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Accelerating Biomedical Discoveries in Aging and Neurodegeneration Through Transformative Neuropathology

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Abstract: Transformative neuropathology is redefining human brain research by integrating foundational descriptive pathology with advanced methodologies to drive discoveries that inform diagnostics, therapeutics, and disease prevention. These approaches, spanning multi-omics studies and machine learning applications, enable the identification of biomarkers, therapeutic targets, and complex disease patterns through comprehensive analyses of postmortem human brain tissue. Yet critical challenges, including sustainability of brain banks, expanding donor participation, strengthening training pipelines, enabling rapid autopsies, and supporting collaborative platforms. Innovations in digital pathology, tissue quality enhancement, harmonized data standards, and machine learning integration offer groundbreaking opportunities to accelerate research in aging and neurodegeneration. Lessons from neuroimaging, regarding progress in establishing common data frameworks and multi-site collaborations, offer a valuable roadmap for streamlining innovations. In this Perspective, we outline actionable solutions to leverage existing resources, envision future opportunities, and advance collaboration to drive translational discoveries and safeguard the sustainability of brain banks underpinning transformative neuropathology.

Keywords: neuropathology; spatial biology; omics; digital pathology; machine learning; biomarkers

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Introduction

The integration of advanced multi-omics, digital pathology, and machine learning with traditional neuropathology is transforming our understanding of brain diseases with profound implications for diagnostics, therapeutics, and prevention. What was once the domain of science fiction is now our tangible reality with: large-scale -omics studies of human brain tissue uncovering novel biomarkers and therapeutic targets, high-throughput digital scanning of microscope slides enabling remote viewing and computerized analysis of spatial biology patterns of disease, and greater availability of neuroimaging and fluid biomarkers to unveil diagnostic and prognostic neuropathologic alterations. Moreover, the high computational capacity provided by machine

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learning is driving unprecedented insights by enabling prediction, discovery, and characterization of subtle patterns across expansive -omics and whole-slide image microscopy datasets. With the goal to explore the significant progress in the study of postmortem human brain tissue, moving from the theoretical potential of applying advanced techniques to the practical reality of modern science in the fields of aging and neurodegenerative diseases, a workshop convened at Banbury Center hosted by Cold Spring Harbor Laboratory. A convergence of expertise in brain banking, neuropathology, high dimensional molecular data (-omics), digital pathology, neuroimaging, computational methods, and machine learning was gathered to discuss approaches to optimize and enhance existing workflows and infrastructure in a rapidly evolving biomedical landscape. We report workshop outcomes to promote new biomedical discoveries and introduce the concept of *transformative neuropathology* (Figure 1), a term we use to describe the integration of foundational descriptive pathology with advanced technologies and methodologies. By defining this paradigm shift, we aim to inspire a reimagining of neuropathology's role in driving innovation and addressing critical challenges in brain disease research. We structure this Perspective by identifying key challenges facing the realm of research-based biorepositories of human brain tissue that can be utilized by as a springboard to inspire future investigations and funding.

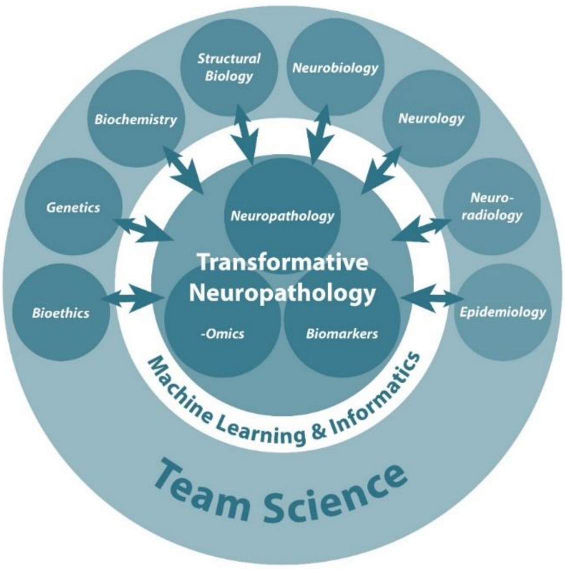

Figure 1. Transformative Neuropathology. Through a convergence of team science collaborations, human tissue-based studies have the unprecedented ability to uncover molecular clues that advance our diagnostic and prognostic understanding of complex brain diseases. The integration of these complementary fields fosters innovative approaches that bridge descriptive pathology with cutting-edge technologies, enabling precise identification of disease mechanisms, predictive diagnostics, and targeted therapeutic strategies. This holistic framework exemplifies the potential of transformative neuropathology in the modern era of advanced biomedical research. (Figure concept adapted from Gutt et al. [125]).

