Review

Neurodegeneration: 2024 update

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Abstract

This review highlights a collection of both diverse and highly impactful studies published in the previous year selected by the author from the neurodegenerative neuropathology literature. As with previous reviews in this series, the focus is, to the best of my ability, to highlight human tissue-based experimentation most relevant to experimental and clinical neuropathologists. A concerted effort was made to balance the selected studies across neurodegenerative disease categories, approaches, and methodologies to capture the breadth of the research landscape. These studies employ a range of classical and state-of-the-art methodologies ranging from clinical pathoanatomical correlative studies to single-cell RNA sequencing, artificial intelligence, and patient-derived human induced pluripotent stem cell models. Key studies include demonstration of the earliest pathological changes in young patients with repetitive head impacts (RHI), elucidation of the longitudinal trajectory of extrapyramidal symptoms in Lewy body disease subtypes, mapping of cell-type specific polygenic risk in Alzheimer's disease to neuropathology, a novel measure of histological brain age acceleration using artificial intelligence, trends in cerebrovascular pathologies over 25 years, associations between RHI and TDP-43 / hippocampal sclerosis, microglia / T-cell interaction in neurodegeneration, the impact of viral exposures on neurodegenerative disease risk, and polyglutamine repeat expansion disorders. This sampling of the literature collectively displays the breadth of the progress being made in the neuropathology of neurodegenerative diseases.

Keywords: Neurodegeneration, Neuropathology, Aging, Alzheimer's disease, Tauopathy, α-synucleinopathy, TDP-43 proteinopathy, Traumatic brain injury

1. Chronic traumatic encephalopathy in young athletes' post-repetitive head impacts

Concussions are extremely prevalent, especially among individuals exposed to repetitive head impacts (RHIs) through contact sports, military service, intimate partner violence, and other means. While these impacts may be symptomatic or asymptomatic in the short term, long-term exposure can lead to severe neurological outcomes, including chronic traumatic encephalopathy (CTE), a degenerative brain disease with varied clinical and neuropathological features. Most research on RHI has focused on older populations, leaving a critical gap in our understanding of how RHIs affect younger individuals. Investigating changes in young athletes is crucial, as it may uncover underlying mechanisms for neuropsychiatric symptoms and identify early triggers for tau accumulation and associated toxicity, potentially informing preventive strategies and interventions.

A study by McKee et al. published in *JAMA Neurology* investigates the neuropathologic and clinical consequences of repetitive head impacts (RHIs) in young contact sport athletes (McKee et al., 2023). Analyzing data from 152 brain donors younger than 30 years from the UNITE Brain Bank, the study characterized the presence and extent of chronic traumatic encephalopathy (CTE) and other neuropathologic abnormalities. The authors found that 41.4 % of the athletes showed neuropathological changes diagnostic for CTE, predominantly mild (stages I or II). Notably, athletes with CTE were more likely to be older and have longer exposure to RHI, particularly American football. CTE positive subjects showed key neuropathologic features, including ventricular enlargement, cavum septum pellucidum, thalamic notching, and the presence of perivascular pigment-laden macrophages in the frontal white matter (Figure 1). Further, the study also examined the clinical symptoms reported by informants using standardized scales, showing that cognitive, behavioral, and mood disturbances were prevalent among the brain donors, regardless of CTE status. Common symptoms included executive dysfunction, impulse control issues, depression, and apathy. This study provides critical insights into the early manifestations of CTE and other brain pathologies in young athletes, emphasizing the need for prospective studies to better understand the specific impacts of RHIs. The study's findings are potentially pivotal for developing strategies to mitigate the long-term effects of RHIs in contact sports.

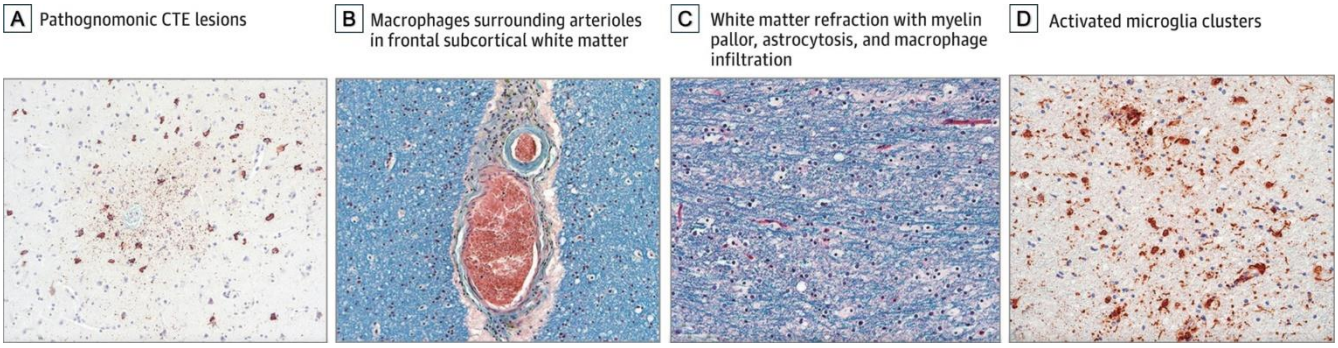

Figure 1. Neuropathological changes in young contact sports athletes. **A**. Immunohistochemistry for hyperphosphorylated tau showing the pathognomonic perivascular lesion. **B**. LH&E showing robust perivascular hemosiderin deposition in the white matter. **C**. LH&E demonstrating white matter rarefaction. **D**. Activated microglial clusters are prominent. Reproduced with modifications under the terms of the CC-BY License (http://creativecommons.org/licenses/by/4.0/).

2. Hippocampal sclerosis with TDP-43 inclusions following repetitive head impacts

Hippocampal sclerosis of aging, characterized by neuronal loss and gliosis primarily in the CA1 region and occurring independently of hypoxic-ischemic injury, is prevalent in the aging population. Most cases also exhibit inclusions positive for trans-active response DNA-binding protein with 43 kDa (TDP-43), a protein that, since its identification as the primary inclusion in amyotrophic lateral sclerosis (ALS) and frontotemporal lobar degeneration (FTLD), has been linked to other disorders including Alzheimer's disease (AD), limbic age-related TDP-43 encephalopathy neuropathologic change (LATE-NC), and chronic traumatic encephalopathy (CTE). The association with CTE is particularly notable and understudied, raising questions about whether these conditions represent co-morbidities or if they have synergistic effects.

