Netherlands Brain Bank

Progress Report 2007-2008

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Objective

The objective of the Netherlands Brain Bank (NBB) is to supply the international scientific community with clinically and neuropathologically well-documented brain tissue, in order to increase the knowledge of the brain and to make the treatment of brain diseases possible.

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Contents

Introduction

It is with great pleasure that I present the 2007/2008 progress report of the Netherlands Brain Bank. In 2006 we embarked on a program to professionalize all our procedures with respect to the entire process of brain banking - from procurement, handling and storage of tissue to distribution to researchers. We are happy that the new procedures have indeed proven effective. Donor registrations, tissue applications and tissue blocks sent to researchers increased significantly in 2007 and 2008. Our new informed consent forms - evaluated by the Medical Ethical Committee of VUmc - are now used. Also, we at the NBB drafted an ethical Code of Conduct for Brain Banks for a European consortium of nineteen Brain Banks, which was signed by all participating Brain Banks in Barcelona in June 2008. The Code of Conduct addresses topics such as the rights of the persons donating their tissue, the obligations of the brain bank with regard to respect and observance of such rights, informed consent, confidentiality, protection of personal data, collecting and managing human biological material, and transparency and accountability within the organization of a brain bank. By writing the Code of Conduct the NBB has set the international standard for brain banking.

I express my gratitude to the *NIN, KNAW, Stichting MS Research, Internationaal Parkinson Fonds* and *Hersenstichting Nederland*, as well as to private donors, for their financial support, which is indispensible for the continuation of the NBB.

I also thank the members of the autopsy team, many of whom are PhD students and technicians who guide and help with the autopsies, also when these occur at night, but who nevertheless perform experiments in the lab the next day. I would also like to express my gratitude to the autopsy assistants and pathologists at VUmc for their willingness to perform the autopsies.

Last but not least, I thank the donors, without whose willingness to donate their brain, worldwide scientific research of the brain and brain disease would not be possible.

Inge Huitinga
Director Netherlands Brain Bank

History

In 1978, brain researcher Professor Dick Swaab (1944) became the director of the Netherlands Institute for Brain Research. For his research on Alzheimer's disease he needed well-documented post mortem human brain tissue. It appeared extremely difficult to obtain brains from demented people with Alzheimer's disease through clinical autopsies in hospitals, since most demented people die at nursery homes. Therefore he decided to start a 'brain bank', where people could register as brain donors during life and which meant a way of collecting, characterizing, storing and disseminating human brain tissue for research purposes worldwide.

In 1985, Dick Swaab, together with neuropathologist Professor Frans Stam (VUmc), officially established the Netherlands Brain Bank (NBB). By promoting the importance of brain tissue for scientific research to nursing home physicians and family members of demented residents, the number of registered brain donors with Alzheimer's disease grew rapidly. In 1990 the NBB started the collection of brain tissue of other disorders as well, such as Parkinson's disease, multiple sclerosis, Huntington's disease and psychiatric disorders. Apart from brain tissue with neurologic or psychiatric disorders the NBB also collects tissue of healthy persons, so-called 'controls'. This control tissue is indispensible if researchers are to be able to make a comparison with the diseased tissue.
An overview of the current organization of the NBB can be found in the Appendix (Figure 12).

Donor Registrations

The NBB is one of the few brain banks in the world with a donor program, which means that the NBB actively tries to motivate people with neurological, psychiatric and neuroendocrine disorders, as well as healthy persons, to register as brain donor at the NBB. With this registration, donors give informed consent to the NBB to perform a rapid autopsy after death and to supply the brain tissue for scientific research to reviewed research projects around the world. The donors also give permission to the NBB to collect medical information from their physicians after they have passed away. Currently, more than 2200 living donors with a variety of disorders are registered at the NBB.

In the period 2007-2008, the NBB developed new registration forms and accompanying informational brochures (informed consent forms). The forms were updated and brought in line with regulations and guidelines issued by international key organizations, such as the Council of Europe, the European Commission, the World Medical Association and the World Health Organization. The NBB paid special attention to the development of a separate brochure on incompetence, a consequence of several neurodegenerative diseases, such as Alzheimer's disease. According to the Dutch Civil Code, persons reasonably unable to determine their will are incompetent to give informed consent. When a representative of the incompetent person (next of kin or designated representative) is allowed to make decisions on behalf of the incompetent person this is called authorization. Scientific research into neurological, psychiatric or neuroendocrine disorders that result in permanent incompetence is of great importance for a better understanding of the causes, pathogenesis and progression of these diseases. Such scientific research is not possible without making use of human tissue. For this reason the NBB not only accepts donors on the basis of informed consent, but also on the basis of authorization.
The informational brochures and registration forms were reviewed by the Medical Ethics Committee of VUmc, officially approved on October 30, 2008 and brought into use on November 1, 2008. They were generally well-received by donors as well as by physicians.

In order to inform our donors about the progress made within the NBB and about the scientific output achieved with material provided by the NBB we embarked on a new venture: an annual newsletter, the first of which has now been sent out.

