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REVIEW

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The contribution of brain banks to knowledge discovery in amyotrophic lateral sclerosis: A systematic review

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Abstract

Over the past decade, considerable efforts have been made to accelerate pathophysiological understanding of fatal neurodegenerative diseases such as amyotrophic lateral sclerosis (ALS) with brain banks at the forefront. In addition to exploratory disease mechanisms, brain banks have aided our understanding with regard to clinical diagnosis, genetics and cell biology. Across neurodegenerative disorders, the impact of brain tissue in ALS research has yet to be quantified. This review aims to outline (i) how postmortem tissues from brain banks have influenced our understanding of ALS over the last 15 years, (ii) correlate the location of dedicated brain banks with the geographical prevalence of ALS, (iii) identify the frequency of features reported from postmortem studies and (iv) propose common reporting standards for materials obtained from dedicated brain banks. A systematic review was conducted using PubMed and Web of Science databases using key words. From a total of 1439 articles, 73 articles were included in the final review, following PRISMA guidelines. Following a thematic analysis, articles were categorised into five themes; clinico-pathological (13), genetic (20), transactive response DNA binding protein 43 (TDP-43) pathology (12), non-TDP-43 neuronal pathology (nine) and extraneuronal pathology (19). Research primarily focused on the genetics of ALS, followed by protein pathology. About 63% of the brain banks were in the United States of America and United Kingdom. The location of brain banks overall aligned with the incidence of ALS worldwide with 88% of brain banks situated in Europe and North America. An overwhelming lack of consistency in reporting and replicability

Abbreviations: AAS, altimetric attention score; AD, Alzheimer's disease; ALS, amyotrophic lateral sclerosis; ALS/FTLD-TDP, amyotrophic lateral sclerosis/frontotemporal lobar degeneration-transactive response DNA binding protein; ALSci, amyotrophic lateral sclerosis cognitive impairment; ALS-FTD, amyotrophic lateral sclerosis-frontotemporal dementia; AMPAR, α-amino-3-hydroxyl-5-methyl-4-isoxazole-propionat; ATXN2, ataxin-2; AUS, Australia; BMAA, β-N-methylamino-l-alanine; BvFTD-MND, behavioural variant frontotemporal dementia- motor neuron disease; *C9orf72*, chromosome 9 open reading frame 72; CB2, cannabinoid receptor 2; CHCHD10, Coiled-Coil-Helix-Coiled-Coil-Helix Domain Containing 10; CHI3L1, chitinase-3-like protein; CHIT-1, chitinase 1; CNS, central nervous system; Con, control; CSF, cerebral spinal fluid; CTXLP, conotoxin-like protein; CXCL12, C-X-C motif ligand 12; DNA, deoxyribonucleic acid; DPR, dipeptide repeat proteins; DSB, double strand breaks; ERVK, endogenous retrovirus-K; FALS, familial amyotrophic lateral sclerosis; FTD, frontotemporal dementia; FTD-TDP, frontotemporal dementia- transactive response DNA binding protein; FTLD, frontotemporal lobar degeneration; FTLD/MND/FUS, frontotemporal lobar degeneration/motor neuron disease/fused-in-sarcoma; FTLD-MND, frontotemporal lobar degeneration- motor neuron disease; HD, Huntington's disease; HERVK, human endogenous retrovirus-K; HSR, heat shock response; LRRC50, leucine-rich repeat-containing protein 50; MND, motor neuron disease; MRC, Medical Research Council; mRNA, micro ribonucleic acid; MS, multiple sclerosis; NACC, National Alzheimer's Coordinating Center; NFT, Neurofibrillary tangles; PD, Parkinson's disease; PNF1, profilin 1; Poly-PR, poly-proline-arginine; PPA, primary progressive aphasia; PPA-MND, primary progressive aphasia- motor neuron disease; PRISMA, preferred reporting items for systematic reviews and meta-analyses; pTDP-43, phosphorylated transactive response DNA binding protein 43; RNA, ribonucleic acid; sALS, sporadic amyotrophic lateral sclerosis; *SOD1*, superoxide dismutase; SZ, schizophrenia; TBK1, TANK-binding kinase 1; TDP, transactive response DNA binding protein; TDP-43, transactive response DNA binding protein 43; UK, United Kingdom; UPR, unfolded protein response; USA, United States of America.

was observed, strengthening the need for a standardised reporting system. Overall, postmortem material from brain banks generated substantial new knowledge in areas of genetics and proteomics and supports their ongoing role as an important research tool.

KEYWORDS
amyotrophic lateral sclerosis, autopsy, brain bank, *C9orf72*, motor neuron disease, pathology, TDP-43

INTRODUCTION

Motor neuron disease (MND) encompasses a heterogeneous group of motor-led neurodegenerative disorders, most commonly presenting as amyotrophic lateral sclerosis (ALS). ALS is characterised by the progressive loss of motor neurons in the cerebral cortex, brainstem and spinal cord, resulting in progressive muscle weakness in the limb, respiratory and bulbar regions.[1–3] In addition, nonmotor symptoms such as apathy, emotional lability, pain, cognitive impairment and frontotemporal dementia are increasingly recognised as a common part of the disease spectrum.[4,5] The progressive nature of ALS results in death, typically from respiratory failure, around 3 years after symptom onset.[6] High efficacy therapies are currently lacking, with only Riluzole and Edaravone offering modest benefits in terms of survival.[7–9] The majority of cases are sporadic, with around 10% occurring on a familial basis, typically due to a repeat expansion in chromosome 9 open reading frame 72 (*C9orf72*).[10,11]

Landmark discoveries over time have shaped our understanding of ALS. Previously, the identification of ubiquitinated cytoplasmic inclusions in sporadic and familial ALS patients[12,13] was considered to be the pathological hallmark of ALS; however, in 2006, a key discovery identified these inclusions to be composed mainly of transactive response DNA binding protein 43 (TDP-43).[14,15] Further subtyping of this TDP-43 identified moderate neurocytoplasmic inclusions, with few dystrophic neurites across all cortical layers, termed Type B, which has become the predominant TDP-43 subtype in ALS.[16] As a result, TDP-43 staging is now the gold standard to categorise the pathological severity of neuropathological disease in ALS.[17]

Over the last two decades, there has been an expansion of in vivo techniques to identify structural and function brain changes across the spectrum of ALS, such as position emission tomography and magnetic resonance imaging.[18,19] However, a significant limitation of these techniques is their inability to provide the resolution needed to assess the cellular and molecular architecture of disease within the brain and spinal cord. As such, analysis of postmortem tissues continues to be an important research tool in identifying disease mechanisms.[20–22] Furthermore, postmortem confirmation of in vivo studies is important to establish the sensitivity and specificity of emerging biomarkers.

From the 1950s, there has been a decline in autopsies. As a consequence, alternate technologies emerged to collect neuropathological material, and in particular, the establishment of immunohistochemistry and molecular biology created an impetus to drive the establishment of brain banks.[23]

Key Points

- The incidence rate of amyotrophic lateral sclerosis currently corresponds to the location of brain banks.
- Majority of brain banks are situated in Europe and Northern America despite incidence of amyotrophic lateral sclerosis increasing worldwide.
- There is a lack of consistent clinical data reporting in the literature.
- Postmortem tissues from brain banks have contributed to significant advances in the areas of genetics and proteomics.

Human brain tissue remains critical to further our understanding of neurodegenerative disease, as it allows clinico-pathological correlations, discovery of gene–protein interactions, their phenotypic expression and the identification of targets for therapeutic intervention. For example, clinico-pathological correlational studies established the continuum of MND and frontotemporal lobar degeneration (FTLD) long before the identification of their shared genetic origins.[24,25] More broadly brain tissue remains the definitive resource in confirming novel hypothetical frameworks of disease biology across the neurodegenerative spectrum.[26]

As autopsy rates decline,[27] it is increasingly important to involve patients, clinicians and the broader ALS community to ensure brain banks remain viable and are able to answer important emerging research questions.[28] However, the impact of brain banks in the field of ALS research has not been previously quantified. Through highlighting research outputs from brain banks, participation in brain donor programmes may be strengthened, providing evidence to support the longer-term viability of these complex resources.

