trophic factors and metabolites [77, 78].

In light of all mentioned above, the early-onset acetylcholine decline in AD cortex followed by depletion of cholinergic innervations might present a knock-on effect of unbalanced evolutionary expansion and upgrades of cholinergic BF and projection association fields. Of note, the degeneration of cholinergic axons in the cortex adheres to a considerable anatomical specificity, with a selection of association areas showing stronger depletion of cholinergic axons, while the motor and anterior cingulate cortex, and sensory areas remain relatively intact [40, 67]. In functional brain imaging studies, there is significant overlap between the DMN and areas undergoing extensive depletion of cortical cholinergic innervations during AD, with ~45-85% of ChAT-positive fibre degeneration reported in temporal, prefrontal, posterior parietal, and orbitofrontal cortices and cingulated gyrus, whereas cholinergic inputs to primary sensory and motor subsystems staying relatively unaffected (5% -15% loss of ChAT-positive axons) [79]. While the extent of amyloid plaque load does not directly correlate with the absolute amount of degenerated cholinergic axons, it correlates significantly with the overall number of lost cholinergic fibres [80]. Importantly, the regional density of residual cholinergic axons in AD seems to reflect differences in premorbid levels of cholinergic innervations, with the most severely affected cortical regions i.e. inferior, medial, and superior temporal association areas appearing almost completely denuded of cholinergic innervations. In contrast, structures with a higher premorbid density of cholinergic innervations retain higher levels of residual fibres [81]. As discussed below, along with extra metabolic and

functional burden, expansion of cholinergic axons with extended innervation fields entail considerable homeostatic consignments related to regulation of APP processing with Aβ production, as well as control of MAP tau phosphorylation and Aβ clearance [77, 78].

The homeostatic hypothesis of the cholinergic system and AD

While supported by a considerable body of experimental evidence, the principal limitation of all models for selective vulnerability of association cortex to AD is that they assign the cause of cortical pathology to intrinsic cortical processes. Also, none of the models explains the age-dependence of the onset of sporadic AD and degeneration of cholinergic neurons [79, 82]. As noted, there is considerable evidence showing an overlap between the cortical amyloid pathology and loss of cholinergic axons [79]. With the progression of the disease, the degenerative process propagates back to onto the source neurons in the BF, and especially in the NBM [83]. It is important to note that neither deposition of Aβ nor the cognitive decline in AD can be solely attributed to the depletion of cortical ACh, as a comparable decrease in cortical ACh activity in subjects with olivo-ponto-cerebellar atrophy reveals neither accumulation of Aβ plaques nor AD-like cognitive deficit [84, 85]. These findings together with overtly intact striatal and brainstem cholinergic systems in the AD brain [86, 87] suggest unique neurobiological characteristics of the BF cholinergic system, which extend its role beyond supply of cortical ACh and neuromodulation. In agreement with this notion, Mesulam proposed that the selective loss of cortical cholinergic innervations in unlikely to be related with cholinergic mechanisms only but may reflect the unique anatomical position and connectivity of the NBM [88].

We and others have shown that in addition to widely appreciated modulator functions, cortical cholinergic innervations might play a key role in the homeostatic regulation of APP processing and clearance of Aβ [89, 90]. As reported by Nitsch et al. [91], activation of M1 and

M3 muscarinic AChR suppresses the amyloidogenic processing of APP with Aβ production. This finding was replicated in neuronal cultures, brain slices, and *in vivo*, with anti-Aβ effects of M1 receptors being attributed to activation of protein kinase C a/ε and downregulation of α-secretase ADAM17 activity (Fisher, 2012). We have shown the significance of cholinergic BF neurons in internalization of Aβ followed by its degradation, which might be of relevance to the maintenance of physiological levels of Aβ in cortical projection fields [77, 78]. Such unique homeostatic role is attributed to cholinergic axons enriched with the p75 neurotrophin receptor (NTR), which is known to bind and internalize Aβ mono- and oligomeric [92], and degrade in lysosomes [77] (Figure 4). In agreement with the homeostatic role of basalo-cortical projections, selective ablation of BF cholinergic neurons or deletion of p75NTR accelerates the deposition of Aβ plaques and associated histopathological changes in the cortex and hippocampus in AD murine models [93-96]. These findings accord with observations in rabbits, which showed progressive accumulation of perivascular Aβ after targeted lesion of BF cholinergic neurons with immune-toxins [97]. The absence of axonal dystrophies in Thy1-hAPP-London/Swe-p75NTR$^{-/-}$ mice, which contrasts with widespread axonal pathology and loss of BF cholinergic cells in Thy1-hAPP-London/Swe-p75NTR$^{+/+}$ genotype [98] supports the important role of p75NTR in mediating neurotoxic effects of Aβ in BF cholinergic neurons. It also suggests that the role of cholinergic inputs to the hippocampus and cortex extend beyond supply of ACh with neuromodulator effects. Such dual functionality of cholinergic innervations accords with results of human autopsies, which revealed a stronger decline in the number of p75NTR expressing BF cholinergic cells in plaque laden AD brains [99], while the loss of p75NTR enhances cholinergic innervation of the cerebral cortex and slows down amyloid pathology with depositions of plaques [100].

With above average activity and higher propensity of Aβ load in the associative cortex, degeneration of p75NTR enriched cholinergic innervations is expected to further exacerbate

the progression of the amyloid pathology. Of note, the increase of Aβ level would overwhelm the proteolytic machinery of cholinergic neurons by internalized Aβ, aggravating the toxicity and lysosomal deficiency, leading to metabolic collapse neuronal degeneration. Unlike double transgenic APPSwe/PS1dE9 mice in which selective ablation of BF cholinergic cells facilitates Aβ load with cognitive decline and memory deficit [95], APPSwe/PS1dE9/p75NTR$^{-/-}$ triple transgenic mice reveal no cognitive decline and memory deficit, despite extensive amyloid pathology in the hippocampus and cerebral cortex [96]. Such dissociation of cognitive and homeostatic functions of the BF cholinergic system, thus, accords with dual, ACh- and p75NTR-dependent functionality, and agrees with the results of mentioned above clinical studies of olivo-ponto-cerebellar atrophies [84, 85]. Contrasting to AD where a widespread loss of BF cholinergic axons and synapses are associated with amyloid deposits and tau pathology in the cortex, degeneration of cholinergic tegmental-pontine neurons, while also accompanied with depletion of cortical ACh, is not accompanied with amyloid pathology.