During 2007 and 2008 730 registration packs were sent out to individuals, neurologists and nursing home physicians. The registration forms can also be downloaded from our website. In total we received 230 new registrations in 2007 and 279 new registrations in 2008 (see Figure 1). Figure 1 not only shows that the total number of annual donor registrations is increasing, but also that the number of female donor registrations increased more rapidly during the last three years than the number of male donor registrations. This is mainly caused by a remarkable increase of the number of female multiple sclerosis (MS) and non-demented control registrations. Since the prevalence of MS is twice as high for females, this likely explains the disproportionate increase of female MS donors in comparison with the number of male MS donors. However, the disproportionate increase of female control donors is rather baffling.

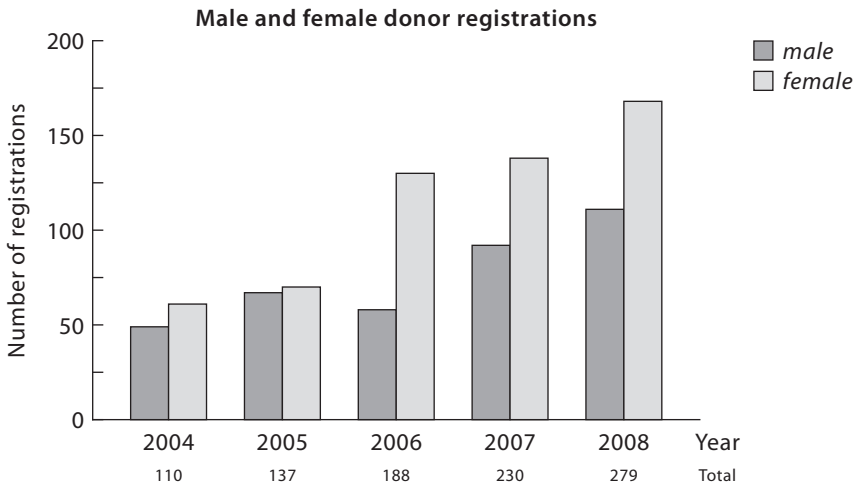

Fig. 1

Figure 2 shows the total number of registered donors in 2007 and 2008, specified by diagnosis. In comparison with previous years, especially the numbers of MS and PD registrations have increased. This is a direct consequence of the reactivated donor programs that have started off in 2006. The increasing requests for MS and PD tissue from the scientific community could not be sufficiently met, which urged the NBB to increase the number of MS and PD donor registrations. To inform people with MS, a promotional DVD has been made that has been distributed within the MS community. Furthermore, people can order the DVD via our Dutch website. The current number of registered MS donors makes up for almost 20% of the total number of registered donors (416 out of 2152). This is relatively high compared to

the incidence of MS in the Netherlands (0.1%, source: RIVM). We attempted to reach people with PD through articles in the magazine of the PD patient organization (see Table 1).

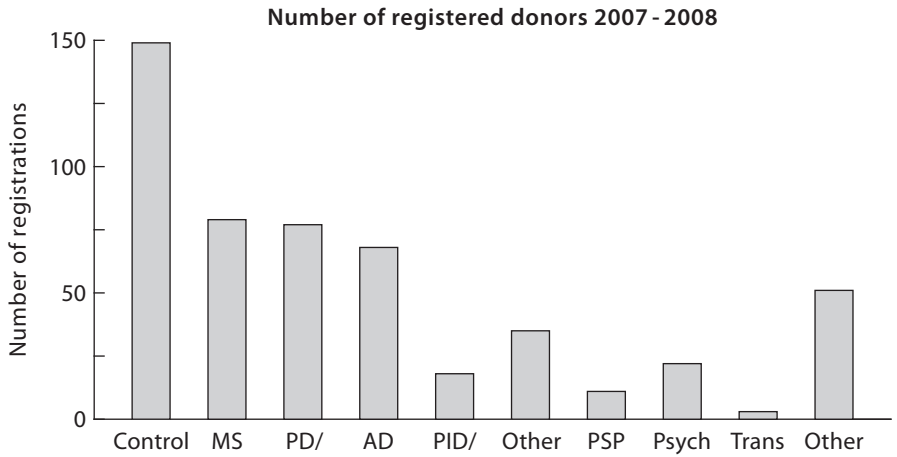

Fig. 2

Clinical cohorts

An effective approach to reach potential new donors is through their physician. The NBB has a loyal group of nursing home physicians, nurses, and neurologists who educate their patients about the possibility of brain donation. In 2007 a new way of reaching donors through physicians was initiated. Many academic hospitals have clinical cohorts of patients with a specific neurological or psychiatric disorder to study disease course and the effect of experimental therapies. These patients are studied longitudinally and therefore many medical data are available in a standardized manner. This makes them a very interesting group for post mortem research. Moreover, these people are willing to participate in research during life and are accordingly often willing to donate tissue after their demise.

Presentations and articles

In the past two years the NBB has put a high priority on raising awareness of the importance of research with human brain tissue and the possibility of brain donation. We visited patient meetings to give presentations on the work of the NBB and the possibility to become a donor. Being able to show them the kind of research that is performed on tissue donated to the NBB, research that might help find a cure, evokes many positive reactions and has led to many new donor registrations.

Table 1 gives an overview of the articles that were published about the work of the NBB in 2007 and 2008. We always make sure to mention that not only patients with neurological or psychiatric diseases, but also healthy control donors are crucial for good scientific research. In that way, we may also persuade many non-diseased family members to register as brain donor.