Prospective Brain Collections & Increasing Representation for Broader Insights

Brain banks, collections, or libraries can serve many functions, such as providing closure to donors' families through diagnostic evaluation, supporting transformative research, providing educational opportunities, and offering training opportunities in neuropathology (Figure 2) [1]. The careful preservation and archiving of brains from individuals who consented for donation by skilled brain bank staff ensure the availability of high-quality tissue, critical to unraveling the complexities of the human brain [2]. This essential work not only provides the foundation for promoting scientific discovery but also strengthens the collaborative framework needed to tackle critical questions in in aging and neurodegenerative research [1,3]. As the biomedical field continues to move from passive

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recruitment to active recruitment, expanding brain donor participation across different backgrounds (i.e., economic status, aging across lifespan, cognitive and motor health, geographic ancestry) becomes even more critical (**see Box 1 with reference to subsection in line with text**).

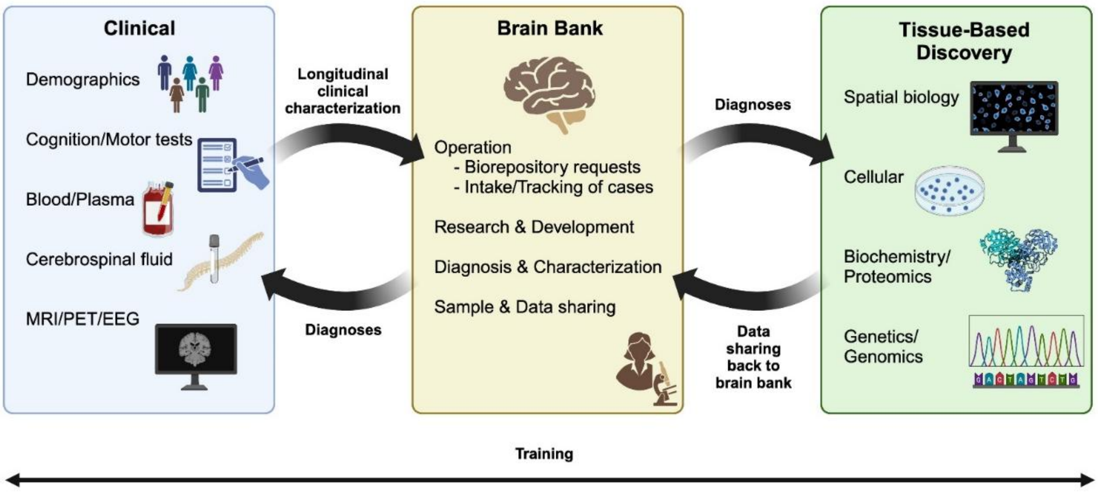

Figure 2. Conceptual Framework of a Brain Bank. The successful brain bioresource will be closely linked to well-characterized clinical cohorts with detailed sequential clinical assessments, often including neuroimaging, and linked biospecimens such as blood and cerebrospinal fluid samples. This allows postmortem-derived data to be linked to data points across the evolution of the disorder under study. With return of -omics data back to brain banks and clinicopathologic data provision to bioinformaticians, the transformative potential remains endless. Informaticians (e.g., data scientist, bioinformatician, biostatistician) trained in the setting of a brain bank could enable a future where externally facing queryable databases drawing from electronic medical records. To ensure privacy and eliminate security concerns over stored genotype-phenotype data, analytic tools could be designed without the ability to decrypt genetic data. Such bidirectional approaches will result in multimodal tissue phenotyping, with digitally scanned slides being linked to protein immunohistochemistry, genomic data, spatial proteomics, and spatial transcriptomic data. Critical to the successful model, funded efforts would be undertaken to make all data available to the research community. Figure created in BioRender.

Future-facing models of long-term research partnerships where engagement spans decades prior to brain donation are exemplified by the Oxford Project to Investigate Memory and Ageing [4], Lothian Birth Cohort 1936 [5], Mayo Clinic Study of Aging [6], Einstein Aging Study [7], Minority Aging Research Study [8], and Brain & Body Donation Program [9]. Recruiting individuals across the aging spectrum may require intentional engagement strategies, such as engaging care partners of study participants already enrolled in longitudinal studies, to ensure a minimum set of consistent antemortem measures (**1.1**). Healthy aging brains provide baseline understanding of age and sex differences in neuroanatomic structures that are key to the development of tissue-based atlases. Partnership with medical examiners could further expand donor recruitment across populations with limited research participation [1,10-12], especially helping to define the age range of histologic changes and their relevance as a control for young-onset disorders (e.g. frontotemporal dementia, Alzheimer's in individuals <65 years [13,14]). Partnerships with ambassadors from the lay public and with clinicians through multi-component program projects further provides mutual opportunities to receive and share knowledge to enhance healthy brain aging [15,16] (**1.2**).