In addition to well-known modulator functions, thus, BF cholinergic projections seem to play an essential homeostatic role in the clearance of Aβ from projection fields, mediated via p75NTR mechanism. With the evolutionary expansion of the association cortex and elaboration of basalo-cortical innervations, cholinergic neurons, thus came under a major strain to maintain their dual, neuromodulator and homeostatic role. Discussed above examples of the dissociation between the cognitive and homeostatic mechanisms of the BF cholinergic neurons is in line with their dual functionality, which contributes towards reduced functional reserve and vulnerability to AD. Whereas the cognitive and mnemonic functions depend on the modulation of the neuronal activity and plasticity by ACh [70, 101], the homeostatic and neuroprotective role involves the regulation of APP metabolism as well as p75NTR-mediated sequestration of Aβ peptide [78, 90], keeping in check the physiological level and activity of Aβ.

Closing remarks

Over the past four million years of human evolution, the brain of our ancestor quadrupled in size, resulting in the brain of the *Homo sapiens*. Such dramatic enlargement of the organ of thought with functional upgrades has been key to the transition of the *Homo* from scavenger to hunter-gatherer, which led to a radical dietary and socio-behavioural change and adaptations. The restructuring of anatomical and functional landscapes of the human brain were accounted for largely by the expansion of the frontal, occipital, and parietal association fields, which evolved to meet the emerging needs and challenges of dynamic and complex organization of the society, leading to a remarkable extension of life expectancy (Figure 1). Even under the high mortality experienced by hunters-foragers, human life expectancy at birth (LE_0) was twice that of chimpanzees [102], which doubled further during the recent industrialization, causing a major extension in older ages with related conditions and diseases.

As it emerges from this review, major adaptive changes in the brain with extension of LE_0 came with considerable costs, conforming to J. H. Jackson's 'doctrine' that evolutionary upgrades of the human nervous system might conceal neurological and psychiatric conditions, which are human-specific. Indeed, the expansion of cortical association fields with reinforcement of cholinergic innervations combined with prolongation of the LE_0 has placed BF cholinergic system under a major homeostatic and metabolic strain, which possibly contributed to the higher incidents of age-related onset of amyloid pathology with downstream degenerative changes (Figure 5). More specifically, the out-of-proportion enlargement of innervation fields of individual cholinergic neurons and extension of the LE_0 lowered the functional reserve of BF cholinergic system and enhanced the homeostatic assignments in terms of Aβ clearance and regulation of APP metabolism, overwhelming their proteolytic and metabolic machinery, which lead to exacerbation of amyloid pathology and the onset of the AD with functional impairments and neurodegeneration. In conclusion, while bearing an array of

adaptive benefits and protective effects, empowering progressive mental facilities, the disproportionate growth of the human cerebral cortex came with some unfavourable effects, with major implication for the neurobiology of aging and global health.

Acknowledgements

This study was supported by the project Sustainability for the National Institute of Mental Health, under grant number LO1611 (PI – CH), with financial support from the Ministry of Education, Youth and Sports of the Czech Republic under the NPU I program. Dr. V. B. O'Leary is supported by the Charles University research program PROGRES Q35 – Neurology.

References

[1] J.H. Jackson, The Croonian Lectures on Evolution and Dissolution of the Nervous System, Br Med J, 1 (1884) 591-593.

[2] E. Bufill, R. Blesa, J. Augusti, Alzheimer's disease: an evolutionary approach, J Anthropol Sci, 91 (2013) 135-157.

[3] M.P. van den Heuvel, L.H. Scholtens, S.C. de Lange, R. Pijnenburg, W. Cahn, N.E.M. van Haren, I.E. Sommer, M. Bozzali, K. Koch, M.P. Boks, J. Repple, M. Pievani, L. Li, T.M. Preuss, J.K. Rilling, Evolutionary modifications in human brain connectivity associated with schizophrenia, Brain, 142 (2019) 3991-4002.

[4] L.C. Walker, M. Jucker, The Exceptional Vulnerability of Humans to Alzheimer's Disease, Trends Mol Med, 23 (2017) 534-545.

[5] 2020 Alzheimer's disease facts and figures, Alzheimers Dement, DOI 10.1002/alz.12068(2020).

[6] G.B.D.N. Collaborators, Global, regional, and national burden of neurological disorders, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016, Lancet Neurol, 18 (2019) 459-480.

[7] T. Arendt, J. Stieler, U. Ueberham, Is sporadic Alzheimer's disease a developmental disorder?, J Neurochem, 143 (2017) 396-408.

[8] A.M. Fjell, I.K. Amlien, M.H. Sneve, H. Grydeland, C.K. Tamnes, T.A. Chaplin, M.G. Rosa, K.B. Walhovd, The Roots of Alzheimer's Disease: Are High-Expanding Cortical Areas Preferentially Targeted?dagger, Cereb Cortex, 25 (2015) 2556-2565.

[9] F.M. Krienen, R.L. Buckner, Human Association Cortex: Expanded, Untethered, Neotenous, and Plastic, in: J.H. Kaas (Ed.) Evolutionary Neuroscience, Academic Press2020, pp. 845-860.

[10] M.A. Hofman, Evolution of the human brain: when bigger is better, Front Neuroanat, 8 (2014) 15.

[11] M.A. Hofman, On the nature and evolution of the human mind, Prog Brain Res, 250 (2019) 251-283.

[12] S.I. Rapoport, Integrated phylogeny of the primate brain, with special reference to humans and their diseases, Brain Res Brain Res Rev, 15 (1990) 267-294.

[13] J.H. Kaas, The origin and evolution of neocortex: From early mammals to modern humans, Prog Brain Res, 250 (2019) 61-81.

[14] G.F. Striedter, Principles of brain evolution, Sinauer Associates, Sunderland, Mass., 2005.

[15] M.A. Raghanti, G. Simic, S. Watson, C.D. Stimpson, P.R. Hof, C.C. Sherwood, Comparative analysis of the nucleus basalis of Meynert among primates, Neuroscience, 184 (2011) 1-15.

[16] K. Semba, Phylogenetic and ontogenetic aspects of the basal forebrain cholinergic neurons and their innervation of the cerebral cortex, Prog Brain Res, 145 (2004) 3-43.

[17] J.D. Gorry, Studies on the Comparative Anatomy of the Ganglion Basale of Meynert, Acta Anat (Basel), 55 (1963) 51-104.

[18] H. Wu, J. Williams, J. Nathans, Complete morphologies of basal forebrain cholinergic neurons in the mouse, Elife, 3 (2014) e02444.

[19] S.E. Perez, S. Dar, M.D. Ikonomovic, S.T. DeKosky, E.J. Mufson, Cholinergic forebrain degeneration in the APPswe/PS1DeltaE9 transgenic mouse, Neurobiol Dis, 28 (2007) 3-15.