Table 1

Date	Name article / radio show (translation)	Name magazine / newspaper
11-2007	Your brain is valuable. Use it well, also after your demise!	Papaver (Magazine for PD patient organization)
21-12-07	Reaching in the dark: How unique research could raise the veil on the origin of Alzheimers disease	Het Financieele Dagblad (Daily newspaper)
28-02-08	Brain donation for pioneering research	Supplement Onze Hersenen to daily newspaper De Telegraaf
05-2008	Everything you always wanted to know about brain donation.	Papaver (Magazine for PD patient organization)
03-06-08	Maximum attention for the Stichting MS Research	Press release on the visit of Her Royal Highness Princess Máxima
17-06-08	For scientific research. Wanted: brains!	De Telegraaf (Daily newspaper)
07-2008	Lab tour of the Netherlands Brain Bank	Alzheimer Actueel (Magazine for AD patient organization)
09-2008	Tissue in storage	Quest Braintainment Magazine
02-10-08	Casa Luna (Radio 1)	N/A (appearance on radio show)
10-2008	The brain deserves better	AMC Status (Magazine for hospital staff)
11-2008	Your brain is valuable. Brain research on donors with dystonia	Tonus (Magazine of dystonia patient organization)
11-2008	Human brain tissue necessary prerequisite for efficient brain research	Rondom MS (Magazine of MS patient organization)

The website of the NBB

Nowadays the internet is very popular among patients trying to learn more about their illness. By making sure that the NBB is mentioned on the websites of the various patient organizations, we try to enhance public awareness of the importance of brain donation. Furthermore, the donor website of the NBB has recently been updated (www.hersenbank.nl). We can keep track of the number of visitors on our website, which allows us to evaluate the success rate of PR activities such as articles in the press or radio interviews (see Figure 3).

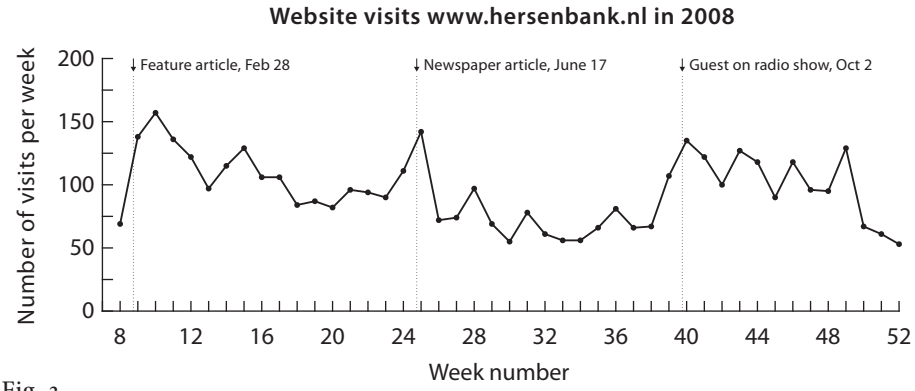

Fig. 3

Future plans

In the upcoming years the NBB will pay special attention to people with psychiatric disorders, such as depression, schizophrenia and various addictions. Even though most psychiatric patients are able to give informed consent, they are often reluctant to register as donors at the NBB. The NBB will therefore work together with psychiatrists and psychiatric nurses to inform them on the importance of brain donation.

The NBB wishes to acknowledge and thank all the donors and their families for their generosity and the invaluable gift they are giving to future generations.

Autopsies

Since 1985 the NBB has performed 3099 brain autopsies. In total, the NBB performed 200 autopsies in 2007 (90) and 2008 (110). Figure 4 shows the number of autopsies in the last 5 years, clearly showing that the number of autopsies in 2008 is higher as compared to previous years. The NBB performs fast autopsies, during which, besides formalin treatment, the tissue is also frozen immediately without fixation. This ensures that high quality of the tissue is guaranteed. Figure 5 shows the autopsies by diagnosis. The NBB anticipates that the number of autopsies of donors who suffered from dementias (e.g. AD, vascular dementia) will continue to increase in upcoming years, due to general ageing of the population.

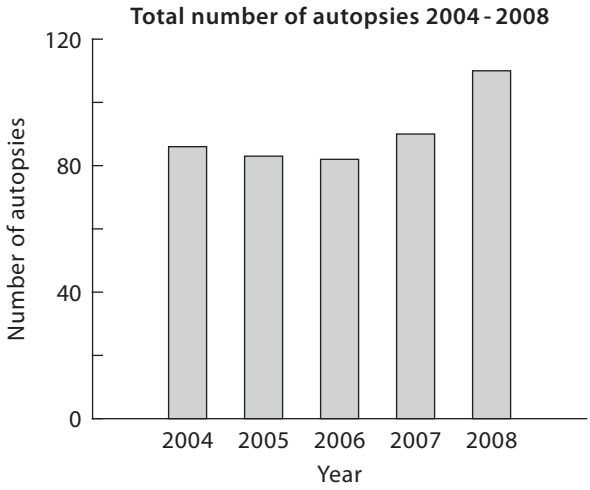

Fig. 4

The mean age at time of death was similar for all our donors: 71.7 in 2007 (range 41 - 99) and 74.6 in 2008 (range 40 - 98). However, there are significant differences between the age at time of death for the different diagnoses. E.g., the mean age for MS donors in 2007 and 2008 was 60.6 years, for Pick's disease it was 67.1, while for non-demented controls the mean age was 81.0 years. These data are in line with the increased risk of a short life expectancy for those suffering from these neurological disorders (Hodges et al., 2003; Sadovnick et al., 1992; Sumelahti et al., 2002).