As such, the present review aims to quantify how data generated from brain banks have influenced and added to our current understanding of ALS over the last two decades. Secondly, we aim to determine the relationship between location of dedicated brain banks and geographic prevalence of ALS. Thirdly, we seek to identify patterns of outcomes reported from previous studies and finally, provide an initial framework for common research reporting standards from brain banks for future research.

METHODS

Search strategy and selection criteria

PubMed and Web of Science were searched systematically using key words "motor neuron disease" OR "amyotrophic lateral sclerosis" OR "frontotemporal dementia" or "frontotemporal lobal degeneration" AND "brain bank" OR "autopsy" OR "postmortem" in the title/abstract. Restrictions were placed on the year of publication (1 January 2005 to 24 June 2021) and language (English). A period reflecting the last 15 years was chosen to reflect contemporary research themes in the context of recent clinical, genetic and molecular discoveries. Data search, screening and data extraction were done by one author (SM). Articles were included if the number of subjects in each study was >10, were in English and were original articles that reported data on material from formal brain banks. Here we defined formal brain banks as institutions that stored brain tissue and clinical information for the purpose of research and distribution. This search strategy was employed to capture data generated using tissue from brain banks as the focus of the study is to highlight the impact of brain banks in contributing to knowledge discovery and as a robust research tool. As a result, we did not include studies where there was no clear research question (e.g. annual reports and descriptive histopathological data) or publications which were single-case or had limited numbers (n < 10) which may reduce the generalisability of findings. Duplicate articles across the two search engines, review articles, meta-analyses and original articles reporting on material exclusively from hospitals or adhoc tissue banking organisations were excluded from the review. These original articles were excluded due to our interest in the impact of dedicated brain banks. This review was conducted using preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines for performing systematic reviews.[29]

A total of 1439 articles were identified. A total of 717 duplicate articles were excluded, and a further 649 articles were excluded after full-text review as they did not meet the inclusion criteria. This resulted 73 articles for the final analysis (see Figure 1). Data were extracted independently by one author (SM) and entered in Excel version 16 for analysis. This included study aims, methods, results, conclusions, sample size, sex of participants, average age at death and disease duration. Thematic analysis was undertaken by textual evaluation of the primary objectives of each study (SM and CJM). This resulted in identification of five broad research themes: clinico-pathological, genetics, TDP-43 protein pathology, non-TDP-43 intraneuronal pathology and extraneuronal pathology. Clinical, demographic and histological information reported in each study was extracted from the methods and results section of each paper.

Clinico-pathological studies are defined as studies where the pathological diagnosis was used to generate knowledge on clinical phenotype or vice-versa. Genetic studies are defined as studies where the aims focused on genes, their expansions, deletions, duplications and repeats. TDP-43 protein pathology studies are defined as studies where the primary aim was to examine TDP-43 pathology or interactions with TDP-43. Non-TDP-43 neuronal pathology studies are defined as studies where the primary aims focused on other proteinopathies occurring within neurons. Extraneuronal pathological studies are defined as studies where the primary findings were located outside neurons, that is, within supporting cells or extracellular fluids.

Location of brain banks

We compared the location of formal brain banks with the prevalence of ALS globally using QGIS version 3.16.14.[30] Latitude and longitude of the brain bank location were captured from Google Maps and input onto Microsoft Excel. Using previously published data, estimated per capita ALS prevalence was determined.[31] This was used to generate a global heatmap of ALS prevalence with the location of brain banks overlayed.

RESULTS

A total of 73 studies, classified into five thematic research categories, were included in this review. Thirteen studies were categorised into *clinico-pathological* (Table 1), 20 into *genetic* (Table 1), 12 into *TDP-43 pathology* (Table 2), nine studies into *Non-TDP-43 neuronal pathology* (Table 2) and 19 studies into *Extraneuronal pathological studies* (Table 2). Tables 1 and 2 report the top five studies from each

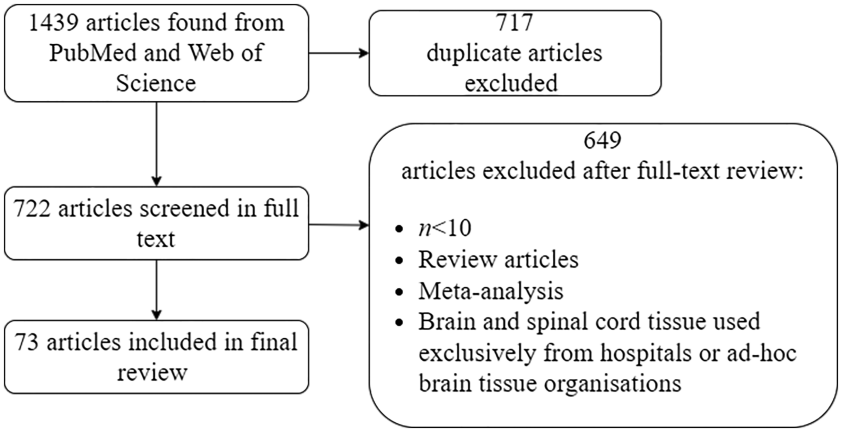

FIGURE 1 Selection strategy of articles included for review

TABLE 1 Clinicopathological and genetic

Author and year of publication	Altmetric score	Aim	Brain bank	No of ALS (M:F)	Disease duration (month)	Age at death (year)	Impact/conclusion
Clinico-pathological							
Vinceti G et al 2019[32]	18	Evaluate the prevalence of PPA in a series of pathologically confirmed cases of FTD-MND spectrum.	University of California, San Francisco Brain bank, USA.	PPA-MND: 10 (7:3) BvFTD-MND: 22 (21:1) ALS: 9 (7:2) Con: 21 (7:14)	PPA-MND: 109.2 BvFTD-MND: 96 ALS: 40.8	PPA-MND: 60.7 BvFTD-MND: 62.5 ALS: 61.5 Con: n/a	About 31% of those with FTLD-MND at postmortem had an early clinical presentation consistent with a PPA.
Umoh ME et al. (2018)[33]	18	Assess the relationship of differences in clinical and pathological phenotypes within the ALS-FTD spectrum.	Emory Alzheimer's Disease Research left, Brain Bank, USA.	ALS: 19 (9:10) ALS-FTD: 10 (7:3) FTD: 13 (7:6) Con:10 (5:5)	ALS: 47.37 ALS-FTD: 62.4 FTD: 69.72	ALS: 59 ALS-FTD: 63.8 FTD: 63.8 Con: 72	Eight modules of co-expressed proteins are significantly different across ALS-FTD disease spectrum, and these correlate with TDP-43 pathology and cognitive dysfunction.
Placek K et al. (2021)[34]	14	Evaluate the polygenic contributions to cognitive dysfunction in patients with ALS.	University of Pennsylvania Integrated Neurodegenerative Disease Biobank, USA.	ALS: 80 (n/a) ALSci: 5 (n/a) ALS-FTD: 2 (n/a)	50.64[a]	63.8[a]	Common genetic polymorphisms may contribute to the risk of cognitive dysfunction in ALS.
Borrego-Écija S et al. (2021)[35]	13	Determine the influence of demographic, genetic and pathological factors on cognitive impairment in ALS.	Neurological Tissue Bank, Hospital Clínic - IDIBAPS Biobank in Barcelona, Spain.	ALS: 64 (30:34) ALSci: 9 (4:5) ALS-FTD: 31 (16:15)	ALS: 42 ALSci: 49 ALS-FTD: 51	ALS: 66.6 ALSci: 71.2 ALS-FTD: 68.7	Cognitive decline is attributed to FTLD diagnosis in most ALS cases but not all. Non-FTLD cases influence cognitive status in older age groups.
Mahoney C et al. (2012)[36]	12	Present detailed retrospective clinical and pathological analysis of a *C9orf72* mutation case series.	University College London, UK.	FTLD *C9orf72*: 19 (n/a)	n/a	n/a	There is significant clinical heterogeneity across *C9orf72* mutation patients. About 36% of FTLD patients with *C9orf72* mutation develop MND.
Genetic							
McCann EP et al. (2020)[37]	26	To characterise the genetic and pathological contribution of CHCHD10 in ALS/FTD patients in Australia.	New South Wales Brain Bank Network, AUS.	ALS spinal cord: 20 (n/a) Control spinal cord: 7 (n/a) ALS motor cortex: 15 (n/a)	ALS spinal cord: 43.2 ALS motor cortex: 44.4 Frontal cortex ALS-FTD: 45.96	ALS spinal cord: 66.85 Con spinal cord: 63.29 ALS motor cortex: 67.87	The loss of function of the genetic variation CHCHD10 may be causative to ALS and/or FTD.

