



CONCISE REVIEW

BRAIN UK: Accessing NHS tissue archives for neuroscience research

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Abstract

The purpose of BRAIN UK (the UK BRain Archive Information Network) is to make the very extensive and comprehensive National Health Service (NHS) Neuropathology archives available to the national and international neuroscience research community. The archives comprise samples of tumours and a wide range of other neurological disorders, not only from the brain but also spinal cord, peripheral nerve, muscle, eye and other organs when relevant. BRAIN UK was founded after the recognition of the importance of this large tissue resource, which was not previously readily accessible for research use. BRAIN UK has successfully engaged the majority of the regional clinical neuroscience centres in the United Kingdom to produce a centralised database of the extensive autopsy and biopsy archive. Together with a simple application process and its broad ethical approval, BRAIN UK offers researchers easy access to most of the national archives of neurological tissues and tumours (<http://www.brain-uk.org>). The range of tissues available reflects the spectrum of disease in society, including many conditions not covered by disease-specific brain banks, and also allows relatively large numbers of cases of uncommon conditions to be studied. BRAIN UK has supported 141 studies (2010–2020) that have generated 70 publications employing methodology as diverse as morphometrics, genetics, proteomics and methylomics. Tissue samples that would otherwise have been unused have supported valuable neuroscience research. The importance of this unique resource will only increase as molecular techniques applicable to human tissues continue to develop and technical advances permit large-scale high-throughput studies.

KEYWORDS

brain bank, human brain, National Health Service, neuropathology, neuroscience

INTRODUCTION

The overall health burden resulting from dysfunction, disease or damage affecting the nervous system is substantial. Examples of common neurological problems include congenital disorders (both genetic and

resulting from a disturbed intrauterine environment), infections, trauma, multiple sclerosis (MS), epilepsy, mental health disorders, stroke and neurodegenerative disorders including dementia, retinal degeneration and tumours. Although significant advances in understanding and treatment have been made in some areas, many of these

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problems have proved disappointingly intractable. Because of increasing life expectancy, maintaining the lifelong health of the nervous system is increasing in importance. Estimates of the global burden of disease indicate that in 2016, neurological disorders were the leading cause of disability-adjusted life-years (DALYS, 276 million) and second leading cause of deaths (9 million).¹ In addition, it is estimated that the global burden of mental illness accounts for a third of years lived with disability (YLDs) and 13% of DALYs.² In Europe alone, neurological disorders account for 41 million DALYS and nearly 2 million deaths.³ The economic cost is vast, estimated in 2012 at €798 billion each year in Europe alone, with an average cost per inhabitant of >€5000.⁴ More than a third of the EU population is said to suffer from mental disorders every year,⁵ and disorders of the brain are identified as a core health challenge of the 21st century.⁶

Recognition of the limitations of animal models and the importance of studying human brain tissue to understand human neurological disease

Animal models of human neurological diseases have an important role to play, particularly in understanding the dynamics of biological processes and cause-and-effect relationships. However, increasingly, their limitations are being recognised. First, they are generally models or simulations of a disease and not the actual disease process itself. Second, laboratory animals have genetic, biochemical, developmental and environmental differences from the human population and consequently have different pathological susceptibilities and responses. Third, animal models can only simulate certain aspects of a disease process, which have to be selected in advance by the researchers, and these may not be the most important aspects. Therefore, there are increasing concerns that some animal models may not fully reflect or replicate the human disease.^{7–18} Some of the problems relate to the development of models based on rare genetically caused variants of diseases which are much more commonly sporadic (i.e., non-genetic) in nature. A good example is the development of the SOD-1 transgenic mouse model of motor neuron disease (MND) after SOD-1 gene point mutations were found (very rarely) to cause MND. For 10–15 years, these mice were studied intensively as a model relevant to common sporadic MND. However, following the discovery of intraneuronal TAR DNA-binding protein 43 (TDP-43) inclusions in sporadic MND, but not in MND caused by mutation of SOD-1, it became apparent that use of the SOD-1 mouse model was something of a red herring.^{11,12,16} Based on a similar rationale, some are questioning the relevance of mutant APP transgenic mice to sporadic Alzheimer's disease.^{7,13,14} An additional example is the difference in selective vulnerability in laboratory animals to cerebral hypoxia/ischaemia which may have been responsible for the failure in human trials of antiexcitotoxic agents to reduce the damage caused by traumatic brain injury and stroke.¹⁹ MS is a further example of a condition for which animal models are used but bear an unclear relationship to the disease process itself; experimental allergic encephalomyelitis (EAE) models have some of the inflammatory and myelin-targeting aspects of the disease,