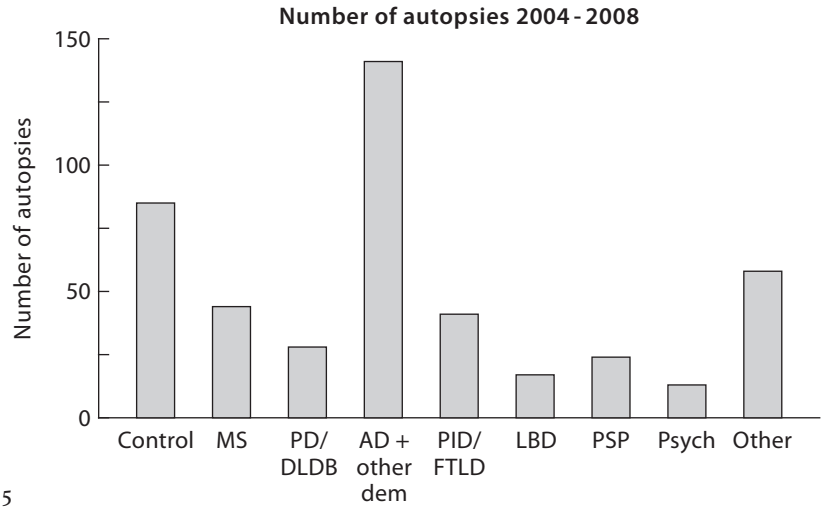

Fig. 5

Post mortem delay

Due to autolytic processes, tissue of the central nervous system quickly decays after death and the time to perform brain autopsy is thus short. The post mortem delay (PMD: time elapsed from a person dying to removal of the brain) depends on several factors: time of notification of the donor's death, distance and time for transportation of the corpse and the availability of brain bank staff to perform the autopsy. Because PMD has been proposed as a tissue quality parameter, several brain banks established rapid autopsy protocols relying on 24/7 availability of staff. The NBB achieves short PMDs, with 65 % of all autopsies having a PMD between 4 to 8 hours, whereas the average PMD of other European brain banks is more than 12 hours, even when they work with a 24/7 availability of staff (manuscript in prep.). Over the last 5 years the average PMD of the NBB autopsies has been extremely constant (Figure 6).

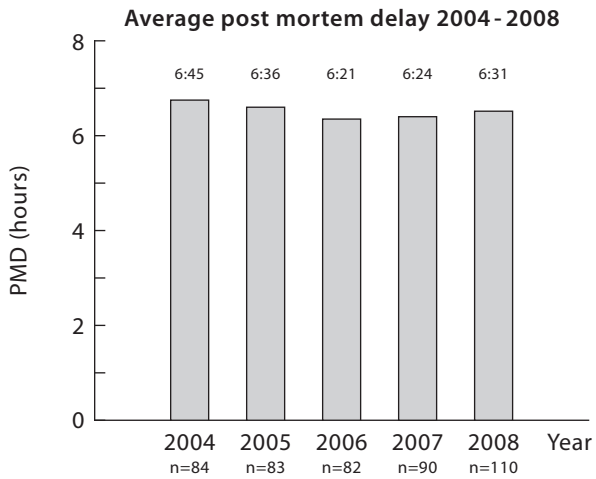

Fig. 6

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Sumelahti, M.L., Tienari, P.J., Wikstrom, J., Salminen, T.M., and Hakama, M. (2002). Survival of multiple sclerosis in Finland between 1964 and 1993. Mult. Scler. *8*, 350-355.

Tissue Supply

In 2006 the NBB reviewed all its current procedures, which not only led to new informed consent forms, but also to professionalization of its application and tissue dissemination procedures. A Material Transfer Agreement (MTA) was drafted and put into use, to ensure the rights and obligations of the recipients of the tissue as well as those of the NBB. For a graphic representation of our application procedures, please see the Appendix (Figure 13). Once the NBB and the research institute have both signed the MTA, which is valid for an indefinite period of time, any researcher within the institute can apply for tissue. The first MTA was signed in June 2007. Since then, more than 40 MTAs have been entered into with universities, research institutes and pharmaceutical companies worldwide.

The number of tissue applications has been on the increase since the introduction of the new procedures (see Figure 7). Researchers have the possibility to place an inquiry on the availability of samples, which in most cases leads to an application. When this concerns a new research project, the application is reviewed by the NBB's scientific committee. If approved, a new project number is assigned and the necessary paperwork is done, after which the tissue is supplied. The review process takes approximately four weeks. When the application concerns an existing, already reviewed, research project, this is called a supplementary application. The possibility to file a supplementary application was introduced in 2007, together with the MTA. Because the original research project has already been approved, this means that the tissue, if available, can be supplied even more quickly.