(Continues)

TABLE 1 (Continued)

Author and year of publication	Altmetric score	Aim	Brain bank	No of ALS (M:F)	Disease duration (month)	Age at death (year)	Impact/conclusion
				Control motor cortex: 4 (n/a) ALS-FTD frontal cortex: 6 (n/a) FTD-TDP frontal cortex: 6 (n/a) Control frontal cortex: 6 (n/a)	Frontal cortex FTD-TDP: 51.96	Con motor cortex: 61.7 Frontal cortex ALS/FTD: 64.5 Frontal cortex FTD-TDP: 64 Frontal cortex Con: 63.83	
Weinreich M et al. (2020)[38]	14	To identify the frequency and phenotype of TBK1 mutations in a cohort of ALS patients.	Sheffield Brain Tissue Bank, UK.	n/a	n/a	n/a	TBK1 mutations were present in 1.38% of ALS cases with no clear genotype–phenotype associations.
Durrenberger PF et al. (2015)[39]	12	To generate comparative genome-wide gene expression data for six neurodegenerative diseases and one psychiatric disorder in order to identify common mechanistic pathways.	1) London Imperial College, UK. 2) Neurobiobank, Munich Germany. 3) Human Brain Tissue Bank in Budapest, Hungary.	AD: 12 (7:5) AD Con: 6 (3:3) ALS: 9 (6:3) ALS Con: 7 (7:0) HD: 10 (7:3) HD Con: 10 (8:2) MS: 10 (5:5) MS Con: 10 (6:4) PD: 12 (6:6) PD Con: 7 (5:2) SZ: 10 (5:5) SZ Con: 10 (5:5)	n/a	AD: 81.33 AD Con: 60.33 ALS: 68.11 ALS Con: 63.86 HD: 59.11 HD Con: 53.7 MS: 49.40 MS Con: 53.10 PD: 81.5 PD Con: 65.86 SZ: 66.30 SZ Con: 61.20	No dysregulated genes were identified to be common across the neurodegenerative disorders studied.
Figueroa-Romero C et al. (2016)[40]	12	Investigate the contribution of dysregulated mRNA mediated dysregulation of genes and biological pathways contributing to sporadic ALS pathogenesis.	National Institute for Child Health and Human Development (NICHD) Brain and Tissue Bank for Developmental Disorders, USA.	ALS: 12 (10:2) Con: 12 (10:2)	n/a	ALS: 56 Con: 55	mRNAs are found in the spinal cord of familial and sporadic ALS patients. These affect the functional pathways and promotes upregulation of 237 genes.

(Continues)

TABLE 1 (Continued)

Author and year of publication	Altmetric score	Aim	Brain bank	No of ALS (M:F)	Disease duration (month)	Age at death (year)	Impact/conclusion
Andrade NS et al. (2020)[41]	12	Evaluate the DPR-mediated DNA damage and the effect of DPR on efficiency of each DNA DSB repair pathways.	1) Georgetown Brain Bank, USA. 2) University of California San Diego, USA. 3) Barrow Neurological Institute, USA.	sALS: 6 (n/a) *C9orf72*+: 5 (n/a) *C9orf72* + ALS-FTD: 1 (n/a) Con: 6 (n/a)	n/a	n/a	Deficits in homology-directed DNA double strand break repair pathways are a novel feature of *C9orf72*-related disease.

Abbreviations: AD, Alzheimer's disease; ALS, amyotrophic lateral sclerosis; ALSci, amyotrophic lateral sclerosis cognitive impairment; ALS-FTD, amyotrophic lateral sclerosis-frontotemporal dementia; AUS, Australia; BvFTD-MND, behavioural variant frontotemporal dementia- motor neuron disease; *C9orf72*, chromosome 9 open reading frame 72; CHCHD10, Coiled-Coil-Helix-Coiled-Coil-Helix Domain Containing 10 Con, control; DNA, Deoxyribonucleic acid; DPR, dipeptide repeat proteins; DSB, double strand breaks; FTD, frontotemporal dementia; FTD-TDP, frontotemporal Dementia- transactive response DNA binding protein; FTLD, frontotemporal lobar degeneration; FTLD-MND, frontotemporal lobar degeneration- motor neuron disease; HD, Huntington's disease; mRNA, micro ribonucleic acid; MS, multiple sclerosis; PPA-MND, primary progressive aphasia-motor neuron disease; PD, Parkinson's disease; PPA, primary progressive aphasia; sALS, sporadic amyotrophic lateral sclerosis; SZ, schizophrenia; TBK1, TANK-binding kinase 1; TDP-43, transactive response DNA binding protein 43; UK, United Kingdom; USA, United States of America.

[a]The numbers reported in this study are not representative of all cases.

category ranked by the publications altimetric attention score (AAS). Where the AAS was the same for multiple articles, the article with a higher 'readers on Medley' score was included in the results section. The AAS reflects a weighted approximate of attention the article generates through media and other nontraditional measures of academic output. This was chosen to ensure that more recently published articles were not disproportionately disadvantaged in this ranking. The remaining studies not listed in the results section can be found in the supporting information Tables S1 to S5.

Clinico-pathological studies

The top-ranking clinicopathological studies broadly focused on clinical phenotypes and cognitive dysfunction (Table 1). These studies highlighted numerous novel findings of clinical relevance. Approximately one third of patients with typical ALS neuropathology have features of early language dysfunction.[32,46] Impaired odour detection in patients was also found to be a useful clinical surrogate to stage extramotor TDP-43 spread.[57] Cognitive dysfunction and extramotor atrophy in ALS was found to be influenced by a polygenic risk profile due to a range of genetic polymorphisms,[34] while cognitive decline in ALS patients was more likely to occur in those with more extensive TDP-43 deposition and additional neuropathological features typical of FTLD.[35] The emergence of cognitive phenotypes across the spectrum of amyotrophic lateral sclerosis-frontotemporal dementia (ALS-FTD) and more widespread TDP-43 deposition appears to depend on the expression of particular protein networks, in particular networks enriched with ribonucleic acid (RNA) binding proteins, and markers of microglial function also appear to drive phenotypic expression.[33]

Several studies establish the association between expansions in *C9orf72*, ALS and frontotemporal dementia (FTD), strengthening the notion that these clinical phenotypes exist on a continuum, while also identifying the neuropathological hallmarks of this mutation, notably the presence of p62 positive inclusions and dipeptide repeat aggregates.[58-60] Survival in those with *C9orf72* mutations was shorter compared with those with sporadic disease (30.5 months vs. 36.3 months),[61] with the majority of the *C9orf72* mutation carriers having FTD alone (59%), followed by FTD-MND (28%).[60] In a separate study, 36% of those with FTLD pathology associated with a *C9orf72* mutation developed MND.[36]