A study by Nicks et al. published in *Acta Neuropathologica* directly addresses the neuropathological association between repetitive head impacts (RHI), chronic traumatic encephalopathy (CTE), and the presence of TDP-43 inclusions and hippocampal sclerosis (HS) (Nicks et al., 2023). The researchers analyzed brain samples from 401 participants with a history of RHI and neuropathologically diagnosed CTE and compared them with 33 individuals diagnosed with HS without CTE. The study found that HS was present in 23.4 % of the CTE cases and that TDP-43 inclusions were present in 43.3 % of the CTE cases. Notably, HS in CTE occurred at a younger mean age (77 years) and was significantly associated with a longer history of contact sports exposure compared to CTE without HS. TDP-43 inclusions were frequently observed in the frontal cortex and often co-occurred with limbic TDP-43 pathology. Structural equation modeling demonstrated a significant association between years of RHI exposure and the presence of hippocampal TDP-43 inclusions through increased CTE stage. The study also showed that TDP-43 inclusions in CTE were predominantly limbic but also involved the frontal cortex, distinguishing it from typical age-related TDP-43 pathologies such as LATE-NC. The presence of TDP-43 inclusions in the hippocampus was significantly associated with HS in CTE, suggesting a pathogenic link between repetitive head impacts, CTE pathology, and the development of TDP-43 proteinopathy and HS. These findings highlight the importance of considering RHI history in the assessment of hippocampal sclerosis and suggest potential therapeutic targets for mitigating the effects of RHI on neurodegeneration.

3. Longitudinal motor decline in diffuse Lewy body disease, Parkinson's disease with dementia, and Alzheimer's disease

Lewy bodies, a common neuropathological finding, are the hallmark of Parkinson's disease (PD) when localized to the substantia nigra, but they can progress to a diffuse pattern leading to Parkinson's disease dementia (PDD). When Lewy bodies are found in the neocortex and associated with dementia as the presenting symptom, this condition is termed diffuse Lewy body disease (DLBD). In patients with DLBD, extrapyramidal parkinsonian features may or may not develop. Lewy bodies are also seen in Alzheimer's disease (AD). However, the extent to which the rates of extrapyramidal motor decline progress in these different contexts is unclear due to the limited number of longitudinal studies with neuropathological endpoints, which are crucial for prognostication, clinical trial design, and further research.

A study by Choudhury et al. published in *Alzheimer's & Dementia* investigates the progression of motor deficits in dementia with Lewy bodies (DLB), Parkinson's disease dementia (PDD), and Alzheimer's disease dementia (AD) using data from the Arizona Study of Aging and Neurodegenerative Disorders (Choudhury et al., 2023). The study included 193 participants with autopsy-confirmed diagnoses: 98 with PDD, 48 with DLB, and 47 with AD. Within the DLB cohort, participants were further categorized into those with parkinsonism (DLB+) and without parkinsonism (DLB-). The researchers utilized the Unified Parkinson's Disease Rating Scale (UPDRS) parts II and III to assess motor function over an eight-year period, employing non-linear mixed effects models to analyze the data. The results revealed that motor deficits progressed most rapidly

in the DLB+ group, with significant worsening in gait and limb bradykinesia compared to PDD and other groups (Figure 2). The study found that baseline UPDRS-II and III scores were highest in the PDD group, followed by DLB+, AD, and DLB-. Over time, the DLB+ group showed a faster progression in UPDRS-III scores compared to PDD, driven by significant declines in gait and limb bradykinesia. The study also highlighted that the presence of parkinsonism in DLB (DLB+) was associated with more rapid motor decline than in DLB- or AD, emphasizing the importance of recognizing and monitoring these symptoms for better clinical management and prognostication. The findings underscore the need for targeted interventions to address motor deficits and suggest that patients may benefit from specific therapeutic strategies aimed at mitigating motor decline. The research provides valuable insights into the differential progression of motor impairments in neurodegenerative dementias, with implications for clinical trial design and patient care.