Building Capacity for Expertise in Neuropathology and Informatics

Historically, brain bank leadership required formal medical training. However, with fewer neuropathologists entering the field, in addition to the need to engage junior neuropathology experts in aging and neurodegenerative research, it has become necessary to expand the range of trained professionals who can develop and manage a brain bank (**Box 2**) [17]. The operations required to

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facilitate brain donation and tissue provision are complex and involve unique expertise that may take years to acquire/master. Neuropathology expertise requires extensive training as an MD or PhD to enable systematic evaluation of age-related histologic changes and a full range of neurologic conditions including neurodegenerative diseases, cerebrovascular lesions, demyelinating and other neuroinflammatory conditions, central nervous system infections, as well as neoplastic, metabolic and neurodevelopmental disorders depending upon the brain bank's focus. As diagnosis may be a small fraction of the abundance of tasks involved in operations, it is imperative to have knowledge on research methodologies and the scientific process when leading a brain bank. Emphasis on training pipelines provided across brain bank networks geared toward neuropathology clinical fellows and neuroscience research trainees is recommended (**2.1**). To further strengthen the future of brain banks with informatics support, data science training with formal training through coursework and hands-on experience is additionally recommended (**2.2**). Ease of access to human brain tissue for qualified investigators is crucial for supporting translational research. The United Kingdom Brain Bank Network[18], Netherlands Brain Bank[19], Parkinson's Progression Markers Initiative (PPMI)[20], Rush Alzheimer Disease Center[21], National Alzheimer's Coordinating Center[22], and National Institute of Health's NeuroBioBank[23], provide an accessible portal for qualified researchers to identify and request human brain tissue. These portals required significant investment in infrastructure and integration of informaticians, for which funds are rarely available, (e.g., data scientist, bioinformatician, biostatistician) to work continually with neuropathology experts with the goal of sustained improvements based on user feedback.

Broader access to neuropathology training for a more novice audience through conference workshops and publicly available neuropathology-based encyclopedias[24] are also recommended to enhance communication between tissue requestors and tissue providers (**2.3**). Given the importance of paired phenotypic data with tissue selection (Figure 2), strengthening collaborations with clinicians to enhance translational potential of tissue-based discoveries and consideration of structured clinical training of brain bank support staff to enhance retrospective abstraction of clinical progression is recommended (**2.4**). Initiatives to enhance sustainability of brain banks amidst ever increasing demand for tissue provision may be found through: infrastructure built into research grants and program projects led by brain bank directors, working with home institutions to create cost recovery mechanisms, partnering with development for philanthropic sponsorship, engaging with leadership for institutional support, collaborating with intramural researchers in field adjacent domains (e.g., cancer research), or applying to government-led opportunities (e.g., National Institute of Health's NeuroBioBank[23]). The Netherlands Brain Bank[25] and Banner Sun Health's Brain & Body Program instituted partial support through a cost recovery model to facilitate staffing for tissue provision[9,26]. The United Kingdom Brain Bank Network adopted a similar cost recovery models, along with the development of harmonized protocols, legal guidance, and administrative guidance for a holistic approach to sustainable brain banking[18].

Innovating Tissue Quality Strategies to Unlock Molecular Insights

Maximizing the potential of molecular discoveries in aging and neurodegenerative research requires innovative strategies to overcome the limitations posed by using archival human brain tissue (**Box 3**). Advances in -omics, including single-cell and spatially resolved methods, enable precise identification of disease signatures[27–35]. High-throughput analysis of frozen or formalin-fixed paraffin embedded (FFPE) brain tissue offers unbiased, multimodal insights into brain physiology and disease, supporting breakthroughs like whole-brain mapping [28,31,35–37], network modeling to uncover druggable targets[38,39], and identification of key post-translational modifications [40,41]. Omics-based research has emerged as a guiding force in the study of both neuronal and glial biology of aging, highlighting pathway dynamics to discern biologic perturbations as exampled in aging[42], Alzheimer's disease [28,43,44], amyotrophic lateral sclerosis[45], Huntington disease[32], Lewy body disease[46], and progressive supranuclear palsy[47]. Deep, quantitative neuropathologic characterization further enables the reconstruction of antemortem trajectories when combined with

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high-dimensional -omics data[48]. These types of work, made possible by broad collaboration and integration of various data modalities, delineate a clear path toward identifying critical phenotypic markers of cellular states for broader consideration of molecular diagnostics (**3.1**). Scientific advances, like those uncovered by cryo-electron microscopy[49–53], are the direct result of innovative approaches to investigate archival brain tissue. A coordinated effort to develop methods for utilizing pre-existing materials (e.g., stored formalin-fixed or frozen tissue) is essential to unlocking the full potential of archival collections. As technology advances, the use of tissue previously considered suboptimal enters into the realm of possibilities (e.g., probe-based technology for FFPE tissue, **3.2**).

New imaging techniques, like array tomography combined with super-resolution microscopy requires non-standard autopsy tissue processing[54,55] including immediate use of fresh tissue upon procurement (**3.3**). This necessitates additional funding to support brain bank staff in performing rapid-response protocols and ensuring timely communication between tissue providers and the research team. Through ongoing collaboration and enhanced tissue innovations, we stand at the precipice of further breakthroughs in understanding pathogenesis holding the promise for alleviating the burden of these devastating diseases on individuals and their families. To future-proof valuable tissue samples for discovery-based -omics methodologies, the continuation of centralized resources is recommended to establish best practices and minimum standards for tissue preparation (e.g., fixation, freezing) and storage (**3.4**). While it may not be possible to overhaul protocols for the entirety of a brain bank's collection to support rapidly advancing -omics techniques, it is crucial to understand the quantitative variables that capture tissue quality for each modality and to underscore the importance of a flexible and collaborative framework between neuropathology experts and researchers to allow for innovative use of tissue[1,54,55].

