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It is with great pleasure that I present the 2011-2012 progress report of the Netherlands Brain Bank, two event-filled years for the NBB.

In 2011 we celebrated our 25th anniversary with a symposium on “Depression and Happiness”. The well-attended event, an evening filled with a variety of lectures, a Q and A session, and interspersed with musical intervals, was concluded with a stand-up routine by Freek de Jonge.

In April 2012, Dr. Wouter Kamphorst was made Officer in the Royal Dutch “Order of Orange-Nassau”, presented by the Mayor of Amsterdam. The honour was awarded to Dr. Kamphorst in recognition of more than 25 years of dedicated neuropathological work for the NBB.

June 2012 saw the start of NBB-Psy, our new national program for psychiatric diseases. The Netherlands Organisation for Scientific Research (NWO) awarded a grant of €3,450,000 from the NWO Large Investment Subsidy program to the NBB-Psy project, an initiative of the NBB and five Dutch university medical centers: UMC Utrecht, Radboudumc (Nijmegen), Academic Medical Center (Amsterdam), VU University Medical Center (Amsterdam) and Erasmus MC (Rotterdam). This grant will be used to actively approach 70,000 psychiatric patients and their family members through patient cohorts and patient societies, in addition to a more general national call for psychiatric brain donor registrations. The program is anticipated to result in autopsies of more than 500 donors with a psychiatric disease over the next 10 years and is expected to force breakthroughs in worldwide post mortem psychiatric research.

The start of NBB-Psy perfectly fits the NBB’s new strategy to shift its focus from general neurological donor programs to focused recruitment of clinically well-characterized neurological and psychiatric patients. For example, patients with Alzheimer’s disease are currently only registered as brain donors if they were diagnosed in the VUmc Alzheimer Center. As a consequence of this shift in focus, the NBB now only welcomes registrations from a limited selection of diseases, which are listed on the
NBB website. This new donor recruitment policy is flexible and will be adjusted as and when necessary.

I am greatly indebted to the Netherlands Institute for Neuroscience, the Royal Netherlands Academy for Arts and Sciences, Stichting MS Research, Internationaal Parkinson Fonds, Internationale Stichting Alzheimer Onderzoek and Hersenstichting Nederland, as well as to private backers, for their financial support, which is indispensable for the continuation of the NBB.

I also thank the members of the autopsy team for their guidance and help with the autopsies, day or night. Many of them are PhD students and technicians who have volunteered to help us out despite their own busy programs and work commitments. Also indispensable are the autopsy assistants and pathologists at VUmc, to whom I would like to express my gratitude for their unstinting willingness to perform the autopsies.

Last but not least, a heartfelt thank you to all our donors and their families, without whom worldwide scientific research of the brain and brain disease would not be possible.

Inge Huitinga  
Director Netherlands Brain Bank
Objectives NBB

The Netherlands Brain Bank was founded in 1985 by Dick Swaab, initially with the sole purpose of obtaining brain tissue for his Alzheimer research. However, he soon realized that a facility where people could register as brain donors for research purposes would greatly benefit other researchers in neuroscience as well. From the very start, the NBB has thus been accepting applications for brain tissue from researchers from all over the world.

It is still the primary objective of the NBB to collect, characterize and disseminate tissue of the human brain and spinal cord for the benefit of scientific research worldwide, with the ultimate goal of increasing the knowledge of the human brain and finding cures for neurological and psychiatric brain diseases.

The NBB organization chart can be found in the Appendix (Figure 15).
Donor Program

The NBB is one of the few brain banks in the world with an active donor program, which means that the NBB actively tries to motivate people with neurological and psychiatric disorders, as well as healthy individuals, to register as brain donors at the NBB. With this registration, donors give informed consent to the NBB to perform a rapid autopsy after death and to donate their brain tissue to reviewed research projects around the world. The donors also give permission to the NBB for the release of their medical information after they have passed away. The registration forms and accompanying informational brochures (informed consent forms) are 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 informational brochures and registration forms, reviewed by the Medical Ethics Committee of the VUmc, were approved on October 30, 2009.

On December 31, 2012, 2702 living donors with a variety of disorders were registered at the NBB.

25th anniversary of the Netherlands Brain Bank
The Netherlands Brain Bank has been performing autopsies and disseminating tissue to researchers for over 25 years now, ever since its inception in 1985. The NBB’s 25th anniversary in 2011 attracted a considerable amount of media attention, culminating in a symposium on “Depression and Happiness” on 15 September 2011 (see figure 1). The public activities and increased media coverage are reflected in an increased number of donor registrations, especially in 2011.

Increased focus of the NBB donor program
In 2011 and 2012 the NBB adapted its registration policy to the demand of the research community by actively encouraging new registrations of control donors and donors with diseases for which brain tissue demand is high. For diseases for which the demand for brain tissue is lower and/or for which the NBB’s current stock is sufficient, we have issued a (temporary) halt to registrations. In addition to

control donor registrations, we currently welcome registrations from donors with the following diagnoses: multiple sclerosis, Parkinson’s disease, frontotemporal dementia, Alzheimer’s disease (only for patients from the VUmc Alzheimer Center), narcolepsy, transsexualism, and psychiatric disorders (especially schizophrenia, depression, bipolar disorder, autism spectrum disorder, obsessive-compulsive disorder, attention deficit hyperactivity disorder, and post-traumatic stress disorder). This list will be adjusted when necessary. Applications of donors with rare diseases are assessed on an individual basis, because it is not feasible to provide an exhaustive list of diagnoses.