[20] S. Boncristiano, M.E. Calhoun, P.H. Kelly, M. Pfeifer, L. Bondolfi, M. Stalder, A.L. Phinney, D. Abramowski, C. Sturchler-Pierrat, A. Enz, B. Sommer, M. Staufenbiel, M. Jucker, Cholinergic changes in the APP23 transgenic mouse model of cerebral amyloidosis, J Neurosci, 22 (2002) 3234-3243.

[21] R.A. Miettinen, G. Kalesnykas, E.H. Koivisto, Estimation of the total number of cholinergic neurons containing estrogen receptor-alpha in the rat basal forebrain, J Histochem Cytochem, 50 (2002) 891-902.

[22] M.A. Raghanti, C.D. Stimpson, J.L. Marcinkiewicz, J.M. Erwin, P.R. Hof, C.C. Sherwood, Cholinergic innervation of the frontal cortex: differences among humans, chimpanzees, and macaque monkeys, J Comp Neurol, 506 (2008) 409-424.

[23] S.A. Youssef, M.T. Capucchio, J.E. Rofina, J.K. Chambers, K. Uchida, H. Nakayama, E. Head, Pathology of the Aging Brain in Domestic and Laboratory Animals, and Animal Models of Human Neurodegenerative Diseases, Vet Pathol, 53 (2016) 327-348.

[24] D. Gunn-Moore, O. Kaidanovich-Beilin, M.C. Gallego Iradi, F. Gunn-Moore, S. Lovestone, Alzheimer's disease in humans and other animals: A consequence of postreproductive life span and longevity rather than aging, Alzheimers Dement, 14 (2018) 195-204.

[25] S.E. Perez, M.A. Raghanti, P.R. Hof, L. Kramer, M.D. Ikonomovic, P.N. Lacor, J.M. Erwin, C.C. Sherwood, E.J. Mufson, Alzheimer's disease pathology in the neocortex and

hippocampus of the western lowland gorilla (Gorilla gorilla gorilla), J Comp Neurol, 521 (2013) 4318-4338.

[26] S.E. Perez, C.C. Sherwood, M.R. Cranfield, J.M. Erwin, A. Mudakikwa, P.R. Hof, E.J. Mufson, Early Alzheimer's disease-type pathology in the frontal cortex of wild mountain gorillas (Gorilla beringei beringei), Neurobiol Aging, 39 (2016) 195-201.

[27] R.F. Rosen, A.S. Farberg, M. Gearing, J. Dooyema, P.M. Long, D.C. Anderson, J. Davis-Turak, G. Coppola, D.H. Geschwind, J.F. Pare, T.Q. Duong, W.D. Hopkins, T.M. Preuss, L.C. Walker, Tauopathy with paired helical filaments in an aged chimpanzee, J Comp Neurol, 509 (2008) 259-270.

[28] R.F. Rosen, Y. Tomidokoro, A.S. Farberg, J. Dooyema, B. Ciliax, T.M. Preuss, T.A. Neubert, J.A. Ghiso, H. LeVine, 3rd, L.C. Walker, Comparative pathobiology of beta-amyloid and the unique susceptibility of humans to Alzheimer's disease, Neurobiol Aging, 44 (2016) 185-196.

[29] S. Prpar Mihevc, G. Majdic, Canine Cognitive Dysfunction and Alzheimer's Disease - Two Facets of the Same Disease?, Front Neurosci, 13 (2019) 604.

[30] D. Insua, A. Corredoira, A. Gonzalez-Martinez, M.L. Suarez, G. Santamarina, M. Sarasa, P. Pesini, Expression of p75(NTR), a marker for basal forebrain cholinergic neurons, in young and aged dogs with or without cognitive dysfunction syndrome, J Alzheimers Dis, 28 (2012) 291-296.

[31] M.K. Edler, E.L. Munger, R.S. Meindl, W.D. Hopkins, J.J. Ely, J.M. Erwin, E.J. Mufson, P.R. Hof, C.C. Sherwood, M.A. Raghanti, Neuron loss associated with age but not Alzheimer's disease pathology in the chimpanzee brain, Philos Trans R Soc Lond B Biol Sci, 375 (2020) 20190619.

[32] M.K. Edler, C.C. Sherwood, R.S. Meindl, W.D. Hopkins, J.J. Ely, J.M. Erwin, E.J. Mufson, P.R. Hof, M.A. Raghanti, Aged chimpanzees exhibit pathologic hallmarks of Alzheimer's disease, Neurobiol Aging, 59 (2017) 107-120.

[33] M.K. Edler, C.C. Sherwood, R.S. Meindl, E.L. Munger, W.D. Hopkins, J.J. Ely, J.M. Erwin, D.P. Perl, E.J. Mufson, P.R. Hof, M.A. Raghanti, Microglia changes associated to Alzheimer's disease pathology in aged chimpanzees, J Comp Neurol, 526 (2018) 2921-2936.

[34] E.L. Munger, M.K. Edler, W.D. Hopkins, J.J. Ely, J.M. Erwin, D.P. Perl, E.J. Mufson, P.R. Hof, C.C. Sherwood, M.A. Raghanti, Astrocytic changes with aging and Alzheimer's disease-type pathology in chimpanzees, J Comp Neurol, 527 (2019) 1179-1195.

[35] S.I. Rapoport, Hypothesis: Alzheimer's disease is a phylogenetic disease, Med Hypotheses, 29 (1989) 147-150.

[36] S.V. Ovsepian, V.B. O'Leary, Neuronal activity and amyloid plaque pathology: an update, J Alzheimers Dis, 49 (2016) 13-19.

[37] H. Braak, E. Braak, Neuropathological staging of Alzheimer-related changes., Acta Neuropathol, 82 (1991).

[38] H. Braak, E. Braak, Staging of Alzheimer-related cortical destruction, Int Psychogeriatr, 9 Suppl 1 (1997) 257-261; discussion 269-272.

[39] D.R. Thal, U. Rub, M. Orantes, H. Braak, Phases of A beta-deposition in the human brain and its relevance for the development of AD, Neurology, 58 (2002) 1791-1800.

[40] M.M. Mesulam, Aging, Alzheimer's disease, and dementia: clinical and neurological perspectives, Oxfor University Press, Oxford, 2000.

[41] R.L. Buckner, The serendipitous discovery of the brain's default network, Neuroimage, 62 (2012) 1137-1145.

[42] M.E. Raichle, The brain's default mode network, Annu Rev Neurosci, 38 (2015) 433-447.