Streamlining Digital Slide Sharing and Analysis to Enhance Translational Potential

The necessity for efficient slide sharing capabilities and neuropathology-centric initiatives are key considerations to realizing the full benefits of digital pathology (**Box 4**). Digital pathology is a versatile technology that continues to advance our understanding of the spatial biology of age-related changes, neurodegenerative lesions, and cerebrovascular insults[56–58]. Whole slide images from diagnostic slides or project-specific slides are scanned at high-resolution to enable the neuropathology expert, clinician, and/or researcher to readily view the entirety of the tissue or focus on specific areas of interest. Digitized slides can be annotated for diagnostic, research, and/or educational purposes. Digitization comes with the added value of integrating computational analytic tools for high-throughput image segmentation of neuroanatomic structures to objectively quantify lesions and histologic changes (**4.1**). Efforts to compare established semi-quantitative scores with digital pathology measures show a strong correlation between the manual scores and digitized measures offering hope toward automated quantification of disease burden[59–61]. Staging systems of neurodegenerative diseases [62–68] are often inherent to the success of consensus initiatives with clinician and scientific partners [69–75]. With digital pathology already benefitting efforts like the Rainwater criteria for progressive supranuclear palsy[74] and McKee criteria for chronic traumatic encephalopathy[66]; we embrace a present reality with continued opportunities to apply machine learning and neural networks to systematically analyze whole slide images that compliment diagnostic procedures in a brain bank[76–80].

Neuropathology-centric initiatives to address the need for slide sharing and hosting efforts may play a crucial role in overcoming local implementation barriers[81] (**4.2**). Notably, the Digital Slide Archive[82], originally designed for cancer research[83], is being adapted for aging and neurodegenerative research, showcasing the potential for global collaboration (**4.3**). In lieu of a central repository, individual brain banks are drawing upon local resources and philanthropy to make their collections digitally available[84]. The benefits of digital pathology go beyond technical aspects. Its integration into clinical practice offers significant potential for improved diagnostics and treatment planning through systematic analyses of autopsied individuals with antemortem clinical data[85,86].

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For example, digital pathology can quantitatively measure histologic changes, enhancing the translational value of postmortem studies that investigate neuroimaging and fluid biomarker changes[87–89]. Moreover, large-scale research efforts stand to gain from the ability of digital pathology to capture the heterogeneity of neurodegeneration in the aging brain, paving the way for more targeted and personalized approaches toward understanding and combating these multifaceted disorders[56,68,90,91]. As the aging and neurodegeneration fields advance, continued exploration, collaboration, and support for an alliance of worldwide brain banks are essential to unlocking the full potential of digital pathology in biomedical research and clinical applications (**4.4**).

Building Collaborative Platforms to Accelerate Tissue-Based Discoveries

Key considerations regarding increased slide digitization and to increasingly linked -omics datasets, are data storage and harmonization of common data elements and file formats (**Box 5**). There is a critical need for data to be harmonized, comply with international data protection laws, and use common data models to allow access and analysis between research groups without not dependence on proprietary software. Looking to the neuroimaging field for inspiration, notable initiatives demonstrating the aspirational power of unity in scientific exploration, comprise among others PPMI[20] and Alzheimer's Disease Neuroimaging Initiative (ADNI)[92]. Recognizing the importance of a central data repository, universal file formats, and need for collaborative platforms – the Laboratory of NeuroImaging (LONI) was founded[93]. LONI's focus on data sharing enhances transparency and harmonization within the neuroimaging community[94], benefitting multi-site interpretation of data. LONI houses and manages ADNI data, enabling the infrastructure for ADNI's harmonization efforts that continue to accelerate progress in understanding Alzheimer's disease and related dementias. ADNI data is used to both test[95] and validate novel hypotheses[96]. However, applicability of ADNI-based findings across economic backgrounds, as well as those having multiple disease etiologies[97], was recognized as a limitation motivating novel recruitment efforts with focused efforts to strengthen study participation[98]. Qualified researchers seeking to reverse engineer postmortem findings[62,63,99] can download data from initiatives like ADNI[100], PPMI[20], and Longitudinal Early Onset Alzheimer's Disease Study[101] to more broadly examine heterogenous biomarker patterns through identification of longitudinal trajectories[102] or toward enhanced molecular diagnostics of fluid biomarkers[103,104]. Conversely, open platforms and online repositories for neuroimaging (e.g. OpenNeuro[105], Neurovault[100]) and high-dimensional molecular data (e.g. Alzheimer' disease knowledge portal[106], Global Parkinson's Genetics Program[107]) enable data deposition from individual groups to enhance reusability of datasets.