Another continuing effort is to increase the quality rather than the quantity of donor registrations through increased recruitment of donors from clinical cohorts, already reported in the progress report for 2009-2010. 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, it is our experience that people who participated in research during their lifetime also tend to be willing to donate tissue after their demise. In 2012, the NBB
continued with this approach by starting a collaboration with the Alzheimer Center of the VUmc (Prof. P. Scheltens, Dr. W. van der Flier and Dr. Y. Pijnenburg). Annually, the Alzheimer Center extensively diagnoses 600 new patients from all over the Netherlands. Because of the relatively large existing collection of Alzheimer brain tissue at the NBB, we currently do not accept registrations of donors with Alzheimer’s disease who are not registered at the VUmc Alzheimer Center. On December 31, 2012, 7 registered donors were part of the Alzheimer Center cohort, 19 donors were part of CARPA cohort (Parkinson’s disease) of the Academic Medical Center Amsterdam, and 28 donors were part of the SCOPA cohort (Parkinson’s disease) of the Leiden University Medical Center.

Lastly, we intend to improve the accuracy of the NBB’s information about living donors, an ambition inspired by the fact that a clinical diagnosis at the time of registration often differs from the diagnosis at the time of a donor’s demise, for example when a control donor develops dementia. In many cases, the NBB does not receive timely notification. We aim to address this by regularly sending questionnaires to registered donors (every five years for control donors and every year for donors with a brain disorder), starting in 2013.

**Newsletter**

In order to keep our donors up to date about the progress made within the NBB and about the scientific output achieved with material provided by the NBB, we started a newsletter for all our registered donors in 2009. The second edition was issued in March 2012 and featured, among other things, the NBB’s 25th anniversary celebrations and an overview of the anniversary symposium, the adjustments made to the donor registration policy, and interviews with a donor and a researcher.

**Registrations**

Figure 2 shows the number of registrations in 2011 and 2012, compared to the registrations in the period 2009-2010. The total number of registrations in 2011-2012 increased considerably in comparison to 2009-2010 (742 vs. 545). This rise can be attributed almost completely to the increase of control donors (almost twofold) and donors with psychiatric diseases, especially depression and bipolar disorder (more than threefold) and clearly illustrates the efficacy of the new donor program strategies of the NBB.

As figure 4 shows, the number of 288 new donor registrations in 2012 is comparable to the numbers of previous years, whereas the number of new donor registrations in 2011 soared to 454, probably as a result of the ample amount of media attention
related to the NBB’s 25th anniversary. Also, generally, media coverage of the NBB has remained relatively high over 2012. In June 2012, the NBB was awarded a large grant from NWO (The Netherlands Organisation for Scientific Research) for the development of a psychiatric brain tissue donor program. In the public media, several articles appeared about our program which emphasized the importance of control donors as well as our main focus: psychiatric diseases. Table 1 specifies the diagnoses of donors with psychiatric diseases who registered at the NBB in 2011 and 2012.

Table 1  New registrations of donors with a psychiatric disease in 2011-2012

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>New registrations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Attention deficit hyperactivity disorder</td>
<td>7</td>
</tr>
<tr>
<td>Autism spectrum disorders</td>
<td>3</td>
</tr>
<tr>
<td>Bipolar disorder</td>
<td>23</td>
</tr>
<tr>
<td>Depression</td>
<td>76</td>
</tr>
<tr>
<td>Obsessive-compulsive disorder</td>
<td>2</td>
</tr>
<tr>
<td>Post-traumatic stress disorder</td>
<td>6</td>
</tr>
<tr>
<td>Schizophrenia</td>
<td>8</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>125</strong></td>
</tr>
</tbody>
</table>
Figure 3 shows how the 2702 donors registered with the NBB on December 31, 2012, are distributed across the different diagnoses. A large number of control donors is necessary, because a considerable number of these donors turn out to have a different diagnosis at the time of death.

In total, the NBB received 454 new registrations in 2011 and 288 new registrations in 2012 (figure 4). After the increase in annual registrations from 2006 onward, the number of registrations per year has stabilized since 2008, with a peak in 2011, likely due to the press activities in 2011 on the occasion of our 25th anniversary. The number of new female registrations remains higher than that of new male registrations. This is mostly due to the relatively higher number of female MS and non-demented control registrations. The two-fold higher prevalence of MS in females probably explains this for MS. We are as yet unable to offer an explanation for the disproportionate increase of female control donors. Such a difference is not seen in organ donation for transplantation purposes (source: www.donorvoorlichting.nl).
The increase and subsequent stabilization of the total numbers of annual registrations is reflected in the annual numbers of autopsies, which have also increased from 82 in 2006 to stable numbers of 120 to 130 in 2010-2012.