Key points

- BRAIN UK networks the diagnostic archives of UK NHS Neuropathology departments and facilitates their use for research.
- The past decade of collaborative activity has resulted in numerous completed studies and resulting publications cover a broad range of neurological diseases.
- Archived tissue that would otherwise have been unused has supported valuable neuroscience research.

but recent human studies have indicated that these are not such important contributors as axonal pathology to permanent disability in sufferers of MS.^{8,9,15,17} Animal models of brain tumours are either tumours arising in the experimental animal, therefore by definition not human tumours, or human tumour cells seeded into the animal, in which case the critical cellular glial and immune environment differs.

Invariably, any hypotheses generated by the use of animal models of neurological disease will have to be tested in human diseased tissue in order to ascertain their relevance. Indeed, much of the basis of classification of neurological diseases and understanding of disease mechanisms has come from, and could only have come from, direct study of human brain tissue. With rapid advances in molecular and proteomic techniques, current and future studies using human brain tissue continue to advance our understanding of this important group of disorders.

The great importance of existing NHS diagnostic archives

Neuropathology involves the study of diseased neurological tissues with identification, characterisation and diagnosis of the specific abnormalities present. For the sake of simplicity, when the word 'brain' is used in this account, we are generally referring to the brain and associated components including the spinal cord, nerves, muscle, eye and samples of other organs when relevant to neurological disease.

Neuropathology has existed for about 50 years as a defined specialty in the United Kingdom, and the services are based in NHS regional clinical neuroscience centres, each with catchment populations ranging from 1 to 5 million. Tissue for diagnostic purposes is derived from post-mortem examinations (autopsies) and samples taken from the living during surgical procedures (i.e., biopsies and resections). After diagnosis, residual tissue is archived long-term according to guidelines issued by the Royal College of Pathologists. This archived residual tissue represents a valuable and unique resource for research. Prior to BRAIN UK, a number of studies, usually on a relatively small scale, had made use of this archived tissue.

However, there had been virtually no systematic nationwide organisation of this resource. Therefore, a very large amount of archived tissue of unique value is available to increase our understanding of neurological disease. Most of the archived tissue is in the form of formalin-fixed paraffin-embedded blocks, with frozen tissue in limited numbers of cases. Paraffin-embedded tissue is ideally suited to re-examination and study with a variety of stains for morphology and by immunohistochemistry with the ever increasing range of specific antibodies which is now available for study of human neurological tissues. Examples of advances in immunohistochemistry include 'functional phenotyping' of microglia²⁰ and highly multiplexed single-cell analysis.²¹ It has long been recognised that DNA in paraffin-embedded tissue is accessible for analysis, either for SNP genotyping^{22,23} or direct DNA sequencing,²⁴ including for analysis of mitochondria²⁵ and the detection of micro-organisms.²⁶ Studies have even indicated that mRNA analysis and gene expression microarrays studies can be performed on selected cases.^{27,28} Remarkably, archived paraffin-embedded tissue is also readily amenable to comprehensive gene methylation analysis by microarrays (methylomics).²⁹ Consequently, many different aspects of disease manifestation and pathogenesis are amenable to analysis. These include study of disease phenotype (morphology, protein localisation) and the influence of genetic variation on disease risk and phenotype. Although much important information has become available with the complete sequencing of the human genome, equally, it has become even more apparent that much brain function and disease is a product of regulators of gene expression and post-translational modifications such as protein cleavage into an activated protein, protein phosphorylation or protein aggregation which require study of the diseased tissue itself.

BRAIN UK

BRAIN UK is not a brain bank with planned prospective collection of donated tissue samples for research. Formal brain banks mostly concentrate on one particular disease process or narrow group of diseases that have characteristics attractive to funders, and typically, they represent chronic diseases that have a high public profile (e.g., Alzheimer's disease, MS and Creutzfeldt-Jakob disease). In contrast, an important feature of BRAIN UK is that it is comprehensive and covers the many other important and common disorders that lack such characteristics. In addition, by pooling large historical archives, BRAIN UK also encompasses significant numbers of rare disorders, for which it is normally very difficult or impossible to gather enough cases for a statistically powered study.