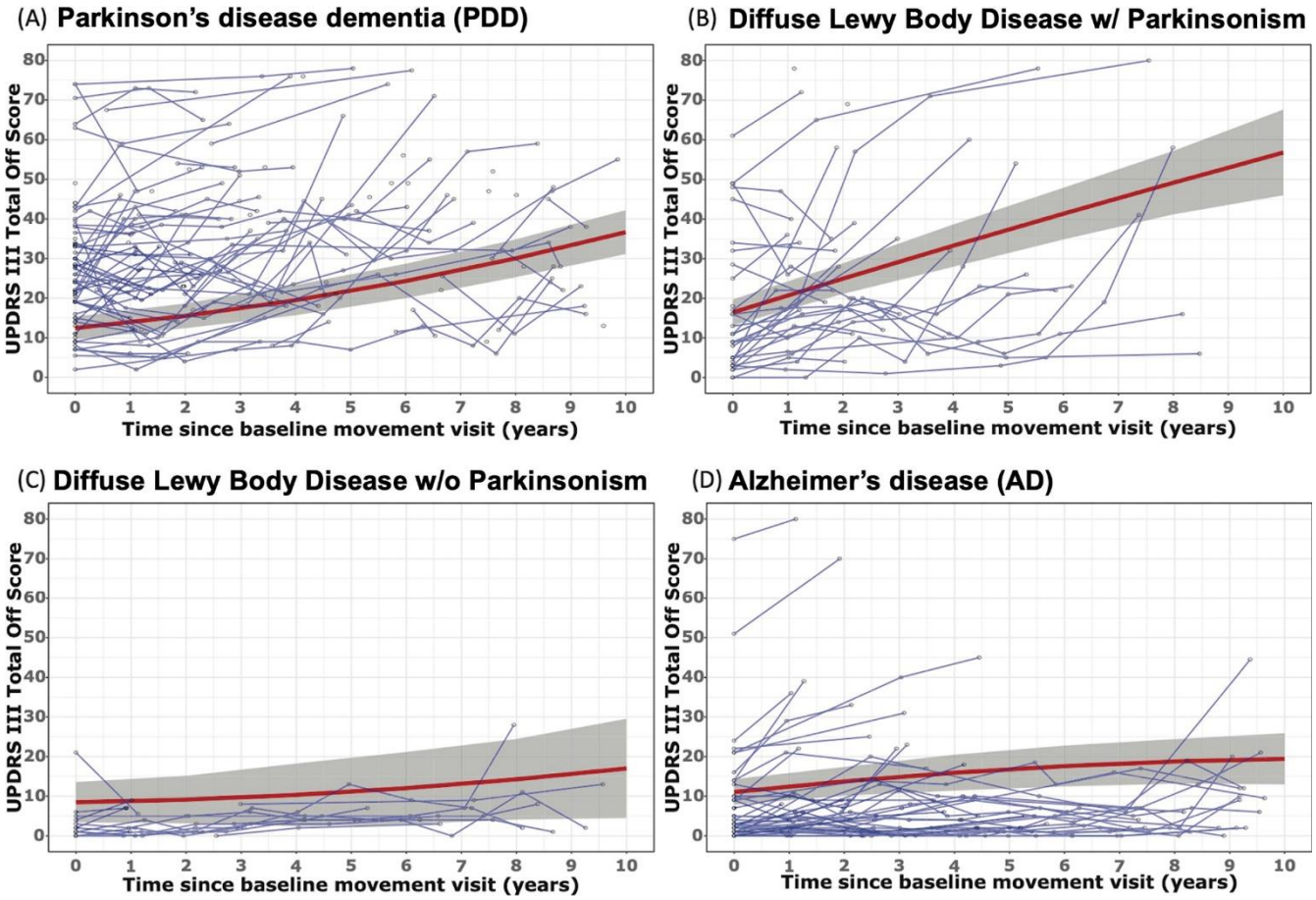

Figure 2. UPDRS-III total scores during off stage examination for each participant and their trajectories for groups: PDD (**A**), DLB+ (**B**), DLB− (**C**), and AD (**D**). Each point represents one movement exam visit and corresponding score. Blue lines depict each participant. Red line represents a mixed model fit line. The shaded area (funnel) surrounding red fit line represents 95 % confidence interval for the mixed model fitted curves. AD, Alzheimer's disease; DLB+, DLB with parkinsonism; DLB−, DLB without parkinsonism; DLB, dementia with Lewy bodies; PDD, Parkinson's disease dementia. Reproduced with modifications under the terms of the CC-BY License (http://creativecommons.org/licenses/by/4.0/).

4. Cell-type-specific Alzheimer's polygenic risk scores

Large-scale genetic studies have uncovered numerous genetic loci associated with Alzheimer's disease (AD), but understanding how the corresponding causal genes contribute to the cellular and molecular mechanisms driving AD remains a major challenge. Since neurodegeneration in AD is a complex, non-cell autonomous process involving interactions between multiple cell types, deciphering how these genes act across different cells is essential for identifying therapeutic targets. Genes expressed by microglia and astrocytes are notably over-represented in genome-wide association studies (GWAS) of AD. However, how these cell-specific genetic changes connect to the neuropathological hallmarks of AD, such as neurofibrillary tangles and amyloid plaques, and ultimately to cognitive decline, remains unclear—a critical gap in our knowledge.

A study by Yang et al. published in *Nature Communications* investigates how cell-type-specific polygenic risk scores (ADPRS) for AD are associated with distinct pathological processes (Yang et al., 2023). By deriving ADPRS from large-scale genome-wide association studies (GWAS) and leveraging single nucleus RNA sequencing (snRNA-seq) data, the researchers assessed the impact of genetic risk localized to different brain cell types, focusing on microglia and astrocytes, on various AD endophenotypes. Using data from the Religious Orders Study and the Rush Memory and Aging Project (ROSMAP), as well as the Anti-Amyloid Treatment in Asymptomatic Alzheimer's (A4) study, the study found that astrocytic ADPRS were primarily associated with amyloid-β (Aβ) pathology, while microglial ADPRS were linked to both Aβ and tau pathologies, as well as cognitive decline. The findings suggest that genetic risks associated with astrocytes contribute to early Aβ accumulation, whereas microglial genetic risks drive later-stage pathological changes and cognitive impairment.

Yang et al. utilized causal modeling to map the contributions of cell-type-specific ADPRS to the sequence of AD pathophysiology. The study suggests that astrocytic genetic risks affect AD primarily through Aβ accumulation in diffuse and neuritic plaques, whereas microglial genetic risks have broader effects on neuritic plaques, tau neurofibrillary tangles, and cognitive decline. This was supported by data from the A4 study, which showed that microglial ADPRS were significantly associated with in vivo tau PET measures, indicating an early role in tau pathology. The research underscores the importance of considering cell-type-specific genetic risks in understanding the progression of AD and highlights potential targets for therapeutic interventions. These insights pave the way for future studies to explore genetically guided approaches to AD treatment, focusing on modulating specific glial cell functions to mitigate disease progression.

5. Histological brain age acceleration using digital neuropathology and artificial intelligence

Understanding mechanisms of human brain aging is increasingly important as the elderly population grows, given the complexity of structural changes that arise from a spectrum of normal and pathological processes affecting functional impairment. One highly effective approach to studying aging is through biological clocks, initially developed using DNA methylation analysis. DNA methylation clocks estimate biological age by measuring methylation patterns at specific CpG sites in the genome, reflecting cellular aging processes. This method can be used to reveal discrepancies between biological and chronological age, providing insights into age acceleration or deceleration that can be linked to environmental and genetic factors.