**Presentations and articles**
In the past two years the NBB has continued to invest time and effort into raising awareness of the importance of research with human brain tissue and the possibility of brain donation. In addition to the media coverage described above, the NBB has visited patient meetings to give presentations on the work of the NBB and on the possibility to become a donor. Being able to show what kind of research 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 2 gives an overview of the articles published about the work of the NBB in 2011 and 2012. We always make sure to mention that patients with neurological or psychiatric diseases and healthy control donors are equally crucial for good scientific research, hoping to persuade family members to register as brain donors as well (see chapter Autopsies).

**Websites of the NBB**
The internet has become a very popular source for 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 boost public awareness of the importance of brain donation. We update our donor website ([www.hersenbank.nl](http://www.hersenbank.nl)) regularly as...
<table>
<thead>
<tr>
<th>Date</th>
<th>Title / description</th>
<th>Medium / additional information</th>
</tr>
</thead>
<tbody>
<tr>
<td>2011/01/03</td>
<td>Interview with Inge Huitinga: ‘Brain donor shortage’</td>
<td>Alzheimer Actueel (magazine patient organization)</td>
</tr>
<tr>
<td>2011/01/05</td>
<td>Interview with Inge Huitinga: ‘Fellowship has been the base of my career’</td>
<td>Rondom MS (magazine patient organization)</td>
</tr>
<tr>
<td>2011/07/23</td>
<td>Interview with Dick Swaab: ‘Living once is enough’</td>
<td>De Telegraaf (newspaper)</td>
</tr>
<tr>
<td>2011/07/31</td>
<td>Extensive interview with Dick Swaab including self-selected television fragments illustrating his life</td>
<td>Zomergasten (TV show)</td>
</tr>
<tr>
<td>2011/09/15</td>
<td>Symposium ‘Depressie &amp; Geluk’ (depression and happiness)</td>
<td>On the occasion of the 25th anniversary of the NBB</td>
</tr>
<tr>
<td>2011/02/09</td>
<td>Presentation: The role of Vitamin D in Multiple Sclerosis</td>
<td>MS organization Gouda</td>
</tr>
<tr>
<td>2011/11/24-25</td>
<td>MS research days</td>
<td>Event of patient organization</td>
</tr>
<tr>
<td>Nov 2011 and Oct-Nov 2012</td>
<td>Radio commercial with Inge Huitinga</td>
<td>MS Research (patient organization)</td>
</tr>
<tr>
<td>2011/12/01</td>
<td>‘Meaningful numbers behind 30 years of MS research’</td>
<td>Brochure MS research Rondom MS (magazine patient organization)</td>
</tr>
<tr>
<td>2011/12/01</td>
<td>‘Huge shortage of brain tissue for Parkinson research’</td>
<td>Papaver (Magazine of Parkinson patient organization)</td>
</tr>
<tr>
<td>2012/01/02</td>
<td>NBB featured in TV show</td>
<td>Labyrint (TV show), episode “Kopzorgen” (head worries).</td>
</tr>
<tr>
<td>June-Oct 2012</td>
<td>Press release and articles announcing the grant for developing a psychiatric tissue program (NBB-Psy)</td>
<td>NWO, KNAW, De Telegraaf, nu.nl, nd.nl (news website Nederlands Dagblad), scienceguide.nl, magazine of Rudolf Magnus Institute of Neuroscience</td>
</tr>
<tr>
<td>2012/04/10</td>
<td>Prize nomination for using alternatives for laboratory animals</td>
<td>Lef in ‘t Lab (‘courage in the lab’) award ceremony; Dutch Society for the Protection of Animals and NKCA</td>
</tr>
<tr>
<td>Oct 2012</td>
<td>‘Biobanks, defrosting lurks’</td>
<td>Medicines (magazine)</td>
</tr>
<tr>
<td>Oct 2012</td>
<td>‘NBB expands collection’</td>
<td>AMC Magazine</td>
</tr>
<tr>
<td>2012/12/01</td>
<td>‘The NBB already has 3500 brains’</td>
<td>Experiment NL, issued by Quest and NOW (magazine)</td>
</tr>
</tbody>
</table>
well, so that our (potential) donors are kept informed about the work of the NBB. The English website of the NBB (www.brainbank.nl) provides researchers with detailed information regarding our procedures, diagnostics and the availability of tissue. In 2012, the NBB set up e-NBB (www.e-nbb.org), an online tissue database where researchers may view the available tissue and make their own preliminary tissue selection. More information about e-NBB can be found in the chapter on Tissue Supply.

New logo
In 2011 and 2012 the NBB has been making continuous efforts to further professionalize its communications. The Netherlands Institute for Neuroscience, of which the NBB is a department, initiated the development of a new logo and changed its Dutch name from “Nederlands Instituut voor Neurowetenschappen” to “Nederlands Herseninstituut”, a name which reflects its activities more clearly. A new logo was developed for the NBB in the same style as the institute’s logo. The NBB’s latest initiative, NBB-Psy, a separate donor program geared towards specific psychiatric disorders, uses two distinct logos, one for communications aimed at donors (red / purple) and one for researchers (blue / green).

At the end of 2012, the NBB began using this new house style in all communication materials: the informed consent packages were changed to match the new look, and new websites and a general informational brochure for donor recruitment were created. The transition was completed in 2013. Figure 5 clearly shows the matching new logos.