BRAIN UK was established with the full support of the British Neuropathological Society and began operating in 2010 and is accessible through the website (<http://www.brain-uk.org>). Originally established to cover tissue derived from post-mortems, BRAIN UK also encompasses samples derived from neurosurgical, neurological

and ophthalmic biopsies. This resource builds on 40–50 years of work of clinical sampling, tissue processing and neuropathological diagnosis, and so BRAIN UK includes the full range of neurological disorders. To our knowledge, it is unique in the world and is a resource available to researchers internationally.

BRAIN UK ORGANISATION

Networking UK regional clinical neuroscience centres

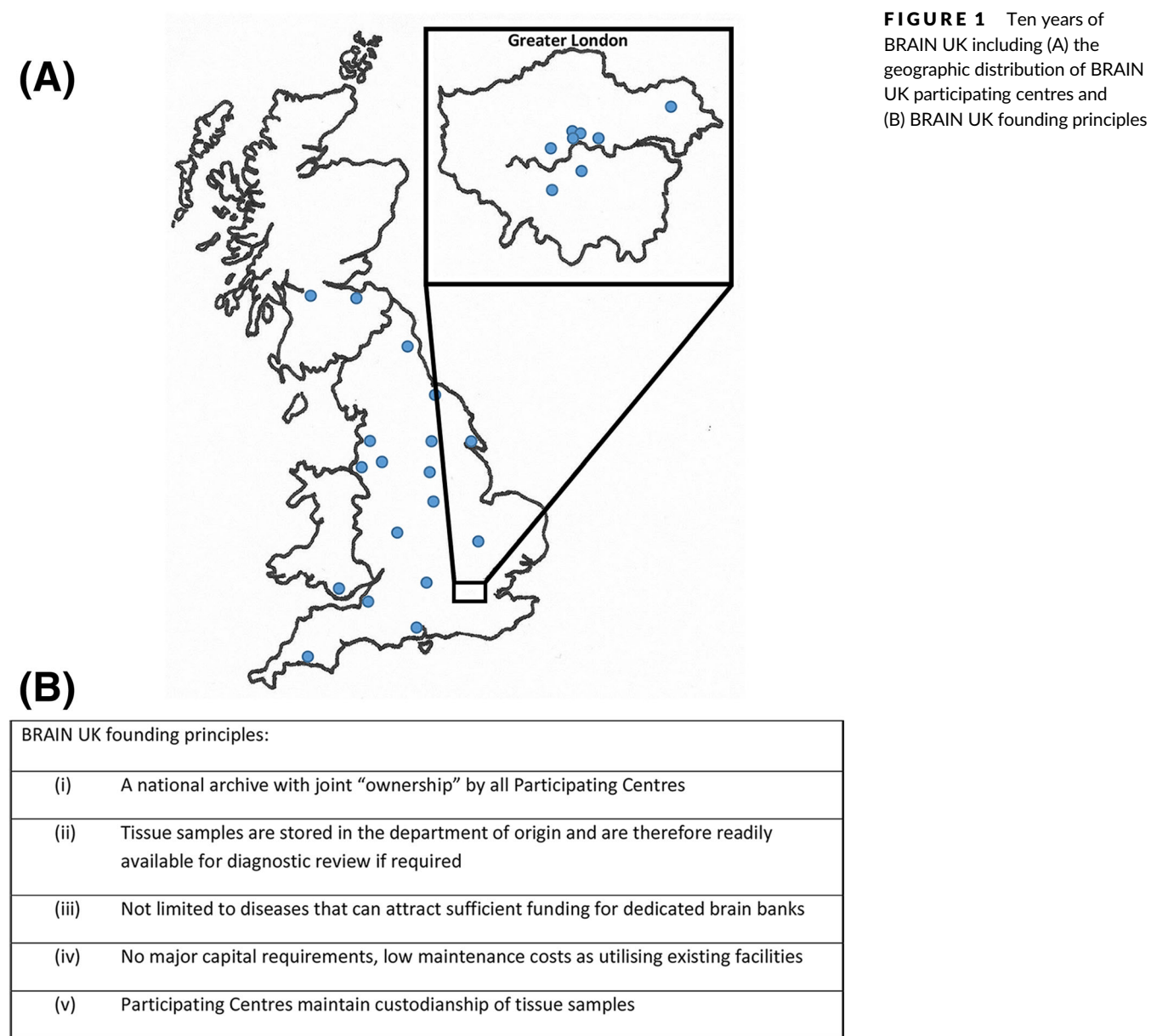
BRAIN UK represents a collaboration of UK neuropathologists who have stewardship over the NHS Neuropathology archives in departments throughout the country, have contributed to building them up over the years and participated in the formation and operation of BRAIN UK to date. The 26 BRAIN UK participating centres provide a wide geographic spread, covering most of the UK population (Figure 1A). BRAIN UK has an identified contact person in each participating centre with whom to liaise about updating tissue databases, individual studies and release of tissue samples. Tissue remains in the individual centres, under NHS stewardship, unless it is requested for a research study (Figure 1B).