Genetic studies

The top-ranking studies related to genetics are listed in Table 1. About 25% of studies focused on *C9orf72*, while the remaining 75% focused on epigenetically altered genes, gene pathways and novel genetic associations. Neuropathological materials were used to confirm that several rare mutations including TANK-binding kinase 1 (TBK1),[38] Profilin 1 (PNF1)[62,63] and Ataxin-2 (ATXN2)[64] are neuropathologically associated with TDP-43. While mutations in Coiled-Coil-Helix-Coiled-

TABLE 2 Cellular pathology

Author and year of publication	Altmetric score	Aim	Brain bank	No of ALS (M:F)	Disease duration (month)	Age at death (year)	Impact/conclusion
TDP-43 pathology							
Tam OH et al. (2019)[42]	128	Determine whether retrotransposon desilencing would be expected in human tissues with TDP-43 dysfunction.	Target ALS human postmortem Tissue core, USA.	ALS: 77 (38:39)	ALS: 40.97	ALS: 65.5	Retrotransposon desilencing is associated with TDP-43 dysfunction and occurs in a subset of 20% of ALS patients.
Dedeene L et al. (2019)[43]	21	Investigate whether cells are involved in the circadian sleep/wake cycle are affected by pTDP-43 aggregates and DPR inclusions in ALS/FTLD-TDP patients with *C9orf72*.	1)UZ Leuven brain biobank (Belgium). 2)Municipal hospital Offenbach (Germany).	ALS *C9orf72+*: 7 (6:1) sALS: 21 (13:8) Con: 3 (2:1)	n/a	ALS *C9orf72+*: 56.7 sALS: 62.1 Con: 63	DPR deposit may influence the sleep/wake disturbances observed in these patients as it was observed in the circadian sleep/wake-associated cells of ALS/FTLD-TDP patients with the *C9orf72* repeat expansion.
Highley JR et al (2014)[44]	18	To determine whether RNA splicing dysregulation is present in lower motor neurons in ALS and in a motor neuron-like cell model and if TDP-43 is associated with RNA splicing.	Sheffield Brain Tissue Bank, UK.	sALS: 3 (2:1) *C9orf72+*: 3 (2:1) Con: 6 (5:1)	n/a	sALS: 65.67 *C9orf72+*: 54.67 Con: 61.67	Loss of nuclear TDP-43 is associated with RNA splicing dysregulation in ALS motor neurons. This contributes to disease pathogenesis.
Manghera M et al. (2016)[45]	17	Evaluate whether TDP-43 expression impacts the expression of human ERVK in ALS patients.	National Institute of Health NeuroBioBank, USA.	ALS: 5 (4:1) Con: 5 (4:1)	n/a	ALS: 61.4 Con: 71.4	ERVK protein aggregation is a novel aspect of TDP-43 misregulation and has a role in motor neuron death contributing toward ALS pathology.
Yang Y et al. (2019)[46]	15	Assess the amount of phosphorylated and nonphosphorylated TDP-43 in the motor brain regions of cases of ALS with and without repeat expansions in the *ATXN2* or *C9orf72* genes.	New South Wales Brain Tissue Resource Centre, AUS.	ALS: 23 (15:8) Con: 10 (5:5)	ALS: 34.32	ALS: 65.78 Con: 71.5	Higher levels of pathologic TDP-43 are a consequence of different posttranslational modifications in genetic ALS cases as TDP-43 levels are similar in genetic and nongenetic cases.
Non-TDP 43 neuronal pathology							
Garson JA et al. (2019)[47]	33	Confirm independently the observation that HERV-K RNA levels are elevated in ALS brain.	MRC Neurodegenerative Disease Brain Bank Network, UK.	ALS: 34 (24:10) Con: 23 (12:11)	n/a	ALS: 66.91 Con: 73.52	No association between elevated cortical HERV-K RNA levels and ALS as recently was found.

(Continues)

TABLE 2 (Continued)

Author and year of publication	Altmetric score	Aim	Brain bank	No of ALS (M:F)	Disease duration (month)	Age at death (year)	Impact/conclusion
Montibeller L et al. (2020)[48]	19	Compare proteostasis regulatory pathways UPR and HSR in the motor cortex and spinal cord of sALS patients.	1)Imperial College ALS Tissue Bank, UK. 2)Brains for Dementia Research Brain bank, Kings College London, UK.	sALS: 10 (8:2) sALS Con: 13 (7:5) FTLD: 20 (n/a) FTLD con: 20 (n/a)	n/a	n/a	Protein homeostasis is strongly and selectively activated in sALS motor cortex and spinal cord.
Gregory JM et al (2020)[49]	14	Compare the regional expression of AMPARs in sALS, *SOD1* (I114T) and *C9orf72* repeat expansion mutations patients.	MRC Edinburgh Brain Bank, UK.	sALS: 3 (2:1) *C9orf72*: 3 (0:3) *SOD1*: 3 (1:2) Con: 3 (2:1)	sALS: 35.33 *C9orf72*: 79.67 *SOD1*: 97.33	sALS: 65 *C9orf72*: 62.67 *SOD1*: 62.67 Con: 63.67	AMPAR subunit dysregulation is extensive across spinal cord, anterior horn, motor and prefrontal cortex in sALS patients. In *SOD1* and *C9orf72* patients AMPAR dysregulation was restricted to spinal motor neurons.
Andres-Benito P et al. (2019)[50]	11	Identify the distribution and location of LRRC50 in the nervous system of sALS patients.	Institute of Neuropathology HUB-ICO-IDIBELL Biobank, Spain.	sALS: 13 (6:7) Con: 13 (8:5)	n/a	sALS: 68.23 Con: 60.46	LRRC50 are present in the C-boutons of spinal cord motor neurons and selected motor nuclei of the brain stem in sALS patients suggesting this is a pathogenic factor in MND.
Schludi MH et al. (2015)[51]	10	Compare the expression pattern of the DPR proteins in rat primary neurons and postmortem brain and spinal cord of *C9orf72* mutation patients.	Neurobiobank Munich, Germany.	FTLD/MND: 8 (6:2) MND: 3 (1:2) FTLD: 3 (2:1) FTLD/MND/FUS: 1 (0:1) Con: 2(1:1)	FTLD/MND: 76.57[a] MND: 22.67 FTLD: 48[a] FTLD/MND/FUS: 48	FTLD/MND: 59.25 MND: 54.33 FTLD: 65.33 FTLD/MND/FUS: 54 Con: 60	DPR protein Poly-PR inclusions are significantly more abundant in FTLD cases than in MND cases, correlating with neuropathological subtypes.
Extraneuronal pathology							
Alonso R et al. (2017)[52]	65	To determine the existence of fungal infection in different regions of the CNS of ALS patients.	Banco de Tejidos CIEN brain bank, Spain.	ALS: 11 (3:8) Con: 4 (2:2)	n/a	n/a	ALS patients are more likely to have intracellular fungal infection compared with controls suggesting a potential role its involvement in disease pathophysiology.