The NBB wishes to acknowledge and thank all donors and their families for their generosity and the invaluable gift they are giving to future generations.
Aim
NBB-Psy is a program of the NBB. Its aim is to establish a resource of human brain tissue of 7 major psychiatric disorders:
- Major depression disorder
- Schizophrenia
- Bipolar disorder
- Obsessive-compulsive disorder
- Post-traumatic stress disorder
- Autism spectrum disorder
- Attention-deficit hyperactivity disorder

Background
The personal, social and economic burden of psychiatric disorders is high and demands better treatment strategies. In order to be able to develop such strategies, an understanding of the underlying etiology and pathophysiology of psychiatric disorders is essential. The use of human brain tissue provides the most direct strategy for developing and testing hypotheses about the molecular and cellular basis of psychiatric disorders. The current availability of human brain tissue from patients with psychiatric disorders is nowhere near sufficient and it is therefore our mission to develop a qualitatively unique tissue program to extend the number of post-mortem brains of extensively phenotyped patients: NBB-Psy (NHB-Psy in Dutch). The resource will be made available to the national and international research community via the application procedures of the NBB. The NBB-Psy program is mainly funded by the Netherlands Organisation for Scientific Research (NWO).

Approach
Together with research groups from 5 Dutch universities (Utrecht, Nijmegen, University of Amsterdam, Vrije Universiteit Amsterdam, Rotterdam), the NBB has developed a strategy based on two strong assets in the Netherlands:
1. The NBB is one of the world's leading brain banks and is well-known for its unique rapid fresh dissection protocols (4-10h after death);
2. The availability of several large and extensively phenotyped cohorts of psychiatric patients.
We will appeal to patients and family members of these cohorts to register as brain
donors at the NBB. Table 3 shows the clinical cohorts that are involved in the program and their number of participants.

To further increase the number of registered donors, we will approach patient and family associations and (long-stay) clinics. We will give oral presentations at patient meetings organized by these associations and at these clinics, and we will hand out brochures to those who are interested in brain donation. Furthermore, we will publish articles on NBB-Psy in the magazines of patient and family associations (Figure 6). Controls will be obtained from the cohorts, from patient organizations and from the regular NBB donor program.

In order to optimize our donor recruitment strategy, we will actively monitor the number of prospective donors approached and the registration rate. Every year we will evaluate what strategy works best for what disorder and determine whether we need to adjust our recruitment strategy.

Table 3  Participating clinical cohorts, (long-stay) clinics and patient and family associations

<table>
<thead>
<tr>
<th>Disorders</th>
<th>Clinical cohorts</th>
<th>Associations</th>
<th>(Long-stay) clinics</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Name cohort</td>
<td>Nr of</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>participants</td>
<td></td>
</tr>
<tr>
<td>Schizophrenia</td>
<td>GROUP</td>
<td>1057</td>
<td>Ypsilon</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>GGZ Centraal</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Anoiksis</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>GGZ Venray</td>
</tr>
<tr>
<td>Bipolar disorder</td>
<td>BIG</td>
<td>2500</td>
<td>Vereniging voor</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Manisch Depressieven en</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Betrokkenen (VMDB)</td>
</tr>
<tr>
<td>Major depression disorder</td>
<td>NESDA</td>
<td>2056</td>
<td>Depressie Vereniging</td>
</tr>
<tr>
<td></td>
<td>NESDO</td>
<td>400</td>
<td></td>
</tr>
<tr>
<td>Obsessive compulsive disorder</td>
<td>AMC OCD cohort</td>
<td>1158</td>
<td>Angst-, Dwang en</td>
</tr>
<tr>
<td></td>
<td>NOCDA</td>
<td>419</td>
<td>Fobie-stichting (ADF stichting)</td>
</tr>
<tr>
<td>Attention deficit hyperactivity disorder</td>
<td>NeurIMAGE</td>
<td>519</td>
<td>Balans</td>
</tr>
<tr>
<td></td>
<td>IMpACT</td>
<td>250</td>
<td>PsyQ</td>
</tr>
<tr>
<td></td>
<td>Clinical adult ADHD cohort</td>
<td>4600</td>
<td>Parnassia-BAVO</td>
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<tr>
<td>Autism spectrum disorder</td>
<td>UMC ASD</td>
<td>998</td>
<td>Nederlandse Vereniging voor Autisme (NvA)</td>
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<tr>
<td></td>
<td>TRAILS</td>
<td>300</td>
<td>Leo Kannerhuis</td>
</tr>
<tr>
<td></td>
<td>BOA cohort</td>
<td>158</td>
<td></td>
</tr>
<tr>
<td>Posttraumatic stress disorder</td>
<td>TraumaTIPS</td>
<td>852</td>
<td>Veteranen Instituut</td>
</tr>
<tr>
<td></td>
<td>AMC cohort PTSD</td>
<td>800</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Police officers cohort</td>
<td>1000</td>
<td>Stichting Arq</td>
</tr>
</tbody>
</table>

Table 3  Participating clinical cohorts, (long-stay) clinics and patient and family associations
Taken together, more than 50,000 people will be approached via the cohorts, associations and clinical settings. With a registration rate of 15-25%, we anticipate collecting at least 230-300 psychiatric and 125-200 control brains in the first 5 years and at least 450-600 psychiatric and 250-500 control brains in the coming 10 years.