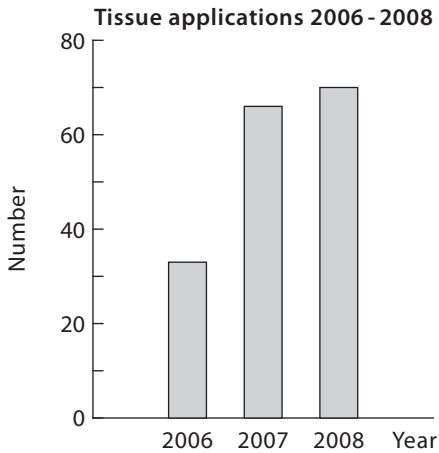

Fig. 7

In 2007 and 2008 there were 19 cases (out of 136) where tissue inquiries did not lead to actual applications. Inquiries can be for new applications as well as for supplementary applications. The main reasons why tissue inquiries or applications foundered are:

- an application form was sent to the researcher, but the researcher never actually applied for tissue;
- the NBB did not have the requested tissue.

The latter shows the need to increase the number of donors with a specific neurological or psychiatric disorder and triggered the NBB's new donor programs, for instance, the ones concentrating on PD and MS referred to in the chapter on Donor Registrations.

In 2007, and especially in 2008, the number of samples supplied increased from 2551 in 2006 to 4402 in 2008. Figure 8 shows the specification of supplied samples by diagnosis in 2007 and 2008. Figure 9 displays the specification of the samples by type of storage. The NBB not only provides frozen or formalin fixed paraffin embedded samples, but also fresh tissue and formalin fixed tissue. The different treatments of the tissue permit the possibility of different kinds of research approaches. The black dots in Figure 10 show to which countries the NBB has provided tissue since 1985. The majority of the tissue is supplied to researchers in the Netherlands and other European countries. However, the NBB also frequently receives tissue requests from, for instance, the United States of America, Israel and Australia.

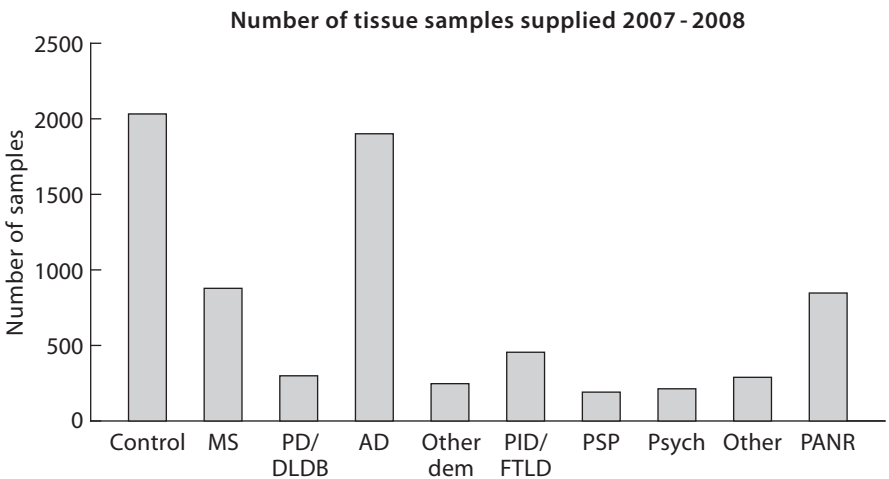

Fig. 8

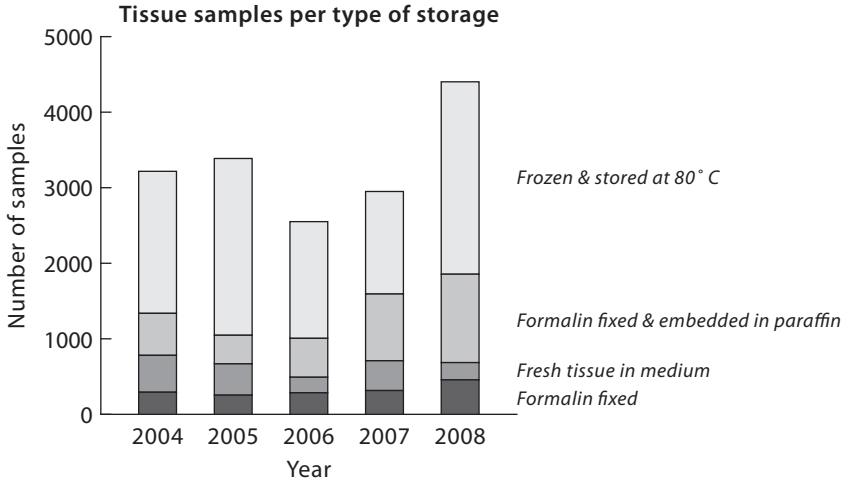
Tissue samples per type of storage
Number of samples
5000
4000
3000
2000
1000
0
2004
2005
2006
2007
2008
Year
Frozen & stored at 80˚ C
Formalin fixed & embedded in paraffin
Fresh tissue in medium
Formalin fixed