As we usher in the next frontiers of neuropathology, harmonizing methodologies and data across research endeavors to promote interoperability standards for common data elements with enough flexibility for local innovation will be critical[108]. However, caution should be applied to mandatory adherence of common data elements to avoid penalization of brain banks who lack funding to update protocols (**5.1**). By implementing case-level tracking system through a digital object identifier (DOI) (**5.2**) in collaboration with bioethicists and establishing a codified brain library through an accessible portal, data tracking, sharing, and harmonization will be enhanced, laying a robust foundation for future advancements (**5.3**). The DOI system will allow brain banks to assess tissue quality through automated feedback from publications and enable researchers to select the highest-quality samples for new studies while integrating findings from earlier analyses. This system could not only increase the value of existing brain tissue repositories but also accelerates biomedical discoveries. A key feature of tissue preservation is systematic neuroanatomic dissection. Looking ahead, the development of a human common coordinate framework[109] emerges as a visionary approach to further enhance harmonization (**5.4**), offering a unified language for researchers worldwide and firmly establishing the biomedical science community in an era of transformative neuropathologic research. Similar approaches were developed for antemortem neuroimaging, such as the "neuromaps" initiative working across multiple brain maps[110]. Currently, annotation of Brodmann areas against the Allen Brain Atlas[111,112] is an increasingly used neuroanatomic

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resource that could be leveraged to create the human common coordinate framework. As spatial biology interrogation of the human brain continues to accelerate, brain banks may consider translating local sampling protocols to publicly available tissue atlas for reporting of regions and Brodmann areas toward wider applicability of tissue-based findings.

Harnessing machine learning to revolutionize brain banking

While attention is primarily focused on applying machine learning for research endeavors seeking to automate tedious, repetitive work and diagnostic applications[113–115], it is imperative to explore the vast spectrum of potential applications beyond these domains (**Box 6**). The untapped potential of machine learning could revolutionize processes beyond diagnostic prediction, to instead focus on 'pain points' in data acquisition and processing in a brain bank. Consider the prospect of expediting quality control workflows through quality control mechanisms where machine learning serves as an adept assistant in expediting tasks and enhancing overall efficiency of brain banking and digital pathology workflows (**6.1**). For instance, the integration of machine learning in decision-making could extend to the realm of selecting suitable cases for specific -omics analyses, streamlining research pathways, and optimizing resource allocation. Moreover, image analysis tools from the private sector[116] are already developed from image sharpening, modulating, and transforming, simply awaiting creative application to histologic images. The journey towards fully harnessing machine learning's potential will entail envisioning and embracing novel use cases that not only enhances outcomes but also fosters a more streamlined and effective ecosystem.

Looking to the future, the power of advancements in computational pipelines could be redirected toward seemingly obsolete techniques. By combining pioneering data processing methods with historic approaches (e.g., Nissl) or routine techniques (e.g., hematoxylin & eosin [H&E] stained tissue), it may be possible to discover intricate markers and insights through simpler and more widely accessible measures. This transformative approach relies on training complex models with high-level data and then distilling that knowledge for application to routine technologies like H&E staining[117]. Computer-driven visualization and data mining from existing slide archives hold immense potential for identifying previously overlooked cellular and subcellular changes[118], as well as enabling integration with genomics[119] and other large-scale data sources. Importantly, adapting machine learning models to basic approaches, such as H&E staining carries little risk. To overcome relative lack of labelled images to inform classification or segmentation models[120], recent vision-language foundation models for pathology have introduced promising solutions. For example, leveraging image-text pairs with descriptions available from medically-oriented social media, Large-scale Artificial Intelligence Open Network[121], educational sources, and images and descriptions from PubMed literature, the OpenPath dataset was developed[120]. These vision-language pathology models enable users to retrieve examples by image-based or natural language searches[120,122]. Moreover, machine learning approaches are already providing an expanded repertoire for -omics studies through integration with light microscopy for isotropic super-resolution of synapses[123], decision-making for gene prioritization[124], and lesion identification[77]. Application of machine learning may play a critical role in facilitating a convergence of data streams (**6.2**), seeking to propel the biomedical science community forward as researchers continue to push the bounds through integration of complex technologies like spatial transcriptomics and electron microscopy to study brain injury[27]. Ultimately, machine learning approaches are a key additional element in the neuropathology expert's toolbox, serving to speed up and enhance their ability to derive meaningful insights from tissue in health and disease.

Conclusions

Advancements in brain banking, tissue-based -omics, digital pathology, and machine learning – along with insights from neuroimaging harmonization efforts – mark an unprecedented era in neuropathology. By coining the term *transformative neuropathology*, we hope to provide a unifying

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framework that highlights the field's evolving role in leveraging advanced technologies to accelerate discovery and translational research. The methods and collaborations discussed here illustrate the vast potential of human brain tissue studies to drive molecular breakthroughs that delay disease progression and emphasize the importance for early disease detection. The rapidly evolving field requires striking a balance between supporting large, comprehensive brain banks and small, more specialized ones. While large brain banks facilitate broad-scale studies and initiatives, smaller brain banks excel in focused, targeted research. Supporting both large and small brain banks ensures that a wide range of research priorities – whether broad or specialized – advance our understanding of the human brain. However, both large and small brain banks often experience understaffing. To ensure their sustainability, tissue requestors and providers must proactively work together. This includes directing funds toward brain banks, fostering partnerships with clinical teams, harmonizing data, and cross training the next generation of researchers. Such efforts will ensure that brain banks remain at the forefront biomedical discoveries, advancing our understanding of aging and neurodegeneration to improve outcomes. By incorporating advanced technologies into human brain tissue research, we can unlock new scientific opportunities for scientific discovery. This integrated approach will ultimately enhance diagnostic precision, enable personalized therapy, and significantly reduce the global burden of neurodegenerative diseases on patients, families, and healthcare systems.