In a study by Marx et al. published in *Acta Neuropathologica*, and led by the author of this review, the authors leverage digital pathology to deploy multiple instance learning (MIL) to estimate brain age from histopathological whole slide images (Marx et al., 2023). Employing an attention-based deep MIL model, the team analyzed digitized post-mortem hippocampal sections to develop an advanced brain age estimation tool, achieving a mean absolute error of 5.45 years (Figure 4). The integration of spatially resolved graph convolutional networks (GCNs) allowed the model to consider neuro-

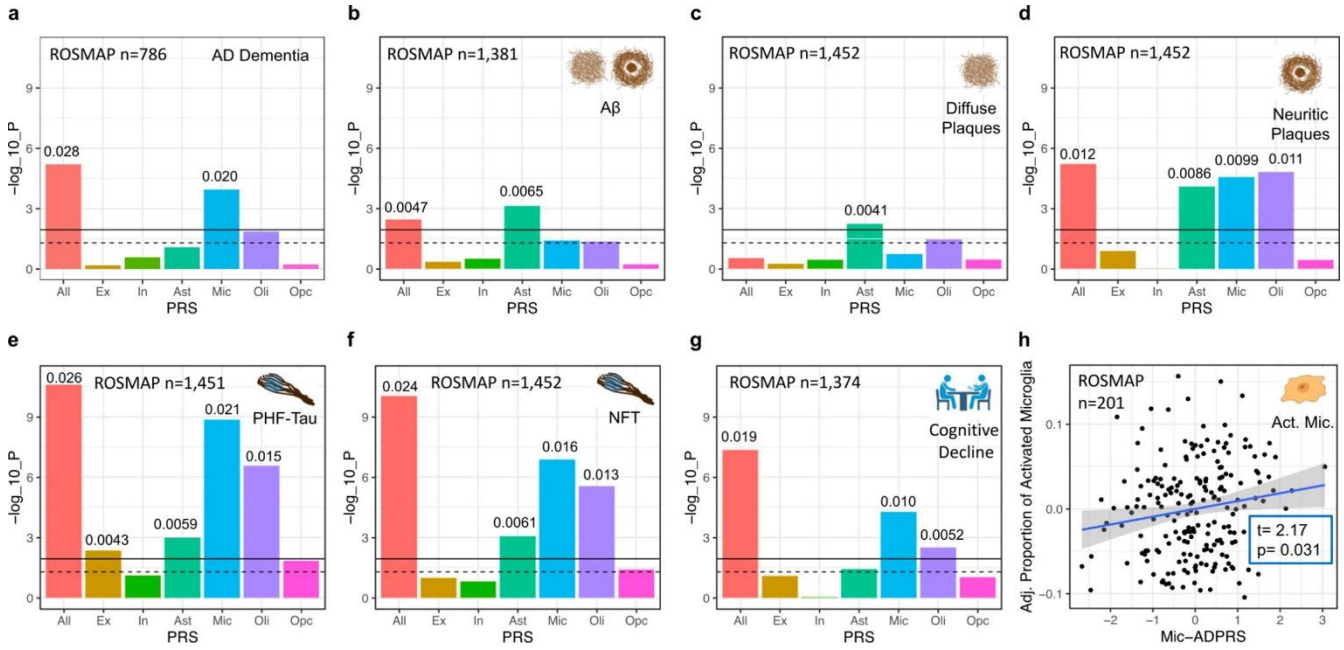

Figure 3. Association of cell-type-specific AD polygenic risk scores. *ROSMAP,* Religious Orders Study/Memory and Aging Project; *AD*, Alzheimer disease; *PRS,* polygenic risk score; *Ex*, Exitatory neurons; *In*, Inhibatory neurons; *Ast*, astrocytes; *Mic*, microglia; *Oli*, Oligodendrocytes; *Opc*, Oligodendrocyte precursors. Reproduced in under a Creative Commons Attribution 4.0 International License (http://creativecommons.org/licenses/by/4.0/)

anatomical context, resulting in a significant improvement over traditional methods. Marx et al. identified robust associations between histopathologic brain age acceleration and clinical and pathological outcomes, which were not evident with gold standard epigenetic measures. Attention heatmaps generated by the model highlighted aging-vulnerable brain regions, such as specific white matter areas and hippocampal subfields, as critical for accurate age estimation. This study emphasizes the potential of histopathological markers to provide deeper insights into brain aging mechanisms. Additionally, the combination of MIL with GCNs presents a novel methodology for predicting brain age, offering promising implications for understanding and diagnosing neurodegenerative diseases and their progression. This innovative approach paves the way for more precise and informative assessments of age-related neuropathological changes. In this context, HistoAge represents a cutting-edge advancement—an AI-driven digital neuropathology tool designed to study brain aging more precisely, leveraging advanced computational techniques to enhance our understanding of age-related changes in the brain.

6. Decline in cerebrovascular pathologies over 25 years

Recently, several studies have suggested that the incidence rate of dementia may be declining, offering hope that improved healthcare and lifestyle factors are influencing this global challenge. However, dementia remains a highly complex disease with multiple underlying causes that are difficult to diagnose in the clinical setting. Both genetic and environmental risk factors play significant roles in the development of dementia, and understanding their interplay over time is critical. Across birth epochs, an enormous number of factors have changed, any of which could potentially influence dementia risk. These include environmental exposures (e.g., air pollution, pesticides), infectious diseases (e.g., herpes, HIV), socioeconomic shifts (e.g., malnutrition), medical advances, dietary and lifestyle trends, technological changes, genetic variations, access to healthcare, longevity, and even epigenetic modifications. Despite recent findings pointing toward declining dementia rates, the precise neuropathological underpinnings of these trends remain unclear. This gap in knowledge presents a major barrier to