Ethics and research governance

BRAIN UK has appropriate ethical approval in place and NHS R&D approvals from all participating centre NHS Hospital Trusts, as statutory requirements. The BRAIN UK ethical approval covers the majority of projects, removing the need for researchers to apply for their own approvals, saving a considerable amount of time and effort for each study. BRAIN UK is overseen by a committee that communicates about every application and holds a minuted meeting once a year. Annual progress reports are submitted to the relevant bodies including the ethics committee, Human Tissue Authority (HTA), funders and the British Neuropathological Society.

Data acquisition

With the assistance of the local staff, a centralised linked anonymised database has been generated that includes diagnosis, laboratory number and simple demographic data including gender and age, location and custodian. Also included in addition to autopsy-derived specimens are neurosurgical biopsies, biopsies of muscle, peripheral nerve, some ophthalmic specimens and CSF cytology. The centralised database includes 35,000 post-mortem cases from nine centres and 120,000 biopsies from seven centres, permitting searches for specific types of specimen to be performed in response to an application from a researcher. Some centres prefer to retain their data locally and perform searches on an as-required basis so that overall BRAIN UK encompasses >500,000 cases within the 26 participating centres.



Centralised application process

BRAIN UK has an online centralised application process (<http://www.brain-uk.org>) guiding the applicants through the submission which involves completion of a form specifying the types of cases required for their study and including a brief justification of the study. Our experience to date has shown that some applicants benefit from guidance in terms of study design and our committee has been able to provide expert guidance to improve the quality of the studies.

Value for money

BRAIN UK is a very lean and efficient system, presenting remarkable value for money for the funders and researchers. To get to a stage at which well-characterised tissue is safely archived requires a complex

multistep process involving people with an array of expertise, typically as follows: (i) clinical assessment of a patient; (ii) obtaining a tissue sample either (a) by surgery to provide a biopsy or (b) a post-mortem examination and brain evaluation and dissection performed by a neuropathologist; (iii) laboratory processing of tissue; (iv) section cutting and histological stains; (v) histological evaluation/diagnosis by a neuropathologist; (vi) appropriate diagnostic coding and registration on participating centre computer system; (vii) storage under HTA-approved systems; (viii) obtaining ethical approval for research study; (ix) selection of suitable samples for a specific research study; (x) retrieval of tissue samples from archive; (xi) cutting of sections and finally, (xii) transportation of sections to the researcher. BRAIN UK bridges the gap, as for tissue specimens made available for research by BRAIN UK steps (i) to (vii) have already been performed and funded within the NHS; steps (x) to (xii) are funded by the researcher's own grant.

ARCHIVED TISSUE THAT WOULD OTHERWISE BE UNUSED HAS SUPPORTED VALUABLE RESEARCH

To the end of 2020, BRAIN UK has supported 141 applications (Figure 2A) including studies of head injury, epilepsy, stroke, infection, genetic and developmental disorders, psychiatric disorders, tumour pathology and genetics, neuroinflammation and neurodegenerative diseases. More than 10,000 cases have been approved for use (Figure 2B), and more than 30,000 individual samples provided to researchers (Figure 2C). Tumour samples have been in particular demand, now comprising more than half of samples provided (Figure 2B,C). The nature and scale of studies supported has varied widely. At one end of the spectrum are student projects and exploratory pilot studies sometimes involving only a handful of cases; such studies are unlikely to have merited the labour involved in a standalone ethical approval application and are unlikely to have taken place without BRAIN UK. At the other end of the spectrum are studies benefiting from the national networking effect of BRAIN UK and drawing together large number of cases of sometimes uncommon conditions. Examples of such larger studies include of chordoma (221 cases from six centres^{30–32}), paediatric brain tumours (488 cases from 14 centres^{29,33–38}) and chronic traumatic encephalopathy (>100 cases from two centres^{39–41}). Feedback from researchers indicates that more than half of the studies could not have been performed without BRAIN UK and there was a significant impact on most of the remainder (Figure 2D). The results of more than 70 studies have been published so far using tissue

sourced via BRAIN UK covering a wide range of categories of disorders (Figure 3).