[43] W. Jagust, Vulnerable neural systems and the borderland of brain aging and neurodegeneration, Neuron, 77 (2013) 219-234.

[44] W.J. Jagust, E.C. Mormino, Lifespan brain activity, beta-amyloid, and Alzheimer's disease, Trends Cogn Sci, 15 (2011) 520-526.

[45] S.V. Ovsepian, V.B. O'Leary, L. Zaborszky, V. Ntziachristos, J.O. Dolly, Synaptic vesicle cycle and amyloid beta: Biting the hand that feeds, Alzheimers Dement, 14 (2018) 502-513.

[46] K. Yamamoto, Z.I. Tanei, T. Hashimoto, T. Wakabayashi, H. Okuno, Y. Naka, O. Yizhar, L.E. Fenno, M. Fukayama, H. Bito, J.R. Cirrito, D.M. Holtzman, K. Deisseroth, T. Iwatsubo, Chronic optogenetic activation augments abeta pathology in a mouse model of Alzheimer disease, Cell Rep, 11 (2015) 859-865.

[47] J.R. Cirrito, K.A. Yamada, M.B. Finn, R.S. Sloviter, K.R. Bales, P.C. May, D.D. Schoepp, S.M. Paul, S. Mennerick, D.M. Holtzman, Synaptic activity regulates interstitial fluid amyloid-beta levels in vivo, Neuron, 48 (2005) 913-922.

[48] F. Kamenetz, T. Tomita, H. Hsieh, G. Seabrook, D. Borchelt, T. Iwatsubo, S. Sisodia, R. Malinow, APP processing and synaptic function, Neuron, 37 (2003) 925-937.

[49] R.L. Buckner, J. Sepulcre, T. Talukdar, F.M. Krienen, H. Liu, T. Hedden, J.R. Andrews-Hanna, R.A. Sperling, K.A. Johnson, Cortical hubs revealed by intrinsic functional connectivity: mapping, assessment of stability, and relation to Alzheimer's disease, J Neurosci, 29 (2009) 1860-1873.

[50] G.N. Elston, R. Benavides-Piccione, J. DeFelipe, The pyramidal cell in cognition: a comparative study in human and monkey, J Neurosci, 21 (2001) RC163.

[51] J. DeFelipe, I. Farinas, The pyramidal neuron of the cerebral cortex: morphological and chemical characteristics of the synaptic inputs, Prog Neurobiol, 39 (1992) 563-607.

[52] G. Perry, M.A. Taddeo, A. Nunomura, X. Zhu, T. Zenteno-Savin, K.L. Drew, S. Shimohama, J. Avila, R.J. Castellani, M.A. Smith, Comparative biology and pathology of

oxidative stress in Alzheimer and other neurodegenerative diseases: beyond damage and response, Comp Biochem Physiol C Toxicol Pharmacol, 133 (2002) 507-513.

[53] E. Tonnies, E. Trushina, Oxidative Stress, Synaptic Dysfunction, and Alzheimer's Disease, J Alzheimers Dis, 57 (2017) 1105-1121.

[54] M.J. Grothe, S.J. Teipel, I. Alzheimer's Disease Neuroimaging, Spatial patterns of atrophy, hypometabolism, and amyloid deposition in Alzheimer's disease correspond to dissociable functional brain networks, Hum Brain Mapp, 37 (2016) 35-53.

[55] R.L. Buckner, A.Z. Snyder, B.J. Shannon, G. LaRossa, R. Sachs, A.F. Fotenos, Y.I. Sheline, W.E. Klunk, C.A. Mathis, J.C. Morris, M.A. Mintun, Molecular, structural, and functional characterization of Alzheimer's disease: evidence for a relationship between default activity, amyloid, and memory, J Neurosci, 25 (2005) 7709-7717.

[56] G. Bartzokis, Age-related myelin breakdown: a developmental model of cognitive decline and Alzheimer's disease, Neurobiol Aging, 25 (2004) 5-18; author reply 49-62.

[57] G. Bartzokis, J.L. Cummings, D. Sultzer, V.W. Henderson, K.H. Nuechterlein, J. Mintz, White matter structural integrity in healthy aging adults and patients with Alzheimer disease: a magnetic resonance imaging study, Arch Neurol, 60 (2003) 393-398.

[58] G. Bartzokis, P.H. Lu, J. Mintz, Human brain myelination and amyloid beta deposition in Alzheimer's disease, Alzheimers Dement, 3 (2007) 122-125.

[59] D.R. Kornack, Neurogenesis and the evolution of cortical diversity: mode, tempo, and partitioning during development and persistence in adulthood, Brain Behav Evol, 55 (2000) 336-344.

[60] D.R. Kornack, P. Rakic, Changes in cell-cycle kinetics during the development and evolution of primate neocortex, Proc Natl Acad Sci U S A, 95 (1998) 1242-1246.

[61] P. Rakic, Specification of cerebral cortical areas, Science, 241 (1988) 170-176.

[62] P. Rakic, Radial unit hypothesis of neocortical expansion, Novartis Found Symp, 228 (2000) 30-42; discussion 42-52.

[63] T. Takahashi, R.S. Nowakowski, V.S. Caviness, Jr., The cell cycle of the pseudostratified ventricular epithelium of the embryonic murine cerebral wall, J Neurosci, 15 (1995) 6046-6057.

[64] R.S. Hill, C.A. Walsh, Molecular insights into human brain evolution, Nature, 437 (2005) 64-67.

[65] A.G. Herzog, G.W. Van Hoesen, Temporal neocortical afferent connections to the amygdala in the rhesus monkey, Brain Res, 115 (1976) 57-69.

[66] H. Stephan, O.J. Andy, The allocortex in primates, Appleton-Century-Crofts, New York, 1970.

[67] C. Geula, M.M. Mesulam, Cortical cholinergic fibers in aging and Alzheimer's disease: a morphometric study, Neuroscience, 33 (1989) 469-481.

[68] S.V. Ovsepian, Enhancement of the synchronized firing of CA1 pyramidal cells by medial septum preconditioning: time-dependent involvement of muscarinic cholinoceptors and GABAB receptors, Neurosci Lett, 393 (2006) 1-6.

[69] S.V. Ovsepian, Differential cholinergic modulation of synaptic encoding and gain control mechanisms in rat hippocampus, Neurosci Res, 61 (2008) 92-98.

[70] S.V. Ovsepian, R. Anwyl, M.J. Rowan, Endogenous acetylcholine lowers the threshold for long-term potentiation induction in the CA1 area through muscarinic receptor activation: in vivo study, Eur J Neurosci, 20 (2004) 1267-1275.