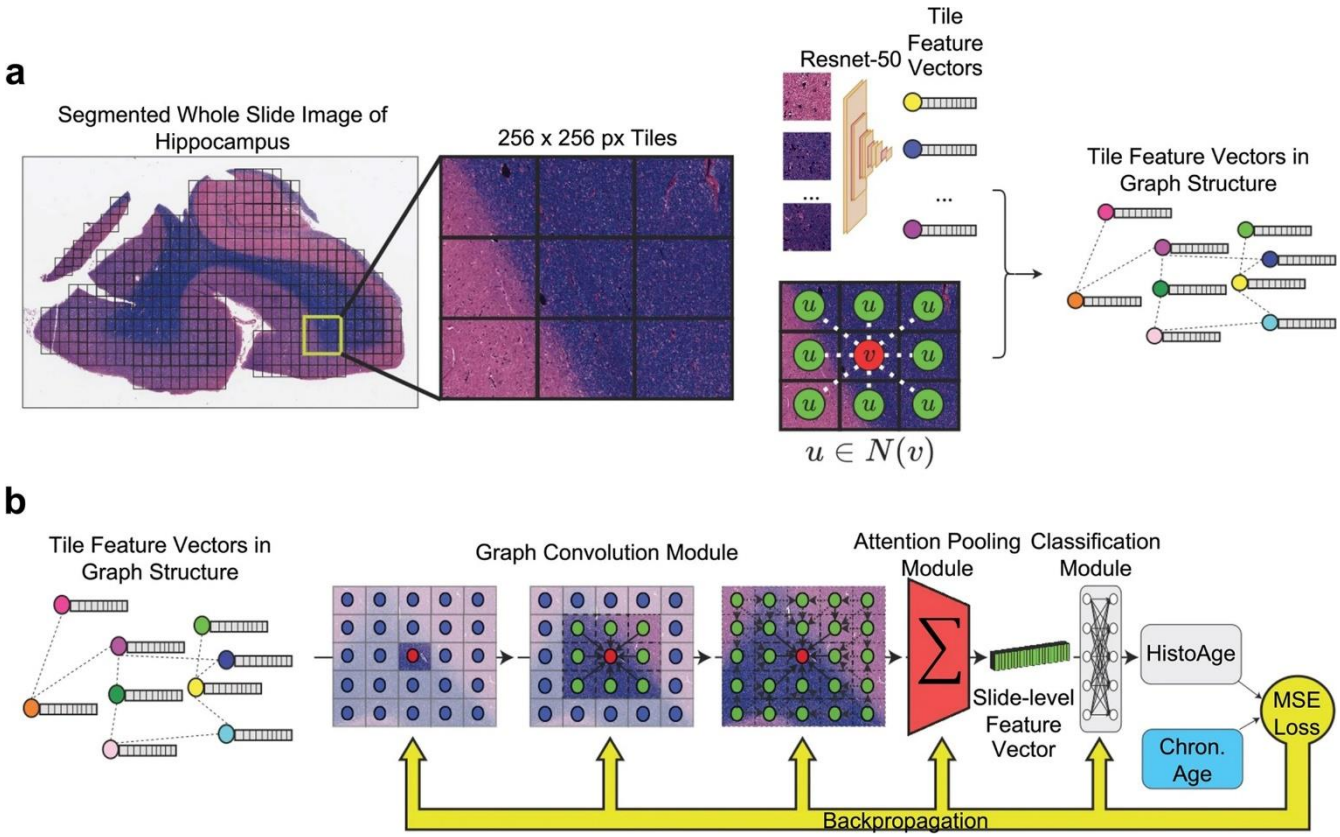

Figure 4. The "HistoAge" pipeline. **a**. Digital whole slide images were broken up into smaller tiles, then run through a neural network that extracts features. These features were linked to adjoining tiles using graph structure. **b.** The features were then used to train a new neural network that predicted age, which was compared to chronological age to estimate age acceleration. Reproduced under the Creative Commons Attribution 4.0 International License (http://creativecommons.org/licenses/by/4.0/).

developing targeted interventions and public health strategies, particularly as the population continues to age and the global burden of dementia grows.

A study by Grodstein et al. published in *JAMA Neurology* examines trends in postmortem neurodegenerative and cerebrovascular neuropathologies over 25 years using data from the Religious Orders Study and the Rush Memory and Aging Project (Grodstein et al., 2023). This comprehensive investigation includes 1,554 deceased participants with complete brain autopsies and neuropathologic evaluations. The study analyzes four birth cohorts spanning from 1905 to 1930 to assess changes in neuropathological outcomes such as Alzheimer's disease (AD), amyloid load, tau tangles, neocortical Lewy bodies, limbic-predominant age-related TDP-43 encephalopathy, atherosclerosis, arteriolosclerosis, and brain infarcts. Strikingly, they found no significant differences in the prevalence of pathologic AD diagnoses across birth cohorts, with age-standardized prevalence ranging between 62 % and 68 %. Similarly, there were no marked changes in global AD pathology or other neurodegenerative pathologies over time. However, an increase in tau tangle density was noted in more recent birth cohorts, suggesting a potential rise in this specific pathology. In contrast, the authors found a dramatic decrease in cerebrovascular pathologies, particularly atherosclerosis and arteriolosclerosis, over the observed period. Age-standardized prevalence of moderate to severe atherosclerosis decreased from 54 % in the earliest cohort (1905–1914) to 22 % in the latest cohort (1925–1930). Arteriolosclerosis showed a similar decline. These findings highlight the impact of improved vascular health on brain aging and suggest that reductions in clinical dementia observed in other studies may be associated with enhanced resilience to neuropathology rather than a decrease in the underlying neurodegenerative pathologies.

Additionally, the study emphasizes the importance of considering both neurodegenerative and cerebrovascular factors in understanding dementia trends and developing public health strategies to address the growing aging population. The results underscore the need for continued efforts to improve vascular health as a means to mitigate the impact of dementia.

7. Microglia-T cell interaction in Alzheimer's disease and tauopathy

The immune system's involvement in neurodegeneration continues to gain increasing attention, with compelling evidence pointing to its critical role in disease progression. The innate immune system, particularly through the activation of microglia, has been at the forefront of research efforts, with these cells being implicated in the inflammatory processes that contribute to neuronal damage. However, a significant gap remains in understanding the role of the adaptive immune system, which, despite being central in autoimmune and infectious diseases, has been comparatively understudied in neurodegenerative disorders. T cells, key players in the adaptive immune response, have received far less focus in neurodegenerative diseases like Alzheimer's. This oversight represents a critical barrier to fully understanding the immune-mediated mechanisms of neurodegeneration. Although not as abundant as in conditions such as multiple sclerosis, T cells may still play an important role in these diseases, offering a potential but underexplored therapeutic target.