FUTURE CHALLENGES

As a consequence of continuing clinical activities in UK NHS regional neuroscience centres, the corresponding diagnostic archives continue to grow at a substantial rate. Many of these specimens can become available for research studies via BRAIN UK. It is essential to continue to add samples to BRAIN UK, not simply to increase numbers, but to maintain relevance in terms of changing patterns of disease in the population, changing diagnostic categories and changing therapies in order to understand, respond and anticipate the future health challenges. Examples of likely important areas include clinically important genetic subclassifications of tumours, understanding rare 'orphan' diseases, the effects of new treatments for neurological diseases on the underlying pathological process, the impact of ageing processes on the CNS and the need to better characterise brain changes underlying mental health disorders. Facilitating accessing to the unique NHS tissue archives can help to support such advances. With appropriate investment, allowing linkage of clinical and imaging data, drawing on national tissue archives, could offer large cohorts for further study, of brain tumours for example, which would be of substantial international importance. However, there are considerable challenges in obtaining funding for a long-term research infrastructure service, as research funding tends to be orientated to support short term time-limited projects.

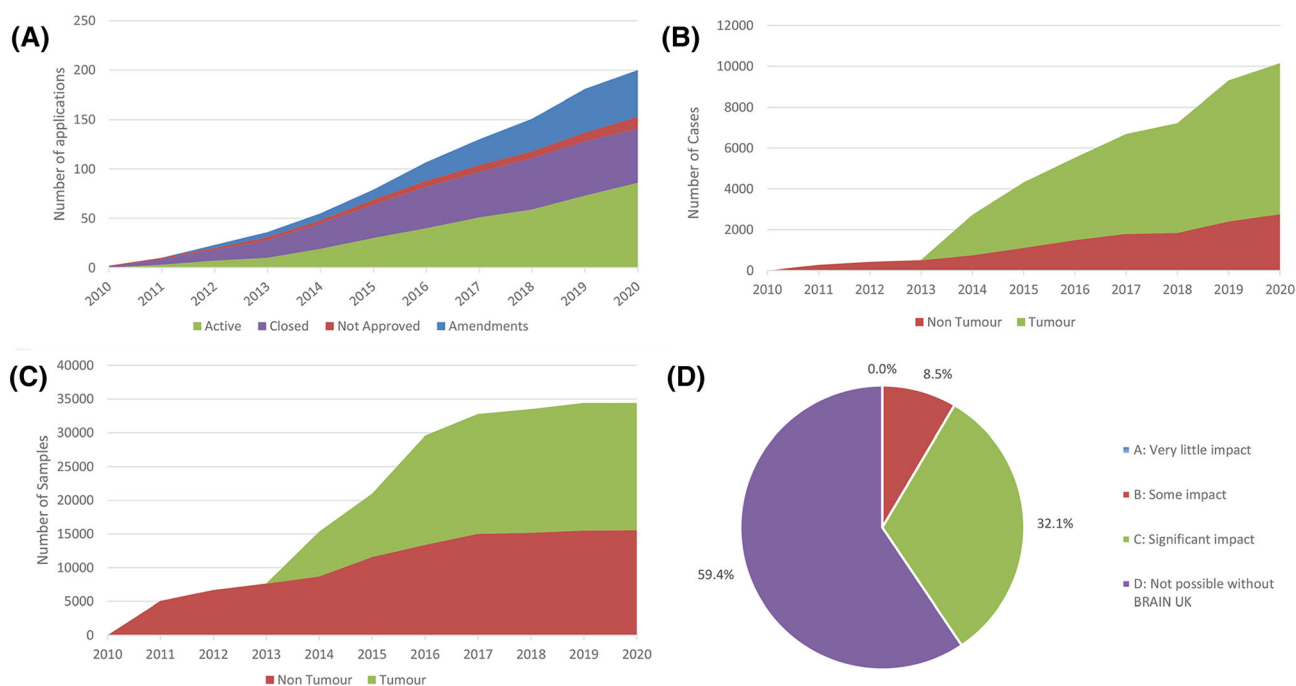


FIGURE 2 Illustration of 10 years of BRAIN UK output with (A) studies approved from 2010–2020 which led to (B) the number of cases approved for scientific use and (C) the samples provided to researchers and (D) the summary of the impact of BRAIN UK on the approved studies