[71] H. Braak, Pigment architecture of the human telencephalic cortex, Cell and Tissue Research, 190 (1978) 509–523.

[72] M.M. Mesulam, E.J. Mufson, A.I. Levey, B.H. Wainer, Cholinergic innervation of cortex by the basal forebrain: cytochemistry and cortical connections of the septal area, diagonal band

nuclei, nucleus basalis (substantia innominata), and hypothalamus in the rhesus monkey, J Comp Neurol, 214 (1983) 170-197.

[73] R.T. Richardson, M.R. DeLong, A reappraisal of the functions of the nucleus basalis of Meynert, Trends Neurosci, 11 (1988) 264-267.

[74] T. Arendt, V. Bigl, A. Tennstedt, A. Arendt, Neuronal loss in different parts of the nucleus basalis is related to neuritic plaque formation in cortical target areas in Alzheimer's disease, Neuroscience, 14 (1985) 1-14.

[75] J.B. Cavanagh, The problems of neurons with long axons, Lancet, 1 (1984) 1284-1287.

[76] L. Ferraiuolo, J. Kirby, A.J. Grierson, M. Sendtner, P.J. Shaw, Molecular pathways of motor neuron injury in amyotrophic lateral sclerosis, Nat Rev Neurol, 7 (2011) 616-630.

[77] S.V. Ovsepian, I. Antyborzec, V.B. O'Leary, L. Zaborszky, J. Herms, J. Oliver Dolly, Neurotrophin receptor p75 mediates the uptake of the amyloid beta (Abeta) peptide, guiding it to lysosomes for degradation in basal forebrain cholinergic neurons, Brain Struct Funct, 219 (2014) 1527-1541.

[78] S.V. Ovsepian, J. Herms, Cholinergic neurons-keeping check on amyloid beta in the cerebral cortex, Front Cell Neurosci, 7 (2013) 252.

[79] M. Mesulam, The cholinergic lesion of Alzheimer's disease: pivotal factor or side show?, Learn Mem, 11 (2004) 43-49.

[80] C. Geula, M.M. Mesulam, D.M. Saroff, C.K. Wu, Relationship between plaques, tangles, and loss of cortical cholinergic fibers in Alzheimer disease, J Neuropathol Exp Neurol, 57 (1998) 63-75.

[81] C. Geula, B.D. Greenberg, M.M. Mesulam, Cholinesterase activity in the plaques, tangles and angiopathy of Alzheimer's disease does not emanate from amyloid, Brain Res, 644 (1994) 327-330.

[82] R. Schliebs, T. Arendt, The cholinergic system in aging and neuronal degeneration, Behav Brain Res, 221 (2011) 555-563.

[83] M.M. Mesulam, C. Geula, Nucleus basalis (Ch4) and cortical cholinergic innervation in the human brain: observations based on the distribution of acetylcholinesterase and choline acetyltransferase, J Comp Neurol, 275 (1988) 216-240.

[84] S.J. Kish, Y. Robitaille, M. el-Awar, J.H. Deck, J. Simmons, L. Schut, L.J. Chang, L. DiStefano, M. Freedman, Non-Alzheimer-type pattern of brain cholineacetyltransferase reduction in dominantly inherited olivopontocerebellar atrophy, Ann Neurol, 26 (1989) 362-367.

[85] Y. Robitaille, L. Schut, S.J. Kish, Structural and immunocytochemical features of olivopontocerebellar atrophy caused by the spinocerebellar ataxia type 1 (SCA-1) mutation define a unique phenotype, Acta Neuropathol, 90 (1995) 572-581.

[86] M. McKinney, M.C. Jacksonville, Brain cholinergic vulnerability: relevance to behavior and disease, Biochem Pharmacol, 70 (2005) 1115-1124.

[87] N.J. Woolf, R.W. Jacobs, L.L. Butcher, The pontomesencephalotegmental cholinergic system does not degenerate in Alzheimer's disease, Neurosci Lett, 96 (1989) 277-282.

[88] M. Mesulam, Cholinergic aspects of aging and Alzheimer's disease, Biol Psychiatry, 71 (2012) 760-761.

[89] A. Fisher, Cholinergic modulation of amyloid precursor protein processing with emphasis on M1 muscarinic receptor: perspectives and challenges in treatment of Alzheimer's disease, J Neurochem, 120 Suppl 1 (2012) 22-33.

[90] S.V. Ovsepian, V.B. O'Leary, L. Zaborszky, Cholinergic Mechanisms in the Cerebral Cortex: Beyond Synaptic Transmission, Neuroscientist, 22 (2016) 238-251.

[91] R.M. Nitsch, B.E. Slack, R.J. Wurtman, J.H. Growdon, Release of Alzheimer amyloid precursor derivatives stimulated by activation of muscarinic acetylcholine receptors, Science, 258 (1992) 304-307.

[92] M. Yaar, S. Zhai, P.F. Pilch, S.M. Doyle, P.B. Eisenhauer, R.E. Fine, B.A. Gilchrest, Binding of beta-amyloid to the p75 neurotrophin receptor induces apoptosis. A possible mechanism for Alzheimer's disease, J Clin Invest, 100 (1997) 2333-2340.

[93] F.J. Gil-Bea, G. Gerenu, B. Aisa, L.P. Kirazov, R. Schliebs, M.J. Ramirez, Cholinergic denervation exacerbates amyloid pathology and induces hippocampal atrophy in Tg2576 mice, Neurobiol Dis, 48 (2012) 439-446.

[94] W. Hartig, A. Saul, J. Kacza, J. Grosche, S. Goldhammer, D. Michalski, O. Wirths, Immunolesion-induced loss of cholinergic projection neurones promotes beta-amyloidosis and tau hyperphosphorylation in the hippocampus of triple-transgenic mice, Neuropathol Appl Neurobiol, 40 (2014) 106-120.

[95] B. Laursen, A. Mork, N. Plath, U. Kristiansen, J.F. Bastlund, Cholinergic degeneration is associated with increased plaque deposition and cognitive impairment in APPswe/PS1dE9 mice, Behav Brain Res, 240 (2013) 146-152.

[96] Y.J. Wang, X. Wang, J.J. Lu, Q.X. Li, C.Y. Gao, X.H. Liu, Y. Sun, M. Yang, Y. Lim, G. Evin, J.H. Zhong, C. Masters, X.F. Zhou, p75NTR regulates Abeta deposition by increasing Abeta production but inhibiting Abeta aggregation with its extracellular domain, J Neurosci, 31 (2011) 2292-2304.