Fig. 9

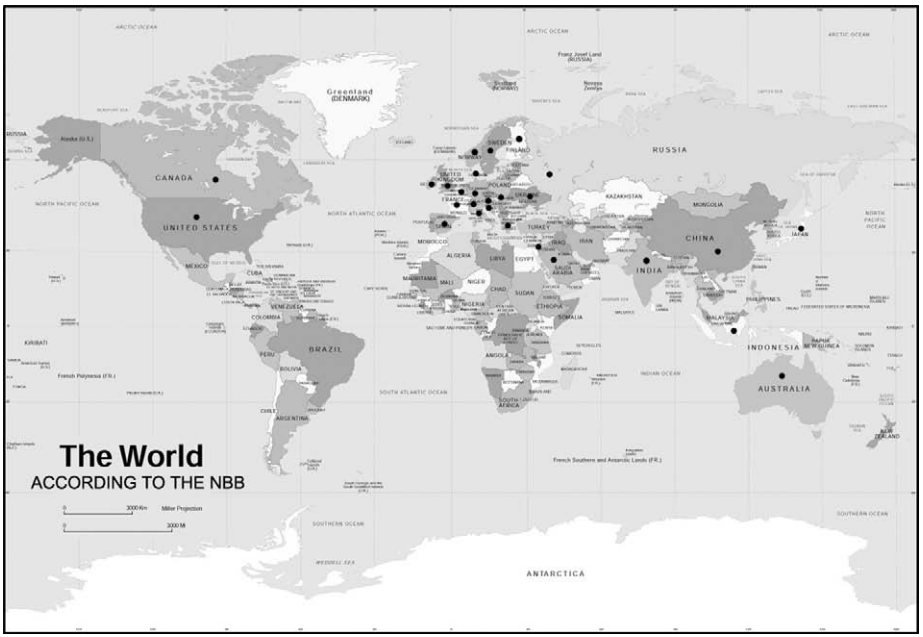
The World
ACCORDING TO THE NBB
CANADA
UNITED STATES
RUSSIA
CHINA
INDIA
INDONESIA
AUSTRALIA
BRAZIL
ANTARCTICA

Fig. 10

BrainNet Europe

BrainNet Europe II (BNE II) is a 'Network of Excellence', established in the 6th Framework Programme of Life Sciences of the European Commission (www.brainnet-europe.org).
The Consortium consists of 19 brain banks across Europe. BNE II is funded by the European Commission in order to carry out work with regard to its objectives, which are, among other things:

- Harmonization of neuropathological diagnostic criteria in Europe;
- Development of gold standards for quality, safety and ethics for obtaining and handling of human tissue;
- Sharing of knowledge and dissemination of the information to neuroscientists and the general public.

The NBB is a longstanding member of the BNE Consortium and an active participant designated to carry out work with regard to the ethical and legal issues in brain banking and recruitment of donors (donor programs). The work within BNE is divided in 'workpackages'. As the leader of a workpackage involving many sensitive issues, the NBB has been engaged in reviewing and adjusting its own policies and standard operating procedures. The NBB aims at achieving the highest possible standards of conduct and becoming the model for all brain banks.

Workpackage 'Legal and ethical issues in Brain Banking'

The legal and ethical issues in brain banking are numerous. Research with human tissue, genetic research and post mortem removal of organs have given rise to many controversies in the media and posed many dilemmas in the fields of law and ethics. Due to the relative novelty of these issues, the law is often lacking in clear instructions and unambiguous guidelines.

As the leader of the workpackage on legal and ethical issues, the NBB has developed a series of documents that should provide a general ethical framework (on Consortium level) and could function as a guideline on the level of the individual organization (on brain bank level). The NBB used a structure which focuses on globally accepted bioethical principles and international doctrine. For this purpose the NBB formulated a BNE Code of Conduct, which covers basic legal rules and bioethical principles involved in brain banking and is been based on various sources available

in the field of bioethics. Such sources include laws, regulations and guidelines issued by international governmental and non-governmental key organizations, such as the Council of Europe, European Commission, World Medical Association and World Health Organization. In June 2008, all BNE II partners signed the Code of Conduct (see Figure 11). The NBB observes all rules and regulations of the Code of Conduct.

The Code of Conduct addresses fundamental topics such as the rights of the persons donating their tissue, the obligations of the brain bank with regard to respect and observance of such rights, informed consent, confidentiality, protecting personal data, collecting and managing human biological material, and transparency and accountability within the organization of a brain bank. As the Code of Conduct only sets a framework of ground rules and general principles, more concrete guidelines are included in another document called the Brain Bank Regulations. To support the daily practice and ensure compliance with the above-mentioned documents, the NBB has also developed a set of model forms and contracts - indispensable in the daily practice of any well-established brain bank. These forms and contracts include Informed Consent forms, Material Transfer Agreements and Confidentiality Agreements and have been made available to all members of the BNE Consortium. Currently the NBB is preparing a publication on the Code of Conduct.

Fig. 11

Workpackage 'Donor program'

The NBB has a longstanding history of donor recruitment and one of the most successful donor programs in Europe, and therefore has accumulated a great deal of experience on the best ways to approach the public for the purpose of donor recruitment. In 2008 the NBB sent out extensive questionnaires to all other brain banks within BNE (with or without active donor program) to make an inventory of all current European brain banks and their mode of operation. Because the number of clinical autopsies is decreasing worldwide, brain banks are necessary to provide well-documented central nervous system tissue for scientific research purposes. Our goal with this study was to make an inventory of the current donor programs in Europe, in order to make recommendations on how to start a successful donor program. Our aim is to publish the results of this study in the course of 2009.

At the BNE 2nd international conference on Human Brain Tissue Research in Munich (December 10-12, 2008), the NBB gave a one-day workshop on Legal and Ethical Issues and Donor Recruitment in Brain Banking in Europe. This workshop contained information on the two workpackages of the NBB and was attended by approximately 50 persons in the field of brain banking.