Boxes

Box 1 | Low autopsy rate for healthy aging and groups with limited representation in scientific research

1.1 Enhanced education on brain donation through outreach

Recommended solutions:

- Specialized brain bank coordinator dedicated to public engagement and education to undersupported communities, ideally working directly with clinical team, brain bank staff, and outreach coordinators.
- Engaging the public through science writing for the layperson (e.g., newspaper articles, social media) and learning from community advisory boards (e.g., respected elders or religious leaders as ambassadors).
- Knowledge sharing through audience-tailored educational material to increase knowledge of brain donation and strengthen confidence in research[126].
- Involving donor families in outreach efforts is a powerful way to emphasize the value of supporting scientific advancement through tissue donation.
- Funded training workshops with travel for brain bank coordinators and outreach specialists to establish expanded brain bank coordinator networks toward.
- Support for shared autopsy technician lists and protocol templates through centralized web-portal to improve efficiency.

1.2 Enhanced efforts to recruit healthy aging and broaden age spectrum of brain donors

Recommended solutions:

- Enhancement of healthy aging and aging across lifespan brain banking process from same recruitment areas as neurodegenerative brains is essential for advancing neuroscientific research, with ongoing efforts focusing on collaborative solutions.
- Partnering with medical examiners to leverage existing infrastructures and training staff in sensitive etiquette when obtaining consent and medical history[1,10–12].

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- Recruiting family members or caregivers of potential brain donors and tapping into support networks to enhance communication and coordination.
- Databased entry of recruitment sources for study consideration.

Box 2 | Dearth of neuropathology experts and informaticians with brain banking knowledge

2.1 Neuropathology training fellowships for MDs and PhDs

Recommended solutions:

- Enhance robust training pipelines within the field of neuropathology for both MD and PhD-trained clinicians and scientists.
- Support of seed projects and training initiatives to bolster the future of research and diagnostics with enhanced training across brain bank networks.
- Funding opportunities for pathway to independence for those finishing their training and moving to faculty positions.
- Brain bank operations training should include didactic courses and experiential learning on leadership, management, accounting, histology, neuroanatomy, and microscopy to fortify the pipeline of neuropathology faculty.

2.2 Data science training and integration

Recommended solutions:

- Dedicated support of postbaccalaureate fellows, with an emphasis on populations historically less represented in research, to enable informatics training through didactic summer coursework and placement with structured mentorship in brain banks and laboratories conducting aging and neurodegeneration research leveraging human tissue.
- Growth of a Training Without Walls project would require an expansive network of brain banks partnering with data scientists and molecular scientists to ensure broad knowledge gained by the trainees and infrastructure strengthening in the modern era of brain banking.

2.3 NeuroPathopedia - Neuropathology-based encyclopedia

Recommended solutions:

- Support for a publicly available online resource cataloguing macroscopic and microscopic features of tissue health, age-related changes, and neurodegenerative diseases would enable acquisition of knowledge, development of key figures, and harmonized understanding of brain changes observed in aging and disease[24,127]. The comprehensive compilation should include meticulously labeled neuroanatomic structures, as well as cellular architecture.
- Digitization of whole slide images with interactive tools would serve as a cornerstone for educating future neuropathology experts, researchers, and clinicians, offering an extensive repository of visual and diagnostic information on the molecular diversity of neurodegenerative diseases and age-related incidental findings.
- Consideration of a citizen science approach to labeling structures/cellular architecture/lesions in tandem with engagement of neuroanatomists and neuropathology experts may enable a unique learning opportunity to expand public health awareness. The encyclopedia of neuropathology (“NeuroPathopedia”) should aim to provide a structured exploration organized by molecular classification with clinical vignettes to reinforce textbook understanding of aging and disease with consideration of atypical presentations for more advanced learners.