(Continues)

TABLE 2 (Continued)

Author and year of publication	Altmetric score	Aim	Brain bank	No of ALS (M: F)	Disease duration (month)	Age at death (year)	Impact/conclusion
Pablo J et al (2009)[53]	50	Screen and quantify the neurotoxic amino acid β-N-methylamino-l-alanine (BMAA) in AD, ALS, HD and control patients.	NIH NeuroBioBank, USA	ALS: 13(9:4) AD: 12(7:5) HD: 8(5:3) Con: 12(8:4)	ALS: 50.76 AD: 78.6 HD: 222	ALS: 69 AD: 78.92 HD: 64.88 Con: 72.67	BMAA in neuroproteins was present in sporadic AD and ALS. This suggests that there is a gene/environment interaction where BMAA can trigger neurodegeneration in vulnerable individuals.
Saul J et al (2020)[54]	26	Investigate global transcriptomic and histopathological changes in postmortem choroid plexus of ALS and nonneurologic disease controls.	1)National Institutes of Health, Neurobiobank, USA. 2) Barrow Neurological Institute ALS Tissue Bank, USA. 3)Target ALS Human Postmortem Tissue Core, USA.	ALS: 57 (29:28) *SOD1*: 1 (1:0) *C9orf72* + ALS: 9 (3:6) sALS: 47 (25:22) Con: 35 (26:9)	ALS: 54.96 *SOD1*: 74 *C9orf72* + ALS: 40 sALS: 50.87	ALS: 59.30 *SOD1*: 50 *C9orf72* + ALS: 63.75 sALS: 64.17 Con: 63.6	There is widespread structural and functional disruption of the blood CSF barrier within the choroid plexus with loss of pericytes around blood vessels.
Andrés-Benito et al. (2020)[55]	23	Identify and validate selected putative biomarkers in the anterior horn of the lumbar spinal cord in sALS patients.	Institute of Neuropathology HUB-ICO-IDIBELL Biobank, Spain.	ALS: 22 (12:10) Con: 17 (10:7)	n/a	ALS: 65.33[b] Con: 61.82	CSF and immunoreactivity both show increased CXCL12 in sALS patients. Hence increased CXCL12 levels in CSF can be used to diagnose sALS.
Espejo-Porras F et al. (2018)[56]	18	To investigate the motor cortex of MND patients to confirm if CB2 receptors are elevated.	London Neurodegenerative Diseases Brain Bank, UK.	MND: 8 (5:3) Con: 6 (1:5)	n/a	MND: 81 Con: 85	CB2 receptors are elevated prior and independent to neuronal loss in the motor cortex. This receptor can be targeted for therapy.

Abbreviations: AD, Alzheimer's Disease; ALS, amyotrophic lateral sclerosis; ALS/FTLD-TDP, amyotrophic lateral sclerosis/frontotemporal lobar degeneration- transactive response dna binding protein; AMPARs, α-amino-3-hydroxyl-5-methyl-4-isoxazole-propionat; ATXN2, ataxin-2; AUS, Australia; BMAA, β-N-methylamino-l-alanine; *C9orf72*, chromosome 9 open reading frame 72; CB2, cannabinoid receptor 2; CNS, central nervous system; Con, control; DPR, dipeptide repeat proteins; CSF, cerebral spinal fluid; CXCL12, C-X-C motif chemokine ligand 12; ERVK, endogenous retrovirus-K; FTLD, frontotemporal lobar degeneration; FTLD/MND/FUS, frontotemporal lobar degeneration/motor neuron disease/fused-in-sarcoma; HD, Huntington Disease; HERVK, human endogenous retrovirus-K; HSR, heat shock response; LRRC50, leucine-rich repeat-containing protein 50; MND, motor neuron disease; MRC, medical research council; Poly-PR, poly-proline-arginine; pTDP-43, phosphorylated transactive response DNA binding protein 43; RNA, ribonucleic acid; sALS, sporadic amyotrophic lateral sclerosis; *SOD1*, superoxide dismutase; TDP, transactive response DNA binding protein; TDP-43, transactive response DNA binding protein 43; UK, United Kingdom; UPR, unfolded protein response; USA, United States of America.

[a]Data from one patient not reported.

[b]Average calculated on missing data.

Coil-Helix Domain Containing 10 (CHCHD10) were not found to be common, reduced expression of CHCHD10 within neurons may have a role in the pathogenesis of sporadic ALS.[37] A genome-wide gene expression study utilising brain materials from 113 individuals with a neurodegenerative condition did not identify commonly dysregulated genes suggesting mechanistically diverse pathogenesis.[39]

Increased activation of deoxyribonucleic acid (DNA) repair genes,[65] and deficits in homology-directed DNA repair pathways were identified in those with *C9orf72* associated ALS.[41] Loci-specific alterations in methylation of genes were identified in the spinal cord but not whole blood in sporadic ALS (sALS) patients,[66] suggesting some phenotypic specificity for these epigenetic markers in prodromal ALS.

Brain bank materials provided confirmation of animal and cellular models of ALS, confirming that similar profiles of protein products occurred in superoxide dismutase (*SOD1*) models and individuals with sALS.[67] Brain tissues were utilised to confirm that abnormalities in RNA processing are critical in disease. Within *C9orf72* carriers, RNA-binding proteins were found to contribute to the formation of p62 positive inclusions,[68] while RNA foci and TDP43 appear to be colocalised within spinal motor neurons but not within cortical motor neurons or extramotor cortex.[69]

TDP-43 pathology studies

Top-ranking TDP-43 pathology studies are listed in Table 2. The highest ranked article identified that high levels of retrotransposons expression are found in postmortem brain of those with ALS. These important gene regulators bind to TDP-43 and undergo silencing which may contribute to TDP-43 aggregation.[42] The role of TDP-43 and related proteins has been explored in a range of extramotor neural networks. Dipeptide repeat proteins (DPR) inclusions, associated with *C9orf72* related ALS, were found to occur in the suprachiasmatic nucleus, though these neurons were devoid of TDP-43 positive inclusions, suggesting that a unique neuropathological insult may occur within sleep/wake regulating cells,[43] as opposed to other brain regions. The specificity of TDP-43 in certain neurodegenerative diseases has also been refined with additional colocalisation of S403-phosphorylated p62 with TDP-43 inclusions in both ALS and Alzheimer's disease (AD) brain tissue but not in other neurodegenerative disorders.[70] Different levels of phosphorylated but not nonphosphorylated TDP-43 have been identified in those with *C9orf72* mutations compared with those with sporadic ALS, suggesting different posttranslational modifications in familial disease.[46] Loss of nuclear TDP-43 has also been implicated in disease pathogenesis, with one study suggesting that this may be due to RNA splicing dysregulation,[44] ultimately leading to mislocalisation of TDP-43.[71] Finally, endogenous retrovirus-K (ERVK) protein has been reported to modulate TDP-43 contributing to accumulation of aggreationg forms of TDP-43 but not wild-type TDP-43 providing support for pro-inflammatory pathways in the patophysiology of ALS.[45]

Non-TDP-43 neuronal pathology

Top-ranking studies are listed in Table 2. Studies in this category examined the role of proteins other than TDP-43 which directly accumulate or impact neurons. Several studies examined pathways which may contribute to neurodegeneration: Ca++-induced excitotoxicity was implicated through the finding of α-amino-3-hydroxyl-5-methyl-4-isoxazole-propionat (AMPAR) dysregulation, particularly in sALS[49]; upregulation of unfolded protein response (UPR) and heat shock response (HSR) genes contribute to activation of the protein homeostasis system in motor cortex and spinal cord.[48] The role of ERVK has again been explored with no association found between elevated cortical ERVK-K RNA levels and ALS,[47] which contrasts a previous study suggesting that ERVK was associated with greater TDP-43 accumulation.[45]

A number of novel proteins were implicated in neuronal death: Increased levels of leucine-rich repeat-containing protein 50 were identified within C-boutons of motor neurons, implicating cholinergic transmission in disease pathogenesis,[50] and conotoxin-like protein (CTXLP), a novel ERVK protein, was associated with upper motor neuron degeneration.[72] γ-synuclein was identified within the dorsolateral column in ALS patients and has been speculated to have a role in disease pathogenesis.[73] While p62 inclusions can occur in ALS and FTD phenotypes, DPR proteins are particularly specific to ALS-FTD patients and are highly predictive of *C9orf72* mutations.[51,74] Finally, brain tissue was used to confirm that a small proportion of patients who develop sporadic FTD have fused in sarcoma (FUS) pathology which has also been observed in rare familial ALS cases due to a mutation in the FUS gene.[75]