Other workpackages

The NBB is also engaged in the workpackages of other BNE members. The NBB technicians and the neuropathologist, for instance, participate in many neuropathological diagnostic trials. During these trials the objective is to improve the staining procedures and to harmonize and optimize neuropathological diagnoses. Moreover, the NBB has been actively involved in the BNE workpackage on public relations, resulting in a new donor flyer and the development of a donor website for brain banks that currently do not have a website to promote their donor program.

Funding of NBB activities within BNE

The tasks of the NBB within the BNE Consortium are quite extensive. Part of the received funding is allocated for subcontracting on advisory work with regard to legal matters. In order to acquire advice and guidance in the field of health law, privacy legislation, intellectual property and legal knowledge with regard to biobanks for research purposes, the NBB was advised by Professor J.K.M. Gevers of the University of Amsterdam, Law Faculty, Department of Health Law.

BNE II Publications

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Finances

The NBB receives structural financial support from the KNAW and the NIN, but apart from that it is almost completely dependent upon grants, donations and the financial contributions that are made by researchers who use NBB material.
The "Stichting tot Ondersteuning van de Hersenbank" (Foundation for the Support of the NBB) was founded in 1986 and helps realize the goals of the NBB by giving financial support. Since January 2008, the foundation is being considered as 'Algemeen Nut Beogende Instelling" (Institution for Public Advancement) by the Dutch Tax Authority. The assets of this Foundation are formed by donations, testamentary dispositions and legacies (Trade Register Amsterdam, S205869).

The work of the NBB would not be possible without the support of numerous foundations, patient organizations, and the enthusiastic dedication of private individuals.

Grants	2007	2008
Structural contribution of the KNAW	€ 215,730	€ 220,054
Structural contribution of the NIN	€ 100,000	€ 100,000
Stichting MS Research	€ 109,036	€ 109,036
Internationale Stichting Alzheimer Onderzoek	€ 10,000	€ 40,000
Internationaal Parkinson Fonds	€ 10,000	
Hersenstichting Nederland		€ 10,000

The necessity of grants

Due to the received funding, the NBB is able to continue brain banking. The costs to make tissue available for research are enormous and without the help of patient organizations the NBB would not be able to maintain its high standards.

The Stichting MS Research (www.msresearch.nl) has funded the NBB for many years, resulting in an increase of the number of MS donors and availability of MS tissue. Due to the special MRI-guided dissection protocol, the autopsy costs for MS are higher than for other autopsies. Moreover, the clinical files of people with MS are often more extensive and their summarization requires a greater effort. Finally, in-depth neuropathological diagnostics of the MS plaques is time-consuming, but indispensible for good tissue dissemination. MS Research covers the costs of all MS - and some control - autopsies.

The funding of the Internationale Stichting Alzheimer Onderzoek (www.alzheimer.nl) has made it possible for the NBB to start the production of a new informative DVD, with the objective to raise awareness on the possibility of brain donation for research purposes, and to start up a DNA bank to keep up with the latest developments in research, where genotyping is becoming the important bridge between clinical and neuropathological characteristics.

The grants of the Internationaal Parkinson Fonds (www.parkinsonfonds.nl) cover the costs of all Parkinson autopsies including donor recruitment activities, which would not be possible without this extra funding.

Funding of the Hersenstichting Nederland (www.hersenstichting.nl) is used to cover donor recruitment, autopsy and administration costs.

Research Projects 2007-2008

The abstracts can be downloaded from our website

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The projects focus on Alzheimer's disease.

Biopta Ltd., Scotland

The project focuses on cerebral blood vessel constriction and dilatation in response to 5-HT receptor agonists and anti-migraine drugs.

H. Lundbeck A/S, Denmark

Lundbeck mainly works in the area of schizophrenia, depression, Parkinson's and Alzheimer's disease.

Neurim Pharmaceuticals Ltd, Israel

Neurodegeneration-linked expression of astroglial markers in ALS and Alzheimer's patients versus healthy human brain.

N.V. Organon, The Netherlands

Radioligand development for peptide receptors.

Otsuka Pharmaceuticals Ltd., Japan

Development of therapeutically and diagnostic approaches of multiple sclerosis and Parkinson's disease.

Pfizer Ltd., United Kingdom

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2008

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Advisory Board

To be installed shortly. For the intended composition, we would like to refer you to the non-hierarchic scheme of the organization of the NBB (see Figure 13).