2.4 Phenotypic data collection and tissue provision

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Recommended solutions:

- Design of a laboratory information system (LIS) with a relational database specific to brain bank operations with a dedicated data manager would facilitate phenotypic data and tissue provision efficiency.
- Support for specialized brain bank database management professionals who have or will undergo training in database management, medical abstraction, and neuropathology.
- Databasing of antemortem data pertaining to clinical progression (e.g., age at symptomatic onset, clinical presentation, cognitive/motor testing), lifestyle risk factors (e.g., sleep quality, hearing loss), cardiovascular risk factors (e.g., physical activity, diabetes mellitus, smoking history), and perimortem events (e.g., details on agonal period, cause of death, metrics of tissue quality) would ideally be available for prospectively followed brain donors.
- Development of a retrospective clinical abstraction form for baseline measures documented at the time of tissue receipt for cases sent into a brain bank. Use of form during review of clinical history at the time of brain cutting may facilitate timely follow up with family members and/or caregivers for any missing data.
- Involving clinicians in the cohort-building process is paramount, especially with any consideration of longitudinal data collection. Their expertise contributes to the identification of relevant variables, refining inclusion criteria, and ensuring that the assembled cohorts are tailored to address specific scientific inquiries.
- Development of a disease agnostic, central repository initiative may draw inspiration from the National Alzheimer's Coordinating Center (NACC)[22], which acts as a central repository for Alzheimer's Disease Research Centers[128] to consider version-controlled data capture of clinicopathologic variables with adherence to coded databases for multisite integration of data.
- Mutual flow of raw data back to the brain bank from tissue requestors to further accelerate progress through a convergence of multimodal data.

Box 3 | Tissue quality innovations needed to maximize molecular discoveries

3.1 Molecular and biochemical diagnostics beyond immunohistochemistry

Recommended solutions:

- Molecular diagnostics beyond immunohistochemistry has the potential to transform neurodegenerative disease management through a deeper understanding of neuropathologic changes, preclinical detection, and individualized treatment.
- Investigation of biopsied brain tissue will rely critically on partnerships with clinicians engaged in shunting for normal pressure hydrocephalus or tissue resection for epileptic patients.
- Evaluation of biopsies from peripheral organs, skin, or biofluids may also gain momentum in this critical area.

3.2 Enhanced efforts for development of methods to utilize existing brain bank materials

Recommended solutions:

- Develop methods to utilize pre-existing materials, as many brain banks have existed for decades and have amassed many precious formalin-fixed and frozen samples.

3.3 Enhancing procurement areas and autopsy response teams for sample collection

Recommended solutions:

- Dedicated specimen procurement facilities designed for tissue procurement would be advantageous. If these facilities are under the auspices of the institute, this may allow for

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enhanced collaborations with the tissue requestor coming to collect the samples and process in the means they need for their individual project instead of placing the onus on brain bank personnel. Many brain banks utilize existing hospital infrastructure or mortuaries for sample collection. This can be difficult at times given the multi-purpose usages of the space.

- Support for rapid-response autopsy teams to enhance postmortem tissue quality and minimize effects of postmortem interval made possible by 24-7 on-call staff.

3.4 Harmonization in tissue preparation (fixative, freezing), storage, and inventory

Recommended solutions:

- Establishment of basic harmonized methods for tissue preparation to accommodate the needs of emerging research technologies, effectively future proofing the collected samples. Centralized resource for best practices with dedicated staff updating minimum needs for fixation and freezing[129].
- Development of brain bank-specific inventory systems, as many inventory systems utilized by brain banks were designed for other research realms (such as biofluid collection and storage) and may not be optimal.
- Application of machine learning identification of macroscopic or microscopic features corresponding to quality control metrics of poor-quality tissue to aide neuropathologic screening for high-quality tissue.

Box 4 | Limited capabilities for digital slide sharing to facilitate harmonization of disease staging and capturing phenotypic heterogeneity

4.1 Neuroanatomic segmentation for digitized slides

Recommended solutions:

- Refine existing brain segmentation software tools to distinguish neuroanatomic boundaries, such as gray matter from white matter with ability to apply quantification algorithms[77]. Innovations in histologic segmentation may consider drawing inspiration from neuroimaging software toolbox like FreeSurfer[130] that would include masking tools to assess neuroanatomic data.
- Masks used to restrict the analysis or visualization of data to a specific region of interest on whole slide images should include recognition of cortical and subcortical structures, laminar distinction, nuclear subdivisions, and subcortical nuclei.

4.2 Slide sharing/hosting efforts

Recommended solutions:

- Open-source generalizable and scalable software employed locally to enable whole slide images to be uploaded for slide sharing purposes following findable, accessible, interoperable, and reusable (FAIR) principles for data sharing.
- Slide scanning systems and their associated entities should work toward conversion of non-proprietary and proprietary file types to a common standard, such as DICOM[131] standard ubiquitously used in radiology or emerging cross-discipline open bioimaging formats such as open microscopy environment's next-generation file format (OME-NGFF)[132].
- Working groups toward the development of recommended terminology used to assign metadata associated with digitized tissue sections, as exampled by naming conventions for brain region sampled (e.g., posthippo refers to posterior hippocampus sampled at lateral geniculate nucleus) and histologic stains (e.g., a-syn refers to α-synuclein). A tiered approach may be warranted with consideration of read-only slides with labelled anatomy for didactic purposes. Another tier with

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downloadable access version for local analysis of shared slides, would additionally require further development of cloud computing infrastructure.

- Dedicated brain banking personnel with coding skills and/or collaborations with computer engineering staff would greatly facilitate communication across multi-site slide sharing efforts.