[97] A.E. Roher, Y.M. Kuo, P.E. Potter, M.R. Emmerling, R.A. Durham, D.G. Walker, L.I. Sue, W.G. Honer, T.G. Beach, Cortical cholinergic denervation elicits vascular A beta deposition, Ann N Y Acad Sci, 903 (2000) 366-373.

[98] J.K. Knowles, J. Rajadas, T.V. Nguyen, T. Yang, M.C. LeMieux, L. Vander Griend, C. Ishikawa, S.M. Massa, T. Wyss-Coray, F.M. Longo, The p75 neurotrophin receptor promotes

amyloid-beta(1-42)-induced neuritic dystrophy in vitro and in vivo, J Neurosci, 29 (2009) 10627-10637.

[99] S.E. Counts, E.J. Mufson, The role of nerve growth factor receptors in cholinergic basal forebrain degeneration in prodromal Alzheimer disease, J Neuropathol Exp Neurol, 64 (2005) 263-272.

[100] L. Qian, M.R. Milne, S. Shepheard, M.L. Rogers, R. Medeiros, E.J. Coulson, Removal of p75 Neurotrophin Receptor Expression from Cholinergic Basal Forebrain Neurons Reduces Amyloid-beta Plaque Deposition and Cognitive Impairment in Aged APP/PS1 Mice, Mol Neurobiol, 56 (2019) 4639-4652.

[101] M.E. Hasselmo, E. Barkai, Cholinergic modulation of activity-dependent synaptic plasticity in the piriform cortex and associative memory function in a network biophysical simulation, J Neurosci, 15 (1995) 6592-6604.

[102] C.E. Finch, Evolution in health and medicine Sackler colloquium: Evolution of the human lifespan and diseases of aging: roles of infection, inflammation, and nutrition, Proc Natl Acad Sci U S A, 107 Suppl 1 (2010) 1718-1724.

[103] I. Antyborzec, V.B. O'Leary, J.O. Dolly, S.V. Ovsepian, Low-Affinity Neurotrophin Receptor p75 Promotes the Transduction of Targeted Lentiviral Vectors to Cholinergic Neurons of Rat Basal Forebrain, Neurotherapeutics, 13 (2016) 859-870.

Figure Legends

Figure 1: Enlargement of the human brain capacity (A) and increase in average life expectancy of the *Homo sapiens* throughout ~ 4 million years of evolution (B).

Figure 2: Demonstration of topographical relationship between cortical regions that underwent significant expansion throughout human evolution (left) with those known as default mode networks (left middle), areas with the highest load of amyloid β peptide (right middle) and undergoing atrophy during AD (right). Adapted with permission [8, 55].

Figure 3: Brain size changes in primates and humans with relatively conserved BF cholinergic nuclei. (A) From top to bottom: illustration photos of brains of the squirrel monkey, macaque, chimpanzee, and human with outlines (dashed, red) of the human brain for better visibility of size differences. Inset histograms illustrate the relative ratio of cholinergic (CH) cell number and brain mass of squirrel monkey (rhodamine red bar), macaque (black bar), and chimpanzee (orange bar) vs. humans (all three superimposed, left bar). Brown bars on the right in all histograms show the ratio of CH cells and brain mass of humans. Note that the ratio of CH cell number and brain mass is the lowest in humans, indicating the lowest number of cholinergic neurons per innervation cortical area. Numbers in panels: blue – cholinergic cell number in NBM, green – the mass of the brain in grams. (B) Schematic of coronal brain sections containing cholinergic forebrain area (black dots, delignated by a red line) illustrating relative conservation of cholinergic nuclei from squirrel monkey to human. Ot - optic tract; ac – anterior commissure; EGP and IGP – external and internal globus pallidus; Th – thalamus; ic – internal capsule; cc – corpus callosum; C – claustrum; P – putamen; Adapted with permission [15].

Figure 4: Demonstration of selective enrichment of BF cholinergic neurons with p75NTR and mediated by this receptor internalization of Aβ peptide by cholinergic neurons with sorting to acidifying late endosomes. (A) Confocal images of rat BF cholinergic area with neurons labelled using ChAT markers specific for cholinergic neurons and IgG-192-CY3 labelling p75NTR enriched neurons. Note a high degree of colocalization. Adapted with permission [103]. (B) Cholinergic neurons in primary neuronal cultures after exposure to Alexa488 labelled Aβ and IgG-192-CY3 (left) and staining with an anti-RAB-7 antibody specific for late endosomes (right). (C) Cholinergic neurons in primary neuronal cultures after exposure to IgG-192-CY3 and core streptavidin fused heavy chain of tetanus toxin, know also to bind to p75 NTR (CS-TeTX-Hc). Courtesy of I. Antyborzec (image taken from the Ph.D. thesis).

Figure 5: Schematic illustration of the proposed sequence of events leading to sporadic AD manifested by depletion of cholinergic innervations and loss in the basal forebrain cholinergic neurons and the onset and progression of amyloid pathology with neurodegeneration in the cerebral cortex.