Extraneuronal pathological studies

Top-ranking studies are listed in Table 2. These studies were varied examining white matter, fungal infections, iron metabolism and neuropathological continuity. ALS patients were more likely to have intracellular fungal infection compared with controls with the range of fungal infections broad, providing a novel contribution to potential causes of ALS.[52] Other neurotoxins have also been examined using brain tissue including cyanobacterial neurotoxin β-N-methylamino-l-alanine (BMAA) which occurs at levels twice as high in ALS compared with control and may provide clues to environmental triggers of disease.[53] Several studies examined changes in white matter pathology with early induction of astrocyte senescence seen in ALS, a greater burden of glial inclusions within oligodendrocytes in those with *C9orf72* mutations compared with those with sporadic ALS.[76] Though in contrast to this, a finding that TDP-43 inclusions are uncommon within white matter with no inclusions identified in corticospinal tracts, cingulum bundle or corpus callosum was also seen.[77] This may be a reflection of the cohort chosen for this study as more extensive white matter pathology has been associated with greater behavioural and cognitive dysfunction.[78] Elevation in pro-inflammatory markers chitinase 1 (CHIT-1) and chitinase-3-like protein (CHI3L1) was also seen within glial cells and correlated with rates of disease progression.[79] Several investigations

confirmed disruption within the blood–brain barrier and choroid plexus, with accompanying loss of pericytes identified.[54] C-X-C motif ligand 12 (CXCL12) was identified at high levels in cerebral spinal fluid (CSF) and tissue from sporadic ALS patients, adding to the range of pro-inflammatory cytokines implicated in ALS.[55] Abnormal iron metabolism has also been suggested with two studies combining magnetic resonance imaging and neuropathology identifying accumulations of neuronal iron in patients with ALS and FTLD pathology.[80] A further study identified that excess iron in ALS appears most prominently within the caudate and subthalamic nuclei.[81]

Reporting of clinical and demographic data

Data from 73 articles identified 83 neurological disease groups, their subtypes as well as controls, which were included in this review. Based on the available data reviewed, this represents 6967 sample contributions (2315 male, 2652 female). However, sex was not universally reported (76.7% of studies) within the samples, with fewer studies reporting age at death (75.3%) and disease duration (43.8%).

Figure 2 highlights the frequency of clinical and pathological data reported. These data were markedly heterogeneous. About 32% of studies did not report any clinical data. Postmortem delay was the most commonly reported clinical variable (28.7%) followed by ALS phenotype (27.4%). Only 9% of studies reported that samples were obtained from individuals meeting current clinical consensus criteria for ALS.[32,38,42,62,70,82,83] Similarly, less than 10% of the papers reviewed reported on concomitant neuropathology or severity of TDP-43 deposition.[17] While most studies used postmortem brain tissue, 9% of studies reported using spinal cord tissue.

Location of brain banks

Postmortem material was obtained from 47 institutions which were either formal brain banks or in some cases a combination of formal brain banks, universities or hospitals. Of the 47 institutions identified in the current study, 41 were from dedicated brain banks and six were universities and hospitals. Twenty-three institutes were in the United States, seven in the United Kingdom, three in Australia, three in Spain, two in Germany, two in Belgium, two in France, one in Netherlands, one in Japan, one in Hungary, one in Canada and one in New Zealand (see Figure 3). Fourteen studies used more than one location to obtain their samples from which six studies used a combination of formal brain banks and universities that store brains. There was mostly concordance between the location of brain banks and regions with countries with higher incidence of ALS; however, regions including Scandinavia notably had no brain banks identified in this study. Furthermore, this review failed to identify any brain banks in South America, Africa and most of Asia.

DISCUSSION

The establishment of brain banks has provided a framework for substantial progress in establishing disease mechanisms in a range of neurological and psychiatric disorders, most notably in Alzheimer's and

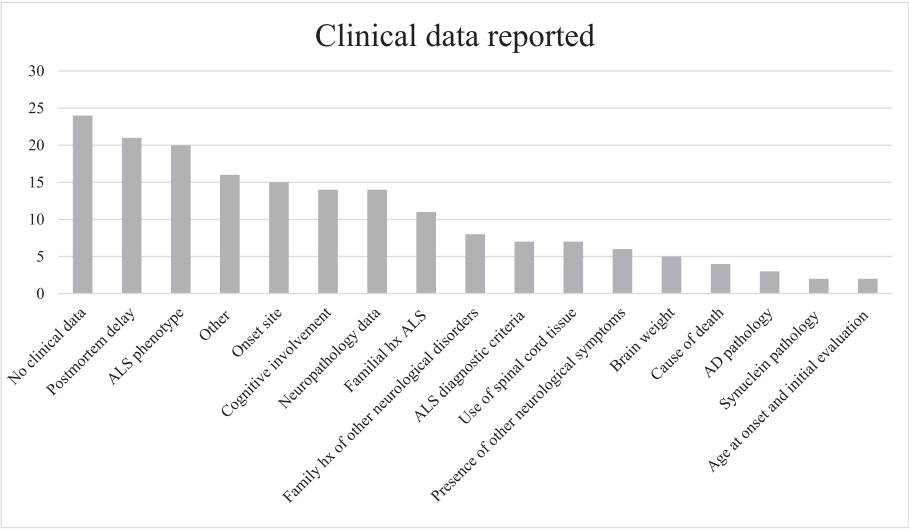

FIGURE 2 Types of clinical data reported in the literature that were identified in this review. Each data point reflects a study that included data in that particular category. Some studies reported more than one category of clinical data. The 'other' category comprises of unique clinical information reported in each study (i.e. not replicated across studies) and includes the following: chronic traumatic encephalopathy stage, education (years), electrophysiology findings, handedness, illness duration at initial evaluation, language features, nationality, odour stick identification test for Japanese, oxidative stress, psychiatric diagnosis, repetitive head impacts exposure, secondary disease classification, traumatic brain injury, traumatic brain injury presence, upper motor neuron degeneration, vascular risk factors and weight change. Abbreviations for other categories: ALS, amyotrophic lateral sclerosis; MND: motor neuron disease; NFT, neurofibrillary tangles

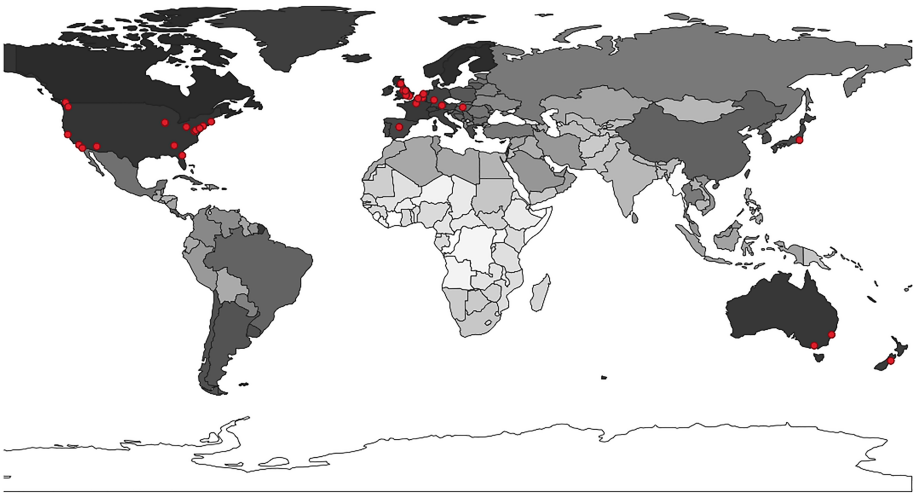

FIGURE 3 Prevalence per capita of motor neuron disease (MND) patients globally. Using the population of MND patients in 2016 from Logroscino et al.,[31] per capita population of MND was mapped against the brain banks identified in this review. The location of brain banks aligns with the prevelance of MND with brain banks primarily in Europe and Northern America.