A study by Chen et al. at the Washington University School of Medicine published in *Nature* investigated the relationship between microglia, T cells, and tau-mediated neurodegeneration (Chen et al., 2023). Using mouse models of amyloid deposition and tau aggregation, they systematically compared the immune responses in the brains of transgenic mice and humans, revealing that tauopathy, but not amyloid deposition, triggers a unique adaptive immune response. Depletion of either microglia or T cells significantly blocked tau-mediated neurodegeneration, suggesting a critical role these immune cells play in the disease process. The study identified a marked increase in T cells, especially cytotoxic T cells, in regions with tau pathology in both mice and human Alzheimer's disease brains, correlating with neuronal loss and dynamic transformations from activated to exhausted states. The researchers utilized single-cell RNA sequencing (scRNA-seq) and single-cell TCR sequencing (scTCR-seq) to map the cellular and molecular signatures of immune cells in the brain. They found that in tauopathy, T cells and microglia formed an immune hub characterized by increased expression of interferon-γ and PDCD1 signaling pathways. Notably, inhibiting these pathways significantly reduced brain atrophy. The study also highlighted the role of microglia in presenting antigens to T cells, promoting their infiltration and activation. This interaction was found to be critical in driving neurodegeneration, as evidenced by the reduction in tau pathology and brain atrophy upon depletion of T cells. These findings underscore the potential of targeting microglia and T cell interactions as a therapeutic strategy for tauopathies and Alzheimer's disease, offering new avenues for treatment by modulating the immune response.

8. Viral exposures linked to neurodegeneration

Growing evidence has increasingly spotlighted the potential causal role of viruses in neurodegenerative diseases (NDDs). Historical examples, such as post-encephalitic parkinsonism, first hinted at this link, and subsequent research has suggested associations with viruses like herpes simplex virus (HSV). The COVID-19 pandemic further intensified speculation regarding viral contributions to neurodegeneration. Most notably, recent studies have strongly linked Epstein-Barr virus (EBV) to multiple sclerosis (MS). This connection is significant because viral infections can be mitigated through vaccination or treated with antivirals, presenting vast new possibilities for preventing or slowing neurodegenerative processes. However, the specific mechanisms by which viral exposures contribute to NDDs remain unclear, representing a critical gap in our understanding and a barrier to developing targeted interventions.

A study published in *Neuron* by Levine et al. examines the association between viral exposures

and the risk of developing neurodegenerative diseases (NDDs) using large-scale biobank data from FinnGen and the UK Biobank (Levine et al., 2023). The researchers identified 45 significant viral-NDD associations in the discovery phase with FinnGen, and successfully replicated 22 of these associations in the replication phase using the UK Biobank. Notably, the strongest association was observed between viral encephalitis (not elsewhere classified/unspecified) and Alzheimer's disease (AD), with a hazard ratio of 30.72 in FinnGen and an odds ratio of 22.06 in the UK Biobank. Other significant associations included influenza with pneumonia, which was linked to an increased risk of five of the six studied NDDs, including AD, amyotrophic lateral sclerosis (ALS), dementia, Parkinson's disease (PD), and vascular dementia (VAS). The analysis highlighted the long-term impact of viral exposures, showing that some associations persisted up to 15 years prior to NDD diagnosis. The study also replicated the association between Epstein-Barr virus (EBV) and multiple sclerosis (MS). Importantly, the findings suggest that vaccination against certain viruses, such as influenza and varicella-zoster, might reduce the risk of developing NDDs. It is important to note that the reverse causality has not been eliminated. The possibility that patients in the pre-symptomatic phases of neurodegenerative disease might be at risk for viral infection needs to be addressed more closely. The study emphasizes the need for more research into the role of viral infections in the pathogenesis of neurodegenerative diseases and suggests that leveraging vaccination and antiviral strategies might offer new avenues for prevention and treatment. These findings underscore the importance of considering viral exposure history in NDD risk assessments and highlight the potential for public health interventions to mitigate these risks.

9. Polyglutamine (polyQ) diseases: ribosomal proteins and tauopathy

Polyglutamine (polyQ) diseases, such as Huntington's disease (HD) and various spinocerebellar ataxias, represent an important yet understudied group of neurodegenerative disorders. These diseases are caused by CAG-repeat expansions in different genes and are characterized by neuronal intranuclear inclusions (NIIs), which play a key role in disease pathology. NIIs are not only central to polyQ disorders but are also observed in normal aging, as evidenced by Marinesco bodies in the substantia nigra and locus coeruleus. However, the formation of NIIs and their precise role in neurodegeneration remain poorly understood, representing a critical gap in knowledge. Addressing this gap through focused research on polyQ disorders and related inclusions is essential for advancing our understanding of these complex diseases and their broader implications for neurodegeneration. Few neuropathological studies focusing specifically on polyQ disorders are published each year, but two notable studies were recently conducted.

One study by Yagita et al. published in *Neuropathology* investigated the ribosomal protein SA (RPSA) in neuronal intranuclear inclusions (NIIs) associated with polyglutamine (polyQ) diseases and Marinesco bodies (MBs) in normal aging brains (Yagita et al., 2024). Utilizing immunohistochemical and biochemical analyses, the researchers examined brain samples from patients with Huntington disease (HD), spinocerebellar ataxia type 3 (SCA3), and normal elderly controls (NCs). The study revealed that RPSA is a common component of NIIs in polyQ diseases and MBs in normal aging. In polyQ diseases, RPSA co-localizes with polyQ aggregations and other proteins such as p62, ubiquitin, and huntingtin, forming a mosaic-like distribution within the NIIs. The nuclear fraction of HD patients' brain samples contained higher levels of RPSA compared to NCs, suggesting an upregulation of RPSA in the diseased state. In contrast, cytoplasmic RPSA expression was reduced in neurons with NIIs, which could imply sequestration of RPSA into the inclusions, leading to its depletion in the cytoplasm. The study also identified that MBs in the substantia nigra of NCs share similar protein components with NIIs, including RPSA and p62, indicating common mechanisms may drive the formation of these intranuclear inclusions. These findings highlight the role of ribosomal dysfunction in both neurodegenerative diseases and normal aging, providing new insights into the pathogenesis of polyQ diseases and the potential impact of ribosomal proteins in neuronal health and disease.

