

# Twenty-first century brain banking: at the crossroads

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**Abstract** Brain banks form an increasingly important resource for research. In view of declining autopsy rates, brain banks are also gaining importance for medical diagnostics, quality control and teaching. In the case of neurodegenerative diseases, brain banks have become drivers of discovery and are yielding invaluable taxonomic references for neuropathologists. This article provides comments on two recent landmark papers in the field (Bell JE et al. *Acta Neuropathol* 2008. doi:10.1007/s00401-008-0358-8; Vonsattel JP et al. *Acta Neuropathol* 2008. doi:10.1007/s00401-007-0311-9). Professionalisation of brain banking standards, ethical principles safeguarding the running of a brain bank and a proposed code of conduct for brain bank staff are outlined and discussed. Special emphasis is placed on the need to enable sustainability of the human brain tissue resource in the face of increased financial pressures on medical institutions and raised public expectations towards ethical human brain banking in a globalised economic environment. It is proposed that brain banks undergo rigorous international audit as a prerequisite for their registration with the relevant national neuropathological society. This promises to be an important safeguard so that proper standards can be assured when tissue is handed out to commercial companies. Honesty, accountability and complete transparency are mandatory to allow long-lasting success of the brain banking operation by guaranteeing that the best possible use is made of the tissue. Preferred access by

private tissue users must be avoided and money must never be allowed to buy access to a brain bank. Since brain banks operate internationally, any mistake made may be felt around the globe and could endanger the public's willingness to donate brains for research. The much-needed increase in the number of control brain donations will only be achievable if broad-based support from the general public can be won and maintained.

**Keywords** Control brain donations · Ethical values · Public trust · Tissue analysis

## Introduction

Understanding how the human brain functions represents one of the greatest scientific challenges. Research on brain diseases has a key role in this quest as the elucidation of pathological defects of normal function has traditionally helped to identify novel biological mechanisms. While animal models can be of great assistance, it is ultimately the structure and function of human brain tissue, both dead and alive (e.g. through imaging) that will need to be analysed in order to reach this goal.

Brain archiving has undergone a significant evolution from the anatomical teaching collections of the eighteenth century to modern brain banks which provide tissue for dissection and, ultimately, consumptive molecular analysis rather than viewing. For the continued use of brain tissue to be sustainable, a constant supply of clinically and histopathologically well-characterised donated brains has to be established and maintained. This can only be achieved with the assistance of patient organisations and acceptance of the idea by the general public. Since brain donations are entirely based on trust, this trust needs to be won and justified.

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This article is dedicated to the brain donors and their families who entrust medical scientists with their precious gift as well as the patient organisations and charities who take forward the idea.

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It is widely established that human body parts cannot be owned or sold and in some countries there is even legislation to reinforce this. However, weak people can be bribed and scandals have come to light where financial gain from human tissues was at the centre of the affair [8]. In fact, the history of the early anatomical teaching collections is intricately linked with the illegal activity of body snatchers and the sinister black-market economy in corpses surrounding them [4]. Therefore, fighting criminality of any sort in connection with human tissue work and, more effectively, preventing it at all cost (*principiis obsta!*) forms an integral part of human brain banking. It does not require much explanation to see that there is a social dimension of brain banking (*vide infra*). The development of new disciplines such as Neuroethics and Neurosciences and the Law [3] illustrate a growing awareness of the societal implications of human brain research. However, a public debate of the truly radical and still maturing view in the neuroscience community that the mind is entirely the product of the brain which presents the ultimate challenge to nearly all religions [5] has not even begun. It is predictable therefore that research work involving human brain tissue will come under much greater public scrutiny in future. The time is now to act and prepare a safe environment for brain banking through international collaboration between the relevant expert bodies. Since brain banks operate internationally, any mistake made may be felt around the globe and could endanger the public's future willingness to donate brains for research. Bottlenecks for the supply of human brain tissue already exist.

Pathology itself is also undergoing a significant transformation. Declining autopsy rates in many countries are further reduced by increasingly strict regulations prescribing exactly which form of consent has to be in place before a post-mortem can be performed. In many cases, the latter will not include consent to do research on the material. All studies involving human tissue should now have ethics committee approval as a standard.