Parkinson's disease research.[84,85] To our knowledge, there has been no previous attempts to quantify the impact of brain banks in ALS research, and to this end, we have identified 73 studies originating from dedicated brain banks in the last 15 years, representing close to 7000 tissue donations, across several research themes: clinicopathological studies, genetic studies, studies related to both TDP-43 and non-TDP-43 neuronal proteins and studies related to extraneuronal proteins. A limitation of this study was the relatively short time period of 15 years chosen and the fact limited studies to those with greater than 10 participants. With any systematic review, search criteria are always somewhat arbitrary but there is a requirement to ensure that an appropriate volume of studies are included and to not overlook important historical or smaller studies which may be of high scientific interest. However, the current search criteria were selected based on key discovery dates; for example, TDP-43, the neuropathological hallmark of ALS was identified in 2006. Several previous review papers such as by Turner et al.[86] and Strong et al.[87] provide overviews of previous key neuropathological findings in the field. More generally, neuropathological tissues derived from humans have been used to inform researchers about the validity of animal or cellular models of disease. Often, these tissues are utilised in experiments within larger studies and as such may not have been identified by the current study. Future studies may seek to examine how tissue resources more broadly support basic science.

Clinicopathological studies

Clinicopathological studies remain a cornerstone of confirming the clinical features of a particular pathological disease. As ALS remains a clinical diagnosis, it is vital that potential clinical phenotypes are validated. Recent examples of brain banks role in this regard include validating the increasing number of nonmotor symptoms in ALS.[5] Examples of this include the finding that progressive aphasia can be a common presenting feature in ALS.[32,42] Brain banks have also been instrumental in establishing new risk factors for ALS, such as traumatic brain injury.[83] Brain banks provide a confirmation of a diagnosis[80]; however, they have also identified a range of secondary pathologies,[51,56,74] often undiagnosed in life, and suggest that similar clinical syndromes can result from multiple pathologies.[74] Many proponents of brain autopsy suggest that the information provided can also be helpful to families, though surprisingly little work has been performed to assess the impact of the information provided following brain autopsy on surviving family members. More generally, brain donation can be seen as empowering for patients, with many donating out of a sense of altruism and a hope their donation will advance medical knowledge.[28] As ALS is increasingly seen as a multisystem disorder, brain banks will continue to have a role in validating emerging clinical phenotypes, as well as providing a mechanistic understanding of why ALS can have such a varied clinical phenotype with apparently similar neuropathological findings.

Brain banks and the molecular genetics of ALS

Around 10% of ALS is familial,[88] with mutations in *C9orf72* accounting for the majority of cases,[89] followed by mutations in *SOD1*.[10] Around 30% of apparently familial cases remain genetically unaccounted for.[2] Since the identification of *C9orf72*, several other genes have been identified as causative of ALS, for example, PFN1[62,63] and TBK1.[38] Brain banks have been critical in confirming the pathogenicity of these mutations and providing an environment to understand how genetic mutations cause disease. *SOD1* mutations are the most commonly used animal models of ALS, allowing for the exploration of disease mechanisms and to develop therapies.[90] However, it is widely known that these models lack the complex milieu of human disease.[90,91] Therapies based on animal models have typically failed to translate into effective interventions and treatments in humans.[92] This is likely due to the inherit differences in the complexity of neural circuits between rodents and humans, which is often a limitation of using such animal models.[91] Neuropathological specimens from patients can offer a more robust assessment of how proteins interact with the

structural components of these circuits in disease.[91] As *SOD1* mutations account for only 2% of cases, there may be a poor concordance between phenotypic expression of *SOD1* mutant mice compared with humans. Major variations in disease biology are also likely with alterations in RNA metabolism more likely in other familial variants.[93] Furthermore, sporadic ALS, ALS with dementia and *SOD1*-negative familial ALS patients all express immunoreactive TDP-43 in which patients with the *SOD1* mutations do not express.[94] Hence, focusing on *SOD1* models alone may lack the granularity to capture the complexity of human disease. Although the use of *SOD1* models is widespread, it is somewhat surprising, albeit informative, to see only one study using brain bank material to confirm the similarity of disease biology in mouse and human tissue.[67] Although, brain tissue has been used to better understand the molecular characteristics of *SOD1* protein, which is thought to have broad implications in both familial and sALS.[95] In contrast to *SOD1*, the last decade has seen a larger volume of publications utilising brain banks to establish the neuropathological features of *C9orf72*-related ALS,[58] in particular the identification of p62 inclusions[68] and DPR inclusions. Additionally, tissue resources have been used to confirm the clinicopathological validity of a number of clinical features in *C9orf72* carriers, including a higher burden of neuropsychiatric symptoms, in particular psychosis,[36] shorter disease duration and more widespread nonmotor dysfunction.[60,61] Important mechanistic work from *C9orf72* carrier brain tissue have demonstrated that RNA misprocessing and the presence of RNA foci within neurons appear to be a hallmark of disease in mutation carriers, which has acted as a stimulus for research into RNA-mediated toxicity in sporadic disease.[69] The immediate availability of tissue resources after the identification of *C9orf72* mutations as a cause of ALS highlights the importance of maintaining prospective collections of brain tissue and clinical data to allow a rapid validation of emerging research.

Brain banks contribution to the understanding of TDP-43 in ALS

The current neuropathological diagnosis of ALS relies on the identification of phosphorylated TDP-43 aggregates within neurons and glial cells, with preference for the motor cortex, brain stem and spinal cord. The staging system provides for four stages where increasing severity is based on the anatomical extent of TDP-43 deposition.[77] Studies from the current review continue to support the notion that TDP-43 mislocalisation and in particular loss of nuclear TDP-43 are important in the pathogenesis of ALS.[44,45] In particular, studies arising from brain bank materials have provided new neuropathological evidence for the cause of many nonmotor symptoms, such as changes in sleep, seen in ALS.[43] The distribution and burden of TDP-43 also has been shown to correlate with the presence of cognitive impairment, extrapyramidal symptoms and neuropsychiatric features.[96] New information from postmortem tissue has also advanced our understanding of the mechanistic processes leading to abnormal TDP-43 accumulation, in particular RNA dysfunction appears critical, with both downstream pathology resulting from abnormal RNA splicing[44] and upstream accumulation of TDP-43 due to elevations in retrotransposons.[42] Several studies support the importance of posttranslational phosphorylation of TDP-43 in the pathogenesis of ALS.[46] The role of TDP-43, a ubiquitously expressed protein whose function is to maintain RNA splicing and regulate transcription, in the pathobiology of ALS has been debated, with several authors suggesting that it is an upstream process resulting from a range of other molecular changes, for example, changes in RNA processing pathway genes and environmental stresses.[97] Brain banks have provided a means to identify these pathogenic pathways which may contribute to disease and upstream TDP-43 phosphorylation; for example, ERVK levels have been associated with TDP-43 dysfunction[45] and neurodegeneration.[72] This in turn has spurned new therapeutic trials using antiretroviral drugs, which show some initial promise as a disease modifying agent.[98] Other non-TDP-43 proteins have also been implicated. For example, DPR proteins, a signature of *C9orf72* related disease, point to unique pathological mechanisms in those who carry this mutation.[51] Other studies have suggested that a more diverse pathological onslaught is occurring in ALS; for example, pathology within glial cells[76] and the presence of γ-synuclein[73] are both reported. These results may explain why targeting single disease mechanisms has thus far resulted in disappointing clinical trial outcomes.[99] Using tissue from dedicated brain banks, which involves characterising antemortem clinical phenotypes, establishing a range of expressed proteins within the tissues and the final neuropathological cytoarchitecture, allows a systems neuroscience approach to identifying important mechanistic processes, for example, identifying pro-inflammatory signalling with resulting epigenetic alterations, protein phosphorylation and cell death.[66,100] Tissue from brain banks has also allowed a more exploratory approach, perhaps because fewer practical limitations are compared with studying living research participants. As an example, one studied considered infective pathological substrates, noting higher levels of intracellular and intranuclear fungi in those with MND, with colonisation occurring before death.[52]