Scientific Committee

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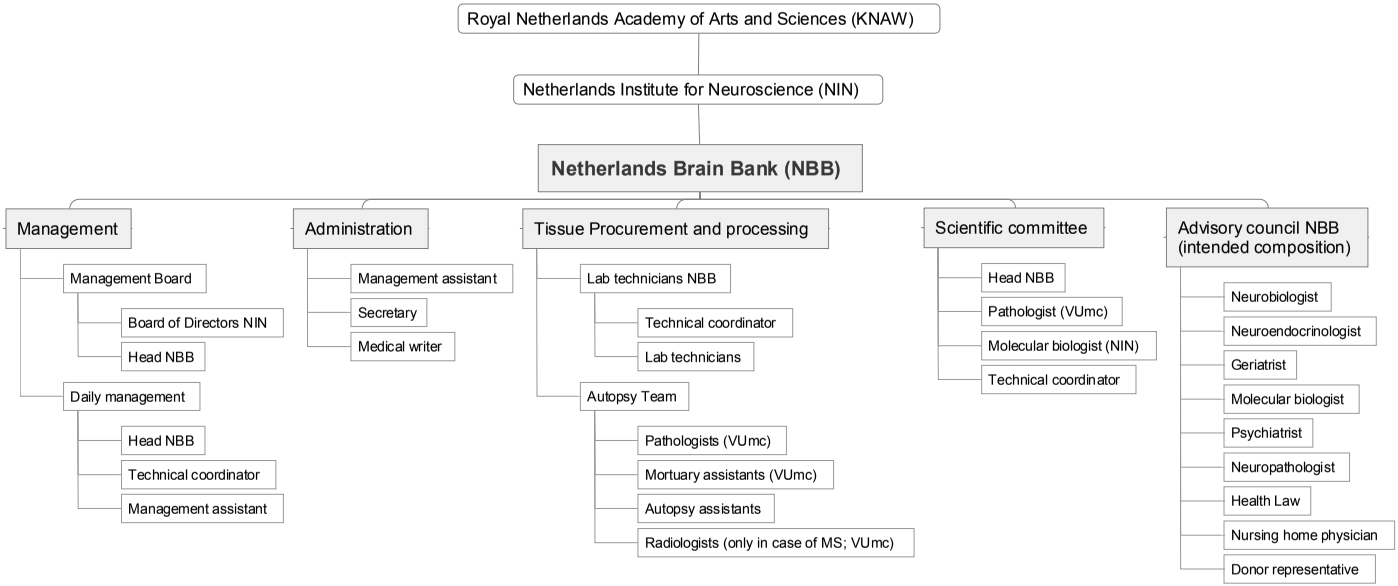
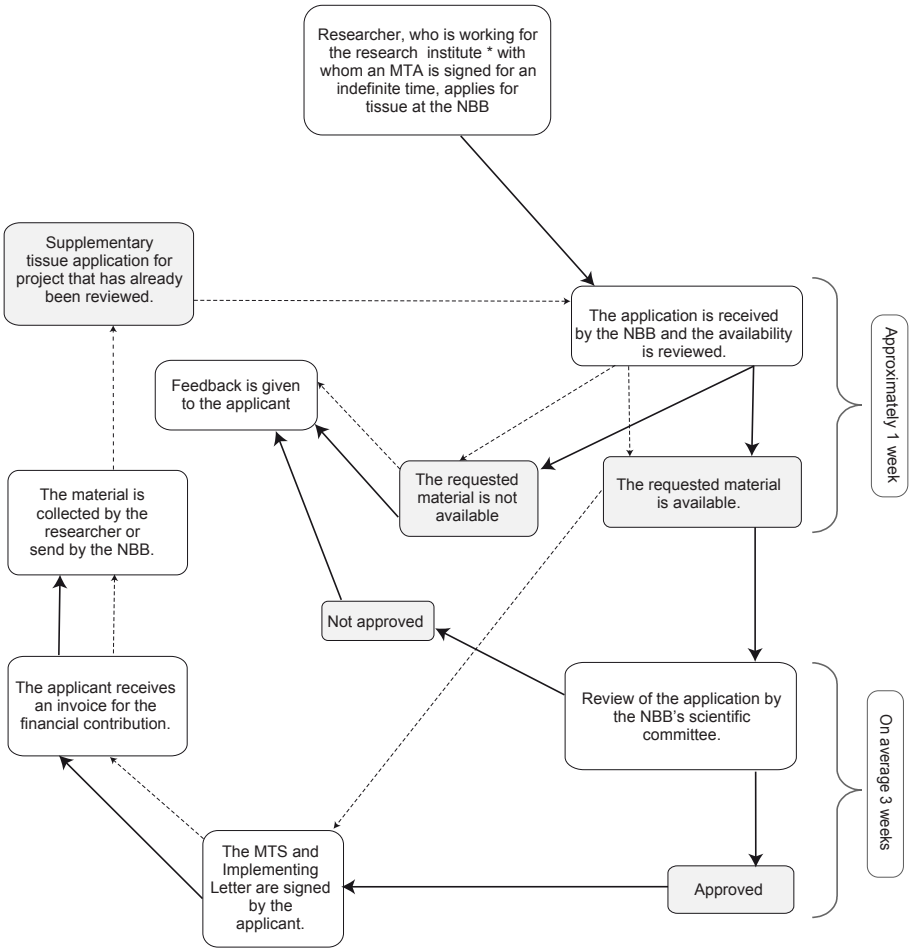
J. Verhaagen (Netherlands Institute for Neuroscience)
J.M. Rozemuller (Pathological Institute, VUmc)
M. Kooreman (NBB)

Fig. 12

Non-hierarchic scheme of the organization of the Netherlands Brain Bank (NBB)



NBB's Procedure of Material Transfer



* The research institute is a legal entity with whom the MTA is signed. Legally, the research institute is thus a party of the agreement. The research institute is thus called "Recipient" of the Material in the MTA and *not* the researcher.
In case no MTA for indefinite time has been signed at the institute/organisation where the researcher is working, the NBB will not supply any tissue. First, the authorized person (head manager or managing coordinator) needs to sign the MTA.

Legend
Application new project: ————
Supplementary application within reviewed project: ----------

Fig. 13