4.3 Neuropathology-centric initiatives

Recommended solutions:

- Dedicated neuropathology-led funded initiatives to ensure a sustained and focused effort to advance the field.
- Integration of both Cores and Projects as part of the funding mechanism should foster innovation. Inclusion of a Computational Core may enable the intricate interplay between data organization, collaborative tools, and machine learning-driven analyses.

4.4 Alliance of worldwide brain banks

Recommended solutions:

- Support for an alliance of worldwide brain banks will be to develop tools and non-proprietary software freely available to all brain banks. Tools are recommended to be designed on heterogeneous datasets from multiple brain banks to ensure generalizability across brain regions, stains, etc. A focus on assessment of established diagnostic features of neuropathology, such as misfolded protein quantification, cerebrovascular pathology, and white matter changes is recommended to enhance operationalized assessment. When adopted with immunohistochemical standards (e.g., antibody clone, pre-treatments) this will allow consistency across all brain banks for grading and staging neuropathologic changes.

Box 5 | Relative lack of common neuropathologic data models and secure storage platforms

5.1 Data harmonization for common data elements

Recommended solutions:

- Development of a comprehensive data framework that can effectively delineate various quality control measures and experimental metrics, offering a coherent system that all can deploy and adopt, as needed. The concept of an inverted pyramid structure advocates for a foundational set of core data elements universally applicable, encompassing fundamental identifiers such as age at death, sex, and geographic location (city, state, country). Building upon this base, specific disease-related variables, carefully chosen based on scientific validation and replication, further enrich the framework. Additionally, the pyramid extends to encompass optional elements (like the inclusion of spinal cord data in Alzheimer's disease cases), and a plethora of experimental variables align with the broad research pursuits within the field.
- Support for adoption of common data elements by brain banks should consider logistics of updating protocols and flexibility to allow for local innovation.

5.2 Sample-level tracking through a universal digital object identifier (DOI)

Recommended solutions:

- Collaborative effort with data/informatics teams to design a method to apply a DOI (free of personal identifiers) to individuals who donated their brain and tissue/data derivatives to enable citation, access, and tracking of available data without disease-specific constraints.
- Collaborative teams should include funds to incentivize brain bank participation to have true partnership and enable back-filling of publicly available datasets. Tangible outcome should

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additionally enable better tissue sharing tracking by brain banks for progress report documentation.

5.3 Codified brain library through an accessible portal

Recommended solutions:

- Safe, secure, and affordable data storage is one of the biggest challenges facing biomedical science, with generated data from individual studies often reaching petabyte scales. Support for a centralized resource for transparency in publications and slide sharing efforts is recommended.
- Dedicated initiative toward the establishment of systematized entry portal with minimum dataset with a robust infrastructure that underpins the accessibility of data. The initiative will seek appropriate open-source software platforms that can effectively facilitate data entry, maintenance, and organization, ultimately enabling widespread community access. This foundation-building process forms the bedrock upon which subsequent advancements can be constructed.

5.4 Common Coordinate Framework

Recommended solutions:

- Implementation of a Common Coordinate Framework (CCF) emerges as an important strategy to enhance analytic harmonization and address the intricacies of neuroanatomic variability of the human brain.
- Fostering agreement and actively implementing a CCF to guide and operationalize sampling procedures to facilitate harmonization across studies. By establishing reference points, the CCF would provide a common language for researchers to navigate the intricate landscape of the human brain, offering a unified framework for spatial representation of neuroanatomic structures at the micro scale. In the pursuit of understanding brain heterogeneity and human variability, the CCF would act as a guiding tool that facilitates consistency in sampling methodologies across institutions.

Box 6 | Emerging need for machine learning to optimize brain bank workflow

6.1 Quality control for digitized slides

Recommended solutions:

- Support for integrated quality control of digitized slides that evaluating slide staining and scan quality would greatly benefit flagging slides for restaining or rescanning prior to downstream analysis efforts. Quality control factors stemming from agonal events, tissue processing, and slide digitization.
- Developing tools to flag or mask artifacts arising from perimortem events may include Swiss cheese artifact, freeze artifact, and autolysis. Tissue processing artifacts may include squamous tissue, tissue folds, tears in the tissue from microtome sectioning, coverslip de-adherence, poor staining and various other types of debris. Slide digitization artifacts may include dust not cleaned from slide or caught under coverslip, as well as blurred/out-of-focus areas.
- Integrated deidentification scripts would enable protected health information to be stripped from slides to avoid relabeling of slides for slide sharing.

6.2 Convergence of diverse data streams

Recommended solutions:

- Toward satisfying the critical need for efficient data organization, funded initiatives leveraging multimodal machine learning models to amalgamate diverse data streams such as histology,

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neuropathology records, genetics, neuroimaging scans, biomarkers, and advanced techniques like multiplexed in-situ hybridization/spatial proteomics in a safe and secure manner would considerably advance the field. A colossal machine learning-driven model to unveil hidden patterns while factoring in potential bias in datasets, overfitting, and hallucinations, catastrophic forgetting, shortcut learning, and correlations would hinge on the ability to establish a coherent structure for organizing brain banking data.

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