**Phenotyping**

Phenotyping of participants of the psychiatric research cohorts has already been done extensively. When participants of the cohorts register as brain donors, they will be asked to give consent for the use of all data collected during the cohort study for research purposes.

Phenotyping of those potential donors who are not included in one of the clinical cohorts will be done with the MINI-Plus interview to confirm the psychiatric diagnosis, or, in the case of healthy controls, to rule out psychiatric symptoms.

For purposes of efficiency and to cause as little burden for the donors as possible, registration is done by means of a medical questionnaire. In addition, we will use web-based questionnaires to generate annual updates on relevant clinical parameters. For these web-based questionnaires, we will build a user-friendly, restricted-access website.

Healthy controls will be requested to fill in the questionnaire every five years (as fewer medical changes are expected to take place compared to patients with psychiatric disorders). The advantage of the regular update is that the health status of the control donors can be monitored during life.
Autopsies and post mortem phenotyping
The rapid autopsies will be performed within the framework of the NBB. Dissection protocols will be developed for each of the seven disorders. These dissection protocols have to comply with the current dissection protocols of the NBB, so that the control tissue can be supplied together with the NBB-Psy tissue. Also, the protocols of the seven disorders should mutually match, in order to be able to compare differences between the psychiatric disorders.
State-of-the-art neuropathological diagnoses will be performed and all data collected during life will be transferred to the NBB, where they will be anonymized, summarized and put into the NBB database. This information will be made available to the researcher. All personal data are fully protected according to national laws and European directives.
The NBB-Psy program is unique, because it uses novel methods to enrich the brain material by:
1. Isolation of primary microglia and astrocytes;
2. Generation of glial cell lines (microglia and astrocytes) from pure glial cells;
3. cDNA and DNA bank of the seven disorders;
4. Human induced pluripotent stem cells (iPSCs).
All the brain material will be made available to researchers via the application procedure of the NBB.

www.nhb-psy.nl
www.nbb-psy.nl
@NHBPsy
Stabilization of annual number of autopsies

Since 1985 the NBB has obtained tissue from more than 3700 brain donors. The NBB performed 124 autopsies in 2011 and 129 autopsies in 2012. The number of autopsies has increased considerably since 2006 but has been stable since 2010. Table 4 shows the number of autopsies specified by diagnosis over the last 2 years. The numbers for 2012 are preliminary due to the delay in performing the post mortem diagnostic procedures, which means that the final diagnosis for 31% of the autopsies performed in 2012 is still pending.

Table 4 Annual numbers of autopsies by disease

<table>
<thead>
<tr>
<th></th>
<th>2006</th>
<th>2007</th>
<th>2008</th>
<th>2009</th>
<th>2010</th>
<th>2011</th>
<th>2012</th>
</tr>
</thead>
<tbody>
<tr>
<td>Contr</td>
<td>n</td>
<td>%</td>
<td>n</td>
<td>%</td>
<td>n</td>
<td>%</td>
<td>n</td>
</tr>
<tr>
<td>AD</td>
<td>30</td>
<td>37%</td>
<td>28</td>
<td>31%</td>
<td>29</td>
<td>26%</td>
<td>28</td>
</tr>
<tr>
<td>FTLD/tau</td>
<td>3</td>
<td>4%</td>
<td>8</td>
<td>9%</td>
<td>16</td>
<td>15%</td>
<td>15</td>
</tr>
<tr>
<td>Other dem</td>
<td>9</td>
<td>11%</td>
<td>7</td>
<td>8%</td>
<td>13</td>
<td>12%</td>
<td>6</td>
</tr>
<tr>
<td>PSP</td>
<td>2</td>
<td>2%</td>
<td>3</td>
<td>3%</td>
<td>5</td>
<td>5%</td>
<td>9</td>
</tr>
<tr>
<td>MS</td>
<td>8</td>
<td>10%</td>
<td>14</td>
<td>16%</td>
<td>9</td>
<td>8%</td>
<td>11</td>
</tr>
<tr>
<td>PD/DLBD</td>
<td>6</td>
<td>7%</td>
<td>7</td>
<td>8%</td>
<td>12</td>
<td>11%</td>
<td>17</td>
</tr>
<tr>
<td>Psych</td>
<td>4</td>
<td>5%</td>
<td>2</td>
<td>2%</td>
<td>4</td>
<td>4%</td>
<td>2</td>
</tr>
<tr>
<td>Other</td>
<td>9</td>
<td>11%</td>
<td>9</td>
<td>10%</td>
<td>5</td>
<td>5%</td>
<td>5</td>
</tr>
<tr>
<td>PANR</td>
<td>1</td>
<td>1%</td>
<td></td>
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<td></td>
<td></td>
<td>40*</td>
</tr>
<tr>
<td>Total</td>
<td>82</td>
<td>90</td>
<td>110</td>
<td>110</td>
<td>127</td>
<td>124</td>
<td>129</td>
</tr>
</tbody>
</table>

* 15 of the autopsies listed as “PANR” are likely to be diagnosed as MS (these patients were clinically diagnosed with MS, a diagnosis that only rarely turns out to be false once the final neuropathological diagnosis has been determined). This brings the likely number of MS autopsies in 2012 to 16. However, PANR-autopsies with a different clinical diagnosis may also turn out to be MS cases.
**Total number of brain donors**

Figure 7 shows the total number of brain donors (3710) from which the NBB has obtained brain tissue since its start in 1985. Most of the tissue was obtained by means of autopsies performed by the NBB itself, but some was acquired from other sources (approximately 1472 donors).