### Professionalisation of brain banking standards

The accompanying two publications, Bell et al. [2] and Vonsattel et al. [7], epitomise a very important development. Both papers deal with different aspects of the required professionalisation of brain banking standards. The first publication [7] is from a leading brain bank in the US that was launched at the beginning of the new millennium by Jean Paul Vonsattel based on many years of personal experience at Harvard. The unique opportunity to design a brain bank at Columbia University from scratch has allowed him to take the processes of tissue preparation to new heights. The paper by his group [7] essentially

represents a manual and I would expect an uninitiated reader to think that some suggestions sound extreme. However, having seen the tissue preparations in this brain bank I would respond that they are exactly what I would want for my brain, if I decide to donate it. Over the years I have also seen establishments where I would definitely not want to donate. The point I would like to make is that the Vonsattel protocols are taking the preparation of human brain tissue for research to a level that is fit for purpose for most if not all contemporary research protocols. The times are definitely over that temporary and largely untrained personnel could be allowed to simply slice up brain tissue following some home-grown scheme and freeze it. Researchers are not well served by this. In addition, there is very rapidly increasing demand for neuroanatomically precise preparations which have been meticulously blocked to avoid freezing artefacts and which are only taken from brains that have been fully and thoroughly diagnosed using the latest neuropathological techniques. Of course, there are cost implications as the skills required are at the consultant level for most of the steps involved but this is what institutions need to recognise before they get involved with brain banking. I would like to refer to the actual article for details including on the useful electronic tracking system for tissue blocks. The latter allows rapid and efficient retrieval (within minutes) of all samples and the distribution of one brain over several freezers to maximise protection of every case should a freezer fail (proper backup systems notwithstanding). It may indeed be a suitable rule of thumb for anyone planning to run a brain bank to consider how they would want the brain of a close relative to be processed and kept and by whom. Because, public expectations are very high which becomes apparent during conversations with potential brain donors and their families, e.g. during brain bank open days.

The second landmark paper [2] highlights networking of brain banks and the need for standardisation of their procedures. Most leading brain banks already operate internationally and it seems a natural step therefore for them to link up and to exchange information. The European Brain-Net consortium is thinking of new ways to make the combined holdings of 18 brain banks accessible via linked databases and web access. Such fundamental developments do not happen without a facilitator and it will remain a lasting achievement of Hans Kretschmar's to have put his unique consortium together. The publication by Jeanne Bell and co-workers [2] illustrates the guidance and the important normative effects that are emanating from this EU funded programme. There are also ramifications affecting core aspects of diagnostic neuropathology as demonstrated by the work packages led by Irina Alafuzoff [1], which can be expected to have a significant impact on the practice of neuropathology. Information on these and many additional

initiatives associated with BrainNet II can be obtained via the project website, <http://www.brainnet-europe.org/>.

Work on human brain tissue represents a considerable privilege. The supply of suitable research-grade material is limited worldwide. Donated brains deserve the best care, which in terms of diagnostic laboratory support and staffing should be at least at the level of the national hospital standard. All brain bank services should be provided by professionally trained personnel led by internationally recognised specialists. Yes, there are cost implications but this is what the general public has the right to expect. Unprofessional behaviour in a brain bank poses its greatest threat. Scrutiny of the implementation and maintenance of professional standards must be in the interest of all brain banks because if irregularities occur in one there may be a domino effect amplified through the media, which can negatively affect the success of brain banks around the globe. Although this may come as a natural development, it is already proposed here that brain banks undergo international audit as a prerequisite for their registration with the relevant neuropathological society at the national level. The executive of the International Society of Neuropathology (ISN) is invited to consider this proposal, which would extend the role of the ISN to overseeing brain banks internationally.

### Brain banking and globalisation

The material value of brain tissue has skyrocketed recently due to increased demand which is met by new limitations of supply that are due in part to legal restrictions but mainly to shortcomings in infrastructure, e.g. the small number of neuropathologists worldwide. The gift of an organ as special as the brain requires the best possible conditions in order for the donated material to be usable to its full potential for research. Any assessment of the costs and the responsibility associated with brain banking needs to take into account the huge investment researchers make who rely on the tissue supplied by brain banks for their work. The material value of brain tissue already exceeds that of the most precious metals and it is conceivable that the required security of buildings and the levels of administrative standards are bound to become as high as for a typical bank.