Location and impact of ALS brain banks

Our systematic review found that brain banks in the United States and United Kingdom accounted for more than half of all brain banks (see Figure 3). All but one brain bank identified were in western countries. No brain banks were specifically dedicated to the study of ALS. Of note, the brain banks reported in this review are not an exhaustive list of all brain banks, as our focus was directed on the contribution of brain banks in the area of ALS. Many brain banks have been set up to examine brain tumours and AD, and indeed, some act as tissue repositories rather than generating primary research data. We sought to quantify the extent of brain banks who recruit ALS participants in order to generate comparisons with other neurological diseases. One of the largest repositories of neuropathological data is the National Alzheimer's Coordinating Center (NACC), in the United States, which in 2018 had conducted over 15,000 neuropathological

examinations,[84] and the Arizona Study of Aging which has amassed over 1600 brains with detailed longitudinal antemortem clinical data. This single resource estimates thay it has generated 350 publications and led to 200 grant funded projects.[85] This highlights the significant differences in neuropathological data collection in ALS, compared with other diseases. The location of the brain banks in this review is concordant with areas with high incidence rates of ALS (see Figure 3),[31] which primarily is throughout western countries, though this in part may reflect better case ascertainment in more highly developed healthcare systems. However, similar high incidence rates are noted in Japan, though only one brain bank was identified in this study. Based on available data, Caucasian individuals appear more likely to develop ALS in comparison with other ethnicities (African-Americans, Hispanic and Asians)[101,102]; however, there is a pressing need for more brain and spinal cord tissue from other ethnicities, either within western brain banks or brank banks in other countries. Recent data suggest differences in pathological processes between South Korean and Australians with ALS,[103] suggesting as yet unknown environmental or genetic factors impact ethnic groups differently, which in turn may have impacts on future therapies. This further underscores the need for a global network of brain banks for ALS. With estimates suggesting a 30% increase in global incidence of ALS by 2030 and a 50% increase in countries such as China and Iran, locations that were not found in our review to have brain banks, there will be an increasing need to develop suitable tissue resources to allow active programmes of future research.[104]

Developing common standards for brain bank studies in ALS

A 2016 study surveyed 60 brain banks across 19 countries to establish common operational standards for brain banking.[105] Twenty-four responses were received mainly from three regions; Europe, North America and Australia. The study found that individual brain banks had developed protocols to meet their researchers' needs and were all affiliated with regional networks.[105] A high proportion of respondents indicated the importance of standardisation but admitted that it did not often occur.[105] The relative bias of responses from English-speaking countries also limits understanding with regard to cultural or linguistic barriers for both brain donation and standardisation of operational procedures. Across the 60 studies identified in this review, there was an overwhelming lack of standardisation, in particular, in reporting clinical information and brain regions sampled. The lack of consistency in reporting basic clinical information including disease duration or sex may have significant impacts on how study results are interpreted, given that these variables have significant impact on both incidence and clinical phenotype of ALS.[106] While it is acknowledged that some studies will focus more on molecular biology than clinical phenotypes, it still remains important that basic data are provided so that future studies which seek to validate these findings can be carried out. While some have proposed an 'Utstein style' approach[107] in data reporting, there are many existing protocols which could be easily adopted by the ALS community. An example of this being the NACC neuropathology form, which is a standardised form of 91 neuropathological parameters.[84] In parallel to this, several studies have developed standardised approaches to antemortem clinical assessment for those wishing to make a future brain donation. An example of this is the Brains for Dementia Research programme in the United Kingdom, which by 2018 had recruited 3276 potential donors and carried out 9804 clinical assessments.[108] Other studies in neurodegeneration have collected standardised physical examination and functional data, neuropsychological scores and a range of other biomarkers from motor paradigms to neuroimaging.[85] In the area of ALS, there have been significant achievements in collecting and centralising clinical data on research particivepants, with large databases like PRO-ACT, an open access data base, holding over eight million de-identified longitudinally collected

TABLE 3 Proposed set of standardised data to be collected/reported

Antemortem data	After death
• Demographics ◦ Age ◦ Sex ◦ Handedness ◦ Ethnicity ◦ Educational attainment	• Details of pathological tissue ◦ Location of brain bank ◦ Time from death to tissue extraction ◦ Tissues storage ◦ Which tissues available (brain/spinal tissue)
• Medical history ◦ Cardiovascular History ◦ Traumatic injuries	• Donor details ◦ Age at death ◦ ALSFRS-R at death ◦ Body regions involved at death
• Social history ◦ Smoker ◦ Occupation	• Gross brain pathology ◦ Weight ◦ Appearance
• ALS related symptoms ◦ Symptom onset date ◦ Site of disease onset ◦ Rate of change of ALSFRS-R ◦ Serial measures of motor function (e.g. grip strength/spirometry)	• Histopathology ◦ Sites of tissue examination (grey matter/sub-cortical/white matter) ◦ TDP-43 ◦ Amyloid ◦ Tau ◦ Alpha-synuclein ◦ Vascular pathology ◦ Other
• Nonmotor assessment ◦ Serial body mass index ◦ Cognitive scores	• Genetic analysis ◦ DNA extraction ◦ Genetic diagnosis
• Other biomarkers ◦ Imaging ◦ Biofluids ◦ Neurophysiology	
• Family history ◦ ALS ◦ Neurodegenerative disease ◦ Psychiatric Illness ◦ Neurodevelopmental disorder	

data points from completed phase II and III clinical trials in ALS from 8600 ALS patients.[109] However, to date, these valuable clinical data have not been linked to neuropathological data.

We suggest that the there is a need to develop a global consortium of ALS brain bank researchers engaged in clinical, molecular and neuropathological studies. This consortium can help establish a network of ALS brain banks with standardised processes covering antemortem clinical assessments, brain and spinal cord harvesting, processing and storage and reporting of neuropathological data (see Table 3). It would be envisioned that studies utilising data from these resources would have easy access to supplementary antemortem and methodological data. More generally, this network could promote training and help expand the presence of brain banks for ALS in regions currently underserved. A similar framework has been adopted in AD by the US National Alzheimer's coordinating centre.[110] The Alzheimer's Association USA also published a guideline for neuropathological assessment.[84] Together, these approaches allow for standardised data collection and therefore increases replicability of data as well as allowing for more streamlined hypothesis testing. A similar model could be implemented within the ALS community and allow global reporting standards to be developed.

This review has highlighted the broad impact brain banks have had on our understanding of ALS over the last 15 years, including the identification of several novel therapeutic targets. However, we suggest that significant intellectual and financial investment will be required if brain banks for ALS are to generate the levels of impact seen in other neurodegenerative disorders.

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CONFLICT OF INTEREST

All authors confirm that there is no conflict of interest.

AUTHOR CONTRIBUTIONS

SM: manuscript drafting, preparation and study concept. MK: revision of manuscript and study concept. GMH and HCT: revision of manuscript and preparation. CJM: manuscript preparation, revision and study concept.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available in the supporting information of this article.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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