During the last couple of years there have been relatively few autopsies of control donors and donors with Alzheimer’s disease, and more of donors with other diagnoses, especially multiple sclerosis and Parkinson’s disease / diffuse Lewy body dementia. This can be explained by the notion that the NBB started out as a brain bank focused on Alzheimer’s disease. During the course of the NBB’s existence the focus has shifted to include other diseases.

Figure 7 Total number of brain donations since 1985 (3710 on December 31, 2012)
Post mortem delay
Due to autolytic processes, tissue of the central nervous system quickly decays after
death and there is thus only a small window of opportunity for brain autopsy. The
post mortem delay (PMD: time elapsed from a person’s demise to completion of
the brain autopsy) depends on several factors: time of notification of the donor’s
death, distance and time for transportation of the body and the availability of brain
bank staff to perform the autopsy. Because PMD has a strong impact on the quality
of the tissue (i.e. RNA, DNA and proteins), several brain banks have 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 in most cases,
even when they work with a 24/7 availability of staff. Over the last 5 years the aver-
age PMD of the NBB autopsies has been extremely stable (figure 8).

Post mortem diagnostics
After completion of an autopsy the brain tissue is fixed in formalin for four weeks.
After fixation, approximately eighteen standard regions of tissue are embedded in
paraffin, cut and (immuno)histochemically stained. These sections are evaluated by
one of our neuropathologists according to the latest international diagnostic criteria.
Together with the clinical diagnosis this provides the definitive diagnosis. The fact
that the final neuropathological diagnosis is often different from the initial clinical
diagnosis emphasizes the importance of performing post mortem diagnostic pro-
cedures. This is illustrated in table 5, which shows the neuropathological diagnoses for the recent autopsies of donors who were clinically diagnosed with Parkinson’s disease. Clinical diagnoses of Parkinson’s disease are followed by a different post mortem pathological diagnosis in a strikingly large number of cases, approximately 30% according to the NBB database. This general estimate is reflected in the numbers for 2010-2012 as well, although the numbers vary strongly per year.

Any possible discrepancies between the clinical and pathological diagnosis must be kept in mind when adjusting the registration policy. Donors recruited with a particular disease in mind may not all be suitable for use in research projects focused on that disease.

Table 5 Final neuropathological diagnoses for Parkinson protocol autopsies

<table>
<thead>
<tr>
<th>Year</th>
<th>PD protocol autopsy</th>
<th>Final diagnosis</th>
<th>n</th>
<th>Diagnosis in PD spectrum</th>
</tr>
</thead>
<tbody>
<tr>
<td>2010</td>
<td>12</td>
<td>PD</td>
<td>1</td>
<td>67%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>PD with dementia</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Alzheimer’s disease / Lewy body variant</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Multi-system atrophy</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cortico-basal degeneration</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Other</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>2011</td>
<td>10</td>
<td>PD</td>
<td>7</td>
<td>100%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>PD with dementia</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>2012</td>
<td>19</td>
<td>PD</td>
<td>5</td>
<td>53% (of the finished cases)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>PD with dementia</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Multi-system atrophy</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Progressive supranuclear palsy</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Control with vascular encephalopathy</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Non-Alzheimer dementia</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Other</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>PA-report not ready</td>
<td>4</td>
<td></td>
</tr>
</tbody>
</table>
Characterization of MS lesions

The NBB has an impressive collection of tissue blocks (4000 fixed or frozen) of more than 175 multiple sclerosis (MS) donors. The NBB dissects approximately 10-30 MS lesions per donor, a number of which is based on post mortem MRI guidance (in collaboration with VUmc) and a number on macroscopical appearance. In addition, tissue is dissected from standard locations for diagnostic purposes. Many tissue samples are mirror blocks of which one side is frozen in liquid nitrogen and the other fixed in formalin and embedded in paraffin. Most mirror blocks and diagnostic blocks have been analyzed using HE, Bodian and Klüver stains, and their histological appearances have been described by the neuropathologist of the NBB. However, standardized information about demyelinating activity, inflammation and neurodegeneration of the tissue blocks is not available, which hampers the effective dissemination of these MS tissues by the NBB.