Not only brain banks operate internationally but also numerous aspects of their working environment are influenced by the now ubiquitous effects of globalisation. This pertains especially to industry and notably drug companies many of which are global players with the buying power of small countries. It may be appropriate to emphasise at this point that there is absolutely nothing wrong with industry collaborations provided high ethical standards are maintained and a ‘secret takeover’ of a brain

bank as a corollary of financial dependencies is prevented. It would be naïve to assume that such a scenario cannot develop in an academic or medical environment. Few business managers employed by academic institutions are trained to understand the problems involved. Furthermore, it has become customary even for leading medical scientists who receive money or perks from industry to declare conflicts of interest, e.g. in the context of scientific presentations or publications as if this would solve the problem. I dare to ask: why is there a conflict of interest in the first place? It is not acceptable for brain bankers to have one. Their mission is too important. Any supply of human tissue to a company must be fully transparent and controlled by the brain bank which in turn needs to be overseen by an independent and ideally international board that is able to provide sufficient backing for tough decisions which may be necessary on occasion. Conflicts of interest would make a brain bank vulnerable. Regular audit should be in place and administered externally to prevent any cover-up of internal failings.

### Enabling sustainability: the social contract

Honest and trustworthy brain bank environments are what the public expects us to create, this is where public trust is anchored and this “contract” with the donors must not be breached. For the successful running of a brain bank one may want to remember Albert Einstein’s “if one cannot trust someone in small matters one cannot trust that person in big ones either”. No compromise should be made on that principle. Obviously, the purpose here is not to inhibit the distribution of tissue but to enable sustainability.

Ethical values will always be under high pressure where governance structures are at odds with sound values. Incompetence and corruption prove to be a fatal mix in a professional environment but they can function together like lubricant once improper business practices have crept in. Thus, should justified concerns arise in relation to brain banking it is appropriate to do a thorough risk assessment and pull the plug if necessary. It may be better not to run a brain bank if required professional standards are not met. Should there be no way to rectify the situation it is mandatory to blow the whistle early enough in order to avoid a possible scandal which could affect other brain banks as well. Support by professional societies for a culture of individual integrity especially in the sensitive area of brain banking appears vital. However, it is ultimately a personal and moral decision where anyone wants to earn their key. Humans do not have a price and dignity cannot be measured or compared. Therefore, commercialisation of any aspect of brain banking represents a problematic development. In order to reinforce a trusting donor relationship,

suitable measures should be put in place within a brain bank such as<sup>1</sup>:

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Proposed code of conduct for brain banks

- Guaranteed professional training of all staff involved
  - The commitment to terminate a brain bank's operation in case of criminal behaviour
  - Exclusion of staff in case of non-compliance with widely accepted medico-ethical and data protection principles
  - Prescribed non-cooperation in case of attempted bribery (industrial and other sponsors)
  - Employment of high quality staff with emphasis on personal integrity and high ethical standards (this seems especially important when considering new non-medically trained personnel)
  - No conflicts of interest acceptable (but institutional compensation possible)
  - Tight control as a basis for professional collaborations with industry
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New roles emerge for neuropathological societies such as a to (1) oversee the practicalities of human brain banking on a national level, (2) organise a reliable audit process, and (3) oversee the training of relevant staff. The quality of a tissue bank laboratory's work needs to be monitored, the inventory of all collected brain tissue samples needs to be checked, and it needs to be established regularly whether a tracking of all the collected material (e.g. through RFID tagging of blocks) is possible. Furthermore, evidence should be sought for a transparent remuneration structure of all staff involved with a tissue bank. Human brain banking, if intended as a service to society, requires adherence to the highest professional and ethical standards.

The public expectation of honest brain banking becomes evident almost instantaneously during any conversation with potential brain donors and their relatives. This is the social dimension of brain banking the importance of which cannot be overestimated. Based on the very nature of their donation, brain donors can never experience a material benefit from it. They make their decision in favour of a donation entirely on the basis of trust. A potential donor's decision is yes or no and there are no grey areas. It is well known that there is nothing more corrosive to the willingness to donate than even the perception of someone "cashing in" on the gift. Therefore, brain bank managers who work at the interface between industry and society have to meet the highest expectations both professionally and ethically.

## Conclusions

The data collected by the World Health Organization (WHO) suggest that brain diseases are responsible for 35%

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<sup>1</sup> This proposal was first made public at a symposium on brain banking held in Tokyo on 31 May 2007 during the 48th Annual meeting of the Japanese Society of Neuropathology.

of Europe's total disease burden, and an analysis of all health economic studies of brain diseases in Europe estimated the total cost of brain disease in Europe alone in 2004 to be Euro 386 billion not taking into account that this burden is set to grow due to the fact that the European population is ageing [6]. Human brain tissue is at the centre of modern brain research. The launch of an international supervisory committee for brain banking, similar to the International Atomic Energy Agency which could be under the auspices of the International Society of Neuropathology (ISN) would seem a reasonable and timely step. The much-needed increase in the number of control brain donations will only be achievable if broad-based support from the general public can be won and maintained.

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