Figure

Click here to access/download;Figure;FIGURE1-RE1.jpg

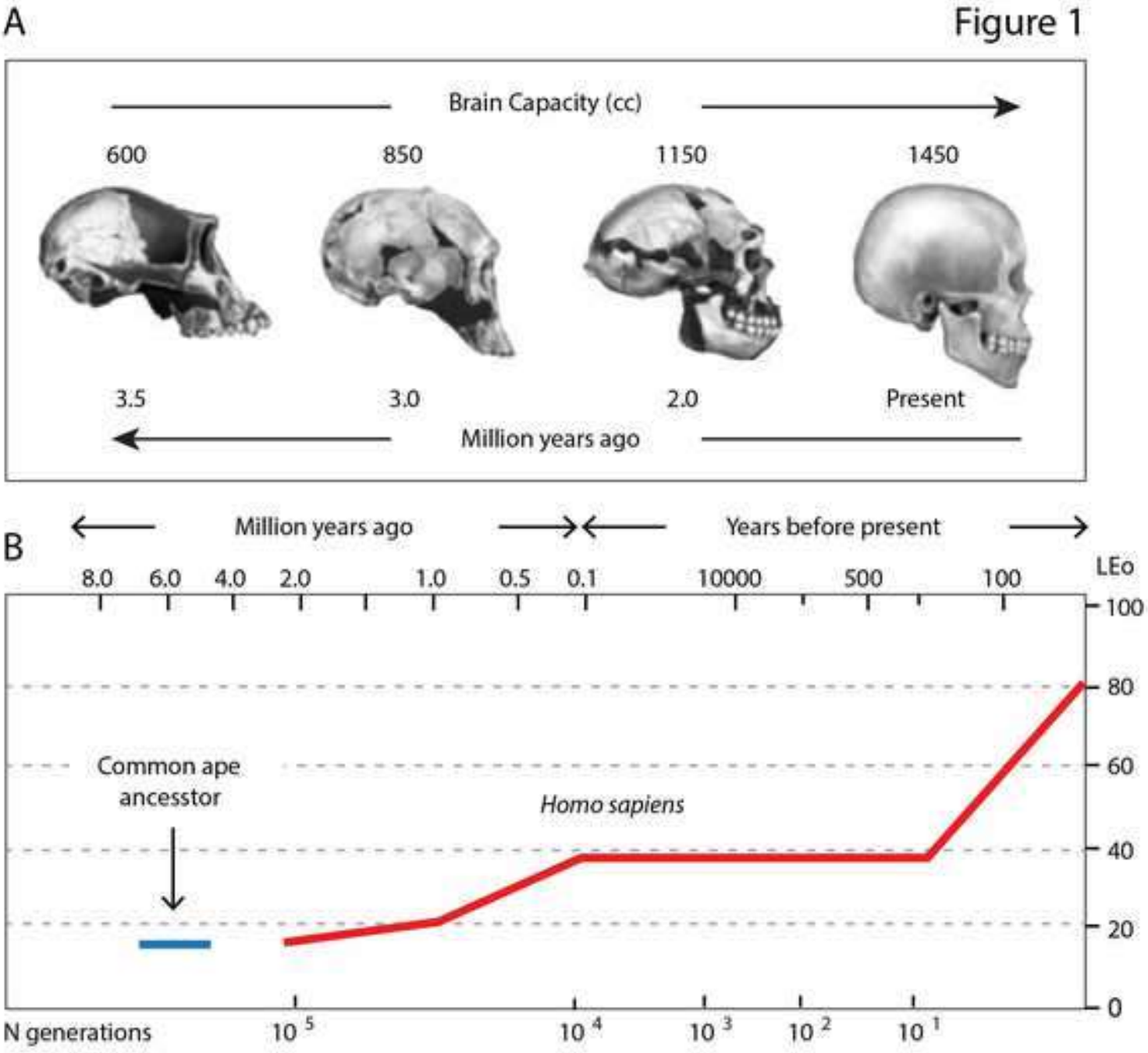
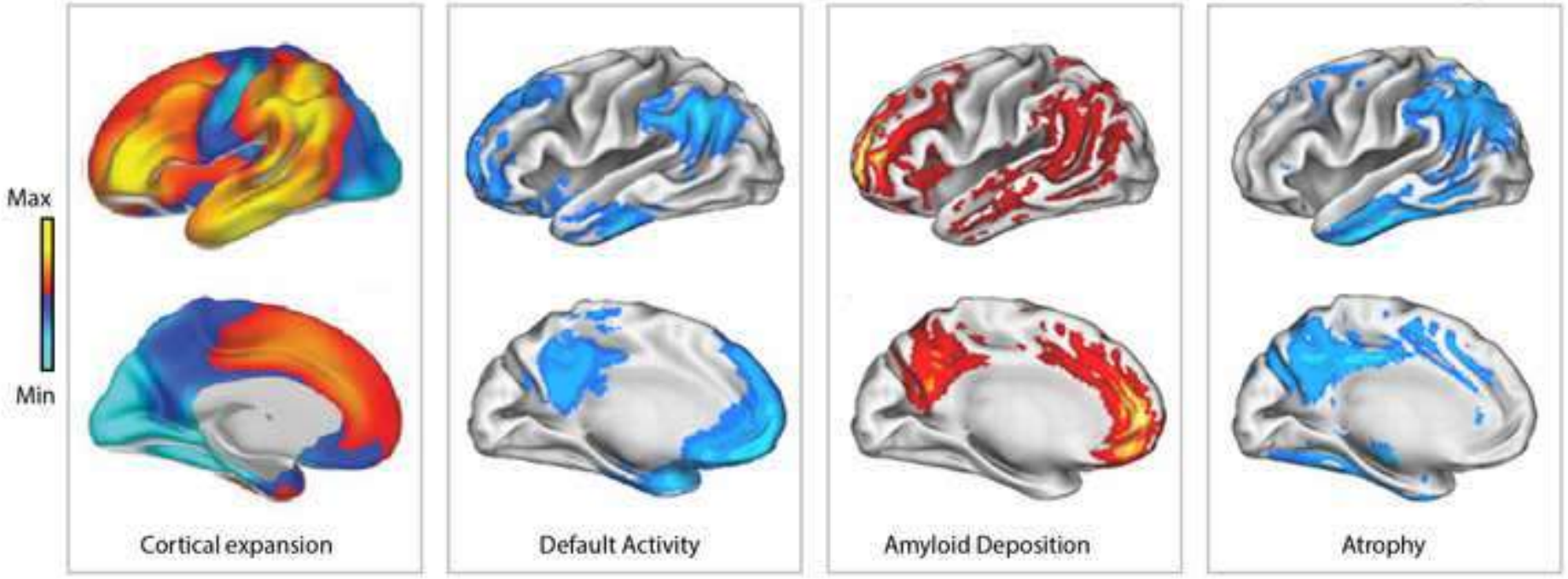
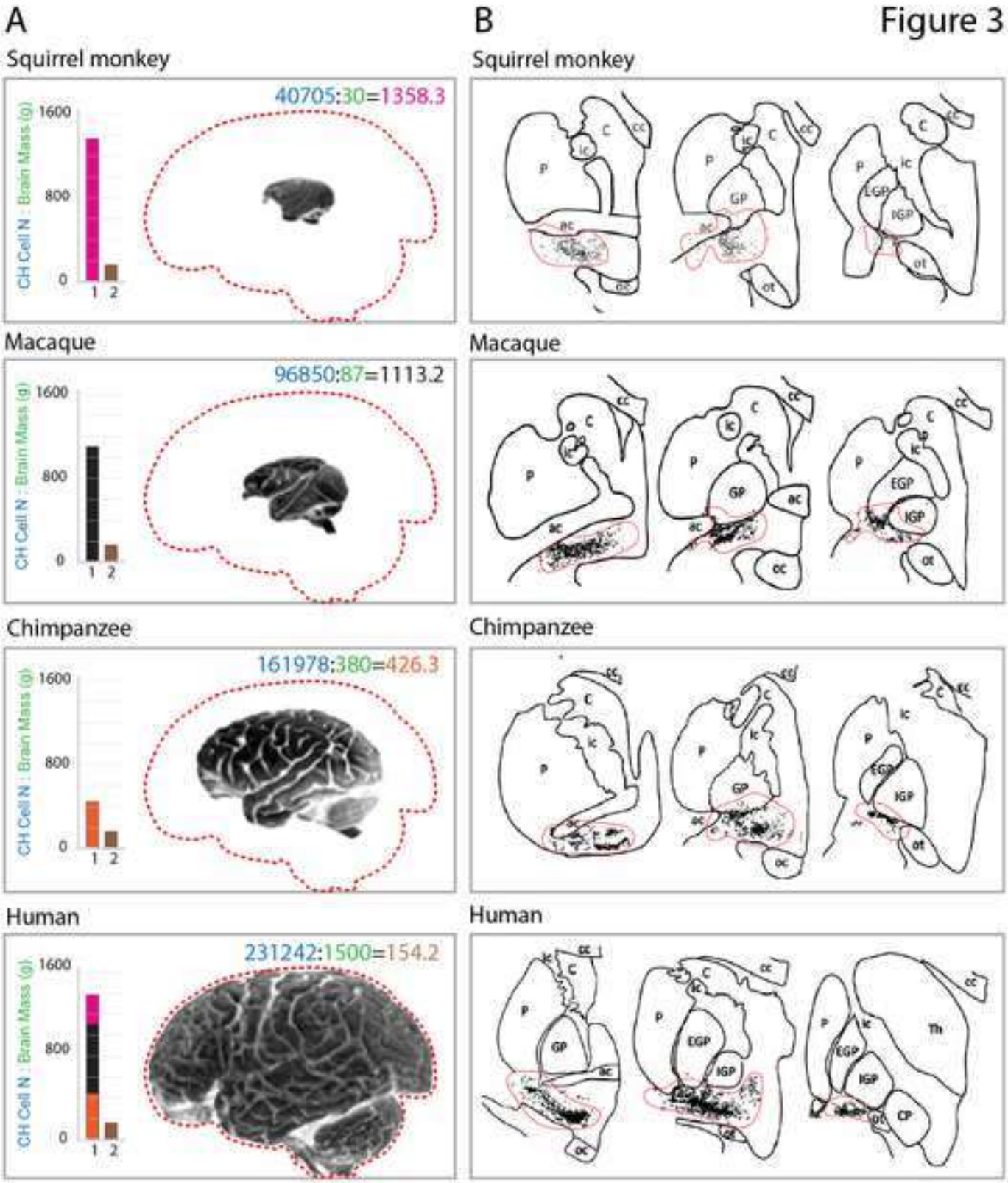