We have cut and stained all tissue blocks of MS lesions and MS tissue blocks dissected for diagnosis for demyelination and inflammation using PLP-HLA double staining and characterized these for inflammation and demyelination. Scores are indicated in photographs of the lesions and provided to the researchers who apply for MS tissue (figure 9). This considerably facilitates dissemination of MS tissue. In addition, we have analyzed SNPs of the glucorticoid receptor, HLA, IL-1, IL-1RA and TNFalpha and measure markers of neurodegeneration (glutamate, neurofilament) and inflammation (s-CD163) in the CSF and extract clinical information from the clinical files of the MS brain donors. This project is a double-edged sword, since it also provides the unique opportunity to study the occurrence, incidence and distribution of the various types and stages of MS pathology, which enables correlation of this information with clinical and genetic characteristics in a large cohort of MS brain donors.

So far we have characterized all tissue blocks of 182 MS patients (until 2012) whose tissue was available at the NBB, and many of these have already been disseminated to research groups upon their official request. The DNA and CFS have been analyzed of a number of the MS brain donors and all clinical reports have been finalized. All data have been transferred to a MS post mortem database. Currently pathological, genetic and clinical data are being analyzed, to investigate whether specific pathology of MS relates to a specific clinical course and genetic background.

This project is financed by the VRIENDENLOTERIJ.
Figure 9  Photographs of MS lesion characterization. Overview of 0.006 mm thick sections of MS lesions of a MS brain donor of the NBB. Myelin is brown, inflammatory activity (macrophages) is black. The number in the MS lesions indicates the type of MS lesion: no lesion (0), active lesion (2 or 3), inactive lesion (4), remyelination (6), in grey matter (5). Subscores indicate the degree of inflammatory activity.

Future plans
The tighter focus of the registration policy the NBB began in 2012 has been supplemented by a new autopsy policy as well. As of the beginning of 2013, the NBB reserves the right to decide not to perform autopsies under certain circumstances, for instance for diagnoses for which current tissue supplies are sufficient and/or for which research demand is low. This is particularly useful for cases in which donors with such a diagnosis are presumed to have become less suitable for research, for example when they have developed brain metastases of peripheral tumours. By March 2013 all donors had been informed in writing of this policy change.
Online tissue database: e-NBB
To professionalize the NBB’s tissue sample dissemination procedure, the NBB has made its tissue database available online. As of late 2011 researchers may browse the database of this online application called the e-NBB (www.e-nbb.org) and make a tissue selection which they can send in along with the tissue application form. In 2012 the e-NBB was used to make a tissue selection for 27 applications. We expect the proportion of applications that make use of the e-NBB to increase as the e-NBB’s existence becomes better known. We encourage this by informing researchers of the e-NBB when we receive a tissue availability inquiry. Although this presumption is not yet supported by hard data, the first year of e-NBB use has given us the impression that the e-NBB has improved the efficiency of the tissue application procedure by decreasing the number of inquiries about tissue availability and the number of applications for tissue that the NBB does not have.

Number of research institutes that receive NBB tissue
In 2006, the NBB undertook to review all its procedures, which led to new informed consent forms and to professionalization of the 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. The first MTA was signed in June 2007. As of 31 December 2012, the NBB has entered into agreement with 101 universities / research institutes and 22 pharmaceutical companies worldwide. Once both parties have signed the MTA, which is valid for an indefinite period of time unless specified otherwise, any researcher within the institute can apply for tissue.

Number of tissue applications
The number of tissue applications has increased since the introduction of the new procedures, but has stabilized since 2009 (figure 10). Of the 96 applications received in 2011, 19 were from for-profit organizations (pharmaceuticals). Of the 98 applications received in 2012, 8 were from for-profit organizations. Researchers may inquire about the availability of samples, which in most cases leads to an application. When it concerns a new research project, the application is re-
viewed 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. For approved new applications in 2011 and 2012, the tissue was delivered on average 101 days after the tissue application date, with a standard deviation of 81 days. The large variance is mostly due to differences in the time needed after approval of the application, i.e. to agree on a suitable tissue selection and to finalize the necessary paperwork.

When the application concerns an existing research project that has already been reviewed, this is called a supplementary application. The option of filing a supplementary application was introduced in 2007, together with the MTA. With the original research project already approved, the requested tissue can be supplied even more quickly, provided that the tissue is available and the type and number of samples are reasonable compared to the original application. For approved supplementary applications in 2011 and 2012, the tissue was delivered on average 37 days after the supplementary application date, with a standard deviation of 57 days.

In 2011 and 2012 there were 15 cases (out of 194) where tissue inquiries led to applications that could not be approved, where approved applications could not be completed, or where the inquiry did not lead to an actual application. The main reasons why tissue inquiries or applications foundered are:
1. an application form was sent to the researcher, but the researcher never actually applied for tissue;

![Figure 10: New and supplementary tissue applications](image)

**Figure 10**
2. the researcher had to cancel the application due to financial problems (rejected grant applications).
There were also a number of applications that could only be partly approved due to tissue scarcity, which shows the need to increase the number of donors with a specific neurological or psychiatric disorder. This was one of the reasons to start donor recruitment efforts among clinical cohorts and to start NBB-Psy, the separate donor program for psychiatric diseases. In addition to tissue from donors with psychiatric diseases, other examples of scarce tissue types are frozen hippocampus samples from control donors and substantia nigra samples from donors with Parkinson’s disease.