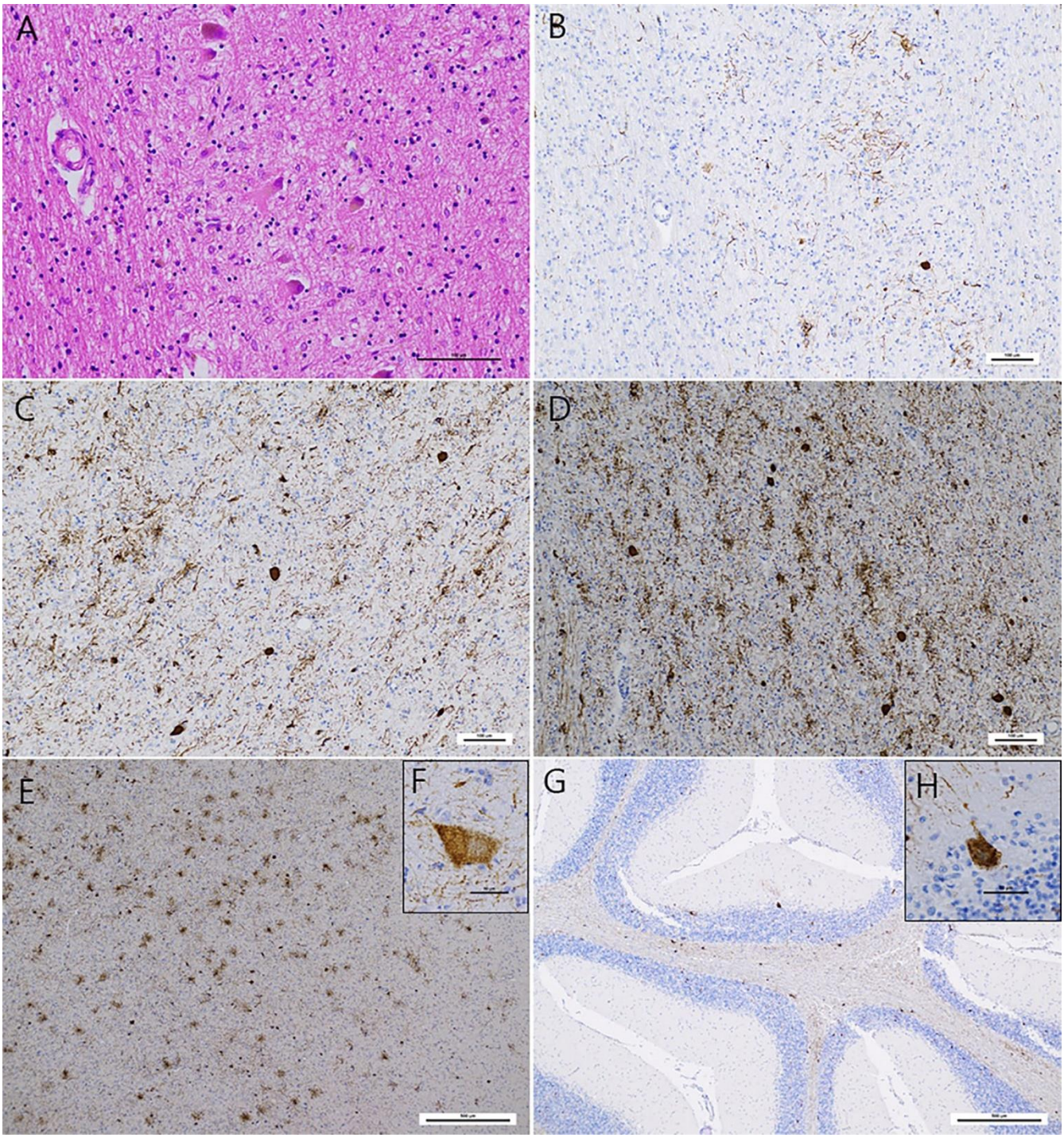

Figure 5. Tauopathy in SCA8. (**A**) In the dentate nucleus of the cerebellum, grumose degeneration was observed. (**B–H**) Immunohistochemistry for p-tau demonstrateed numerous globose-type NFTs, threads, and tufted astrocytes in the dentate nucleus (**B**), internal globus pallidus (**C**), subthalamic nucleus (**D**), precentral gyrus (**E, F**), and cerebellum (**G, H**). In the precentral gyrus, Betz cells were diffusely granular positive for p-tau (**F**). Purkinje cells were also positive for p-tau (**H**). HE staining (**A**); immunohistochemistry for p-tau (**B–H**). Scale bars: 100 µm in (**A–D**), 500 µm in (**E, G**), 25 µm in (**F, H**).

A second study also published in *Neuropathology* by Yonenobu et al. examined tauopathy in spinocerebellar ataxia type 8 (SCA8), suggesting that this variant might display unique tauopathic features (Yonenobu et al., 2023). The researchers analyzed post-mortem brain samples from patients diagnosed with SCA8. SCA8 is characterized by neuronal loss and gliosis predominantly in the cerebellum and brainstem, which aligns with the clinical manifestations of the disease. Additionally, Purkinje cell loss is a consistent finding, accompanied by Bergmann gliosis and dentate nucleus degeneration. Intriguingly, the investigators uncovered a unique tauopathy. Unlike other spinocerebellar ataxias, SCA8 exhibited tau-positive neuronal and glial inclusions, particularly in the brainstem and cerebellum. This finding not only expands the neuropathological spectrum of SCA8 but also provides new insights into its underlying mechanisms, paving the way for future research on targeted therapeutic strategies. Intriguingly, SCA8 is an atypical polyglutamine disorder, with the polyQ tract encoded from the anti-sense strand, raising a possible explanation for why the tauopathy described for SCA8 might be unique. The study emphasizes the importance of recognizing these unique pathological features to improve the diagnosis and understanding of SCA8.