Figure 2



Figure

Click here to access/download;Figure;FIGURE3-RE1.jpg



Figure

Click here to access/download;Figure;FIGURE4-RE1.jpg

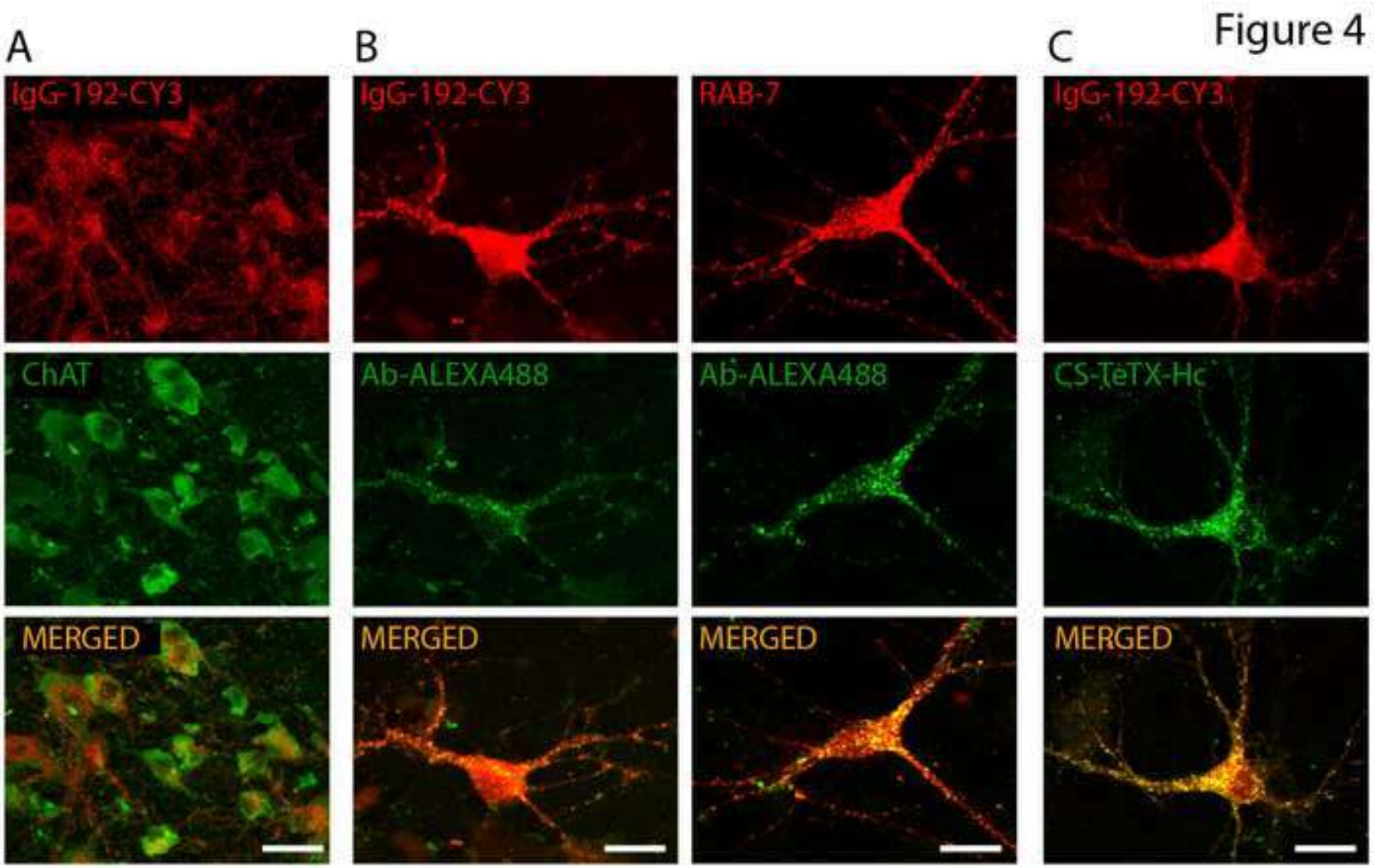


Figure 5