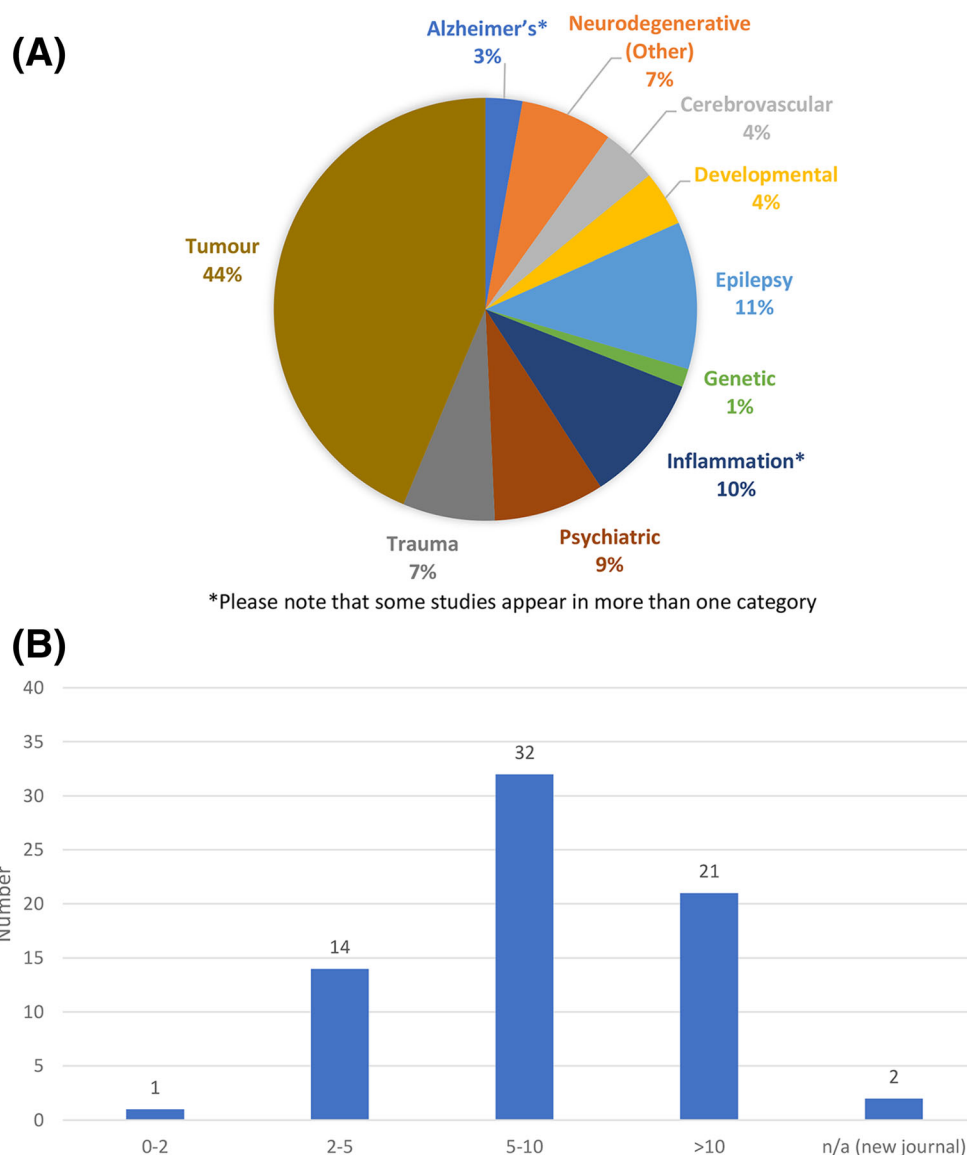


FIGURE 3 Achievement of BRAIN UK as illustrated by (A) BRAIN UK-supported publications by disease category and (B) impact factors of the journals hosting the publications

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CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest.

ETHICS STATEMENT

Ethical approval for BRAIN UK was obtained from the South Central—Hampshire B Research Ethics Committee (REC) Ref: 19/SC/0217.

AUTHOR CONTRIBUTIONS

All authors contributed to establishing and running of BRAIN UK; all contributed to writing of the manuscript.

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PEER REVIEW

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DATA AVAILABILITY STATEMENT

Not applicable.

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