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Conflict of interest

The author reports no conflicts of interest.

Disclosure statement

Generative artificial intelligence tools, specifically OpenAI's GPT-4, were used in the preparation of this manuscript. These tools assisted in drafting and refining portions of the text. The final content has been reviewed and edited by the author to ensure its accuracy, originality, and compliance with the journal's authorship and integrity guidelines. The author takes full responsibility for the content of the manuscript.

References

Chen, X., Firulyova, M., Manis, M., Herz, J., Smirnov, I., Aladyeva, E., Wang, C., Bao, X., Finn, M. B., Hu, H., Shchukina, I., Kim, M. W., Yuede, C. M., Kipnis, J., Artyomov, M. N., Ulrich, J. D., & Holtzman, D. M. (2023). Microglia-mediated T cell infiltration drives neurodegeneration in tauopathy. Nature, 615(7953), 668–677. https://doi.org/10.1038/s41586-023-05788-0

Choudhury, P., Zhang, N., Adler, C. H., Chen, K., Belden, C., Driver-Dunckley, E., Mehta, S. H., Shprecher, D. R., Serrano, G. E., Shill, H. A., Beach, T. G., & Atri, A. (2023). Longitudinal motor decline in dementia with Lewy bodies, Parkinson disease dementia, and Alzheimer's dementia in a community autopsy cohort. Alzheimer's & Dementia: The Journal of the Alzheimer's Association, 19(10), 4377–4387. https://doi.org/10.1002/alz.13357

Grodstein, F., Leurgans, S. E., Capuano, A. W., Schneider, J. A., & Bennett, D. A. (2023). Trends in Postmortem Neurodegenerative and Cerebrovascular Neuropathologies Over 25 Years. JAMA Neurology, 80(4), 370–376. https://doi.org/10.1001/jamaneurol.2022.5416

Levine, K. S., Leonard, H. L., Blauwendraat, C., Iwaki, H., Johnson, N., Bandres-Ciga, S., Ferrucci, L., Faghri, F., Singleton, A. B., & Nalls, M. A. (2023). Virus exposure and neurodegenerative disease risk across national biobanks. Neuron, 111(7), 1086-1093.e2. https://doi.org/10.1016/j.neuron.2022.12.029

Marx, G. A., Kauffman, J., McKenzie, A. T., Koenigsberg, D. G., McMillan, C. T., Morgello, S., Karlovich, E., Insausti, R., Richardson, T. E., Walker, J. M., White, C. L., Babrowicz, B. M., Shen, L., McKee, A. C., Stein, T. D., PART Working Group, Farrell, K., & Crary, J. F. (2023). Histopathologic brain age estimation via multiple instance learning. Acta Neuropathologica, 146(6), 785–802. https://doi.org/10.1007/s00401-023-02636-3

McKee, A. C., Mez, J., Abdolmohammadi, B., Butler, M., Huber, B. R., Uretsky, M., Babcock, K., Cherry, J. D., Alvarez, V. E., Martin, B., Tripodis, Y., Palmisano, J. N., Cormier, K. A., Kubilus, C. A., Nicks, R., Kirsch, D., Mahar, I., McHale, L., Nowinski, C., … Alosco, M. L. (2023). Neuropathologic and Clinical Findings in Young Contact Sport Athletes Exposed to Repetitive Head Impacts. JAMA Neurology, 80(10), 1037–1050. https://doi.org/10.1001/jamaneurol.2023.2907

Nicks, R., Clement, N. F., Alvarez, V. E., Tripodis, Y., Baucom, Z. H., Huber, B. R., Mez, J., Alosco, M. L., Aytan, N., Cherry, J. D., Cormier, K. A., Kubilius, C., Mathias, R., Svirsky, S. E., Pothast, M. J., Hildebrandt, A. M., Chung, J., Han, X., Crary, J. F., … Stein, T. D. (2023). Repetitive head impacts and chronic traumatic encephalopathy are associated with TDP-43 inclusions and hippocampal sclerosis. Acta Neuropathologica, 145(4), 395–408. https://doi.org/10.1007/s00401-023-02539-3

Pomeshchik, Y., Velasquez, E., Gil, J., Klementieva, O., Gidlöf, R., Sydoff, M., Bagnoli, S., Nacmias, B., Sorbi, S., Westergren-Thorsson, G., Gouras, G. K., Rezeli, M., & Roybon, L. (2023). Proteomic analysis across patient iPSC-based models and human post-mortem hippocampal tissue reveals early cellular dysfunction and progression of Alzheimer's disease pathogenesis. Acta Neuropathologica Communications, 11(1), 150. https://doi.org/10.1186/s40478-023-01649-z

Yagita, K., Sadashima, S., Koyama, S., Noguchi, H., Hamasaki, H., Sasagasako, N., & Honda, H. (2024). Ribosomal protein SA is a common component of neuronal intranuclear inclusions in polyglutamine diseases and Marinesco bodies. Neuropathology: Official Journal of the Japanese Society of Neuropathology, 44(1), 31–40. https://doi.org/10.1111/neup.12927

Yang, H.-S., Teng, L., Kang, D., Menon, V., Ge, T., Finucane, H. K., Schultz, A. P., Properzi, M., Klein, H.-U., Chibnik, L. B., Schneider, J. A., Bennett, D. A., Hohman, T. J., Mayeux, R. P., Johnson, K. A., De Jager, P. L., & Sperling, R. A. (2023). Cell-type-specific Alzheimer's disease polygenic risk scores are associated with distinct disease processes in Alzheimer's disease. Nature Communications, 14(1), 7659. https://doi.org/10.1038/s41467-023-43132-2

Yonenobu, Y., Beck, G., Kido, K., Maeda, N., Yamashita, R., Inoue, K., Saito, Y., Hasegawa, M., Ito, H., Hasegawa, K., Morii, E., Iwaki, T., Murayama, S., & Mochizuki, H. (2023). Neuropathology of spinocerebellar ataxia type 8: Common features and unique tauopathy. Neuropathology: Official Journal of the Japanese Society of Neuropathology, 43(5), 351–361. https://doi.org/10.1111/neup.12894