**Tissues disseminated for research projects**

Figure 11 shows the specification of supplied samples by diagnosis in 2011 and 2012, compared to the tissue supply in 2007-2010. Since 2008 the number of supplied tissue units has increased. This increase is equally distributed across the different diagnoses. As the NBB aims to increase the number of disseminated tissue samples, we will begin to explore possibilities to do so in 2013.

In line with the tissue applications, the majority of tissue samples were supplied to researchers affiliated to universities or other non-profit organizations. In 2011, 470 units out of a total of 4664 tissue units were supplied to for-profit organizations (pharmaceutical companies). In 2012, 4678 tissue units were supplied, of which 59 to for-profit organizations.
Figure 12 shows the specification of the samples by type of storage. The NBB not only provides frozen or formalin-fixed paraffin-embedded (FFPE) samples, but also fresh tissue and formalin-fixed tissue. The different treatments of the tissue allow different kinds of research approaches. In general, FFPE samples are especially suitable for performing immunohistochemistry and morphometric studies. For RNA and protein analysis studies mainly frozen tissue is used. The proportion of supplied fresh tissue has been increasing since 2009, which reflects the increased usage of tissue cultures and glial cell isolations in research.

**Database mining**

In addition to the NBB’s collection of brain tissue samples, our database contains a wealth of clinical and neuropathological information about the donors. When researchers receive tissue, this is accompanied by the information files for all donors of whom they have received samples. However, the information in the database also provides ample research opportunities on its own. Over the last few years, there has been an increase in the number of requests from researchers who would like to analyze data from the NBB database without the actual use of brain tissue. In 2012, the NBB has formulated standardized guidelines for these situations in terms of financial contribution and corporate authorship, which can be found on the website. In the future, we intend to increase awareness regarding this possibility among researchers in order to enable more studies to make use of the valuable data.

![Supplied tissue units per year by type of storage](image-url)
The possibilities of analysis of brain banks databases were an important topic of the MacBrain symposium (December 6th, 2012), organized by the Institute for Computing and Information Sciences (Radboud University Nijmegen) in cooperation with the NBB. The goal of the symposium was to provide researchers and practitioners with an overview of the cutting edge research on core aspects of integrative research of brain diseases, combining data management, machine learning and clinical and pathological studies.

Figure 13 Announcement for the MacBrain symposium
The NBB receives structural financial support from the Royal Netherlands Academy of Arts and Sciences (KNAW) and the Netherlands Institute for Neuroscience (NIN), but apart from that it is almost completely dependent upon grants, donations and the financial contributions from researchers who use NBB material.

### Grants

<table>
<thead>
<tr>
<th>Source</th>
<th>2011</th>
<th>2012</th>
</tr>
</thead>
<tbody>
<tr>
<td>Structural contribution from the KNAW</td>
<td>€ 224,144</td>
<td>€ 224,144</td>
</tr>
<tr>
<td>Structural contribution from the NIN</td>
<td>€ 100,000</td>
<td>€ 100,000</td>
</tr>
<tr>
<td>Stichting MS Research</td>
<td>€ 106,254</td>
<td>€ 106,254</td>
</tr>
<tr>
<td>Internationale Stichting Alzheimer Onderzoek</td>
<td>€ 29,648</td>
<td>€ 24,706</td>
</tr>
<tr>
<td>Internationaal Parkinson Fonds</td>
<td>€ 25,000</td>
<td>€ 25,000</td>
</tr>
<tr>
<td>Hersenstichting Nederland</td>
<td>€ 12,000</td>
<td>€ 12,000</td>
</tr>
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</table>

### Grant for NBB-Psy

<table>
<thead>
<tr>
<th>Source</th>
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</tr>
</thead>
<tbody>
<tr>
<td>NWO (Netherlands Organisation for Scientific Research)</td>
<td>€ 3,450,000*</td>
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</table>

* This funding was jointly granted to the NBB and the five participating Dutch university medical centers for setting up the separate NBB-Psy program, as described in the chapter on Registrations. The project and its budget are coordinated by the NBB under the responsibility of the KNAW.

### The necessity of grants

The costs to make tissue available for research are approximately € 800,000 per year. Without the help of patient organizations the NBB would not be able to maintain its high standards, and it is only thanks to the funding the NBB receives that it is able to continue brain banking.

The Stichting MS Research (MS Research Foundation; [www.msresearch.nl](http://www.msresearch.nl)) has been funding the NBB for many years, resulting in an increase of the number of MS donors and in the 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 the summarization of their medical information requires a greater effort. Lastly, in-depth neuropathological diagnostics of the MS plaques is time-consuming, but indispensable for good
tissue dissemination. MS Research covers the costs of all MS autopsies and of some control autopsies.

The funding by the Internationale Stichting Alzheimer Onderzoek (International Foundation for Alzheimer Research; www.alzheimer.nl) has made it possible for the NBB to start up and maintain a DNA bank to keep up with the latest developments in research, where genotyping is becoming the important bridge between clinical and neuropathological characteristics. Previous support from the ISAO (11-01-2007 to 10-31-2009) allowed us, among other things, to produce a promotional DVD on the work of the NBB. € 17,000 of this grant was allocated to the production of the DVD. In 2011 and 2012 many copies of the DVD were distributed among (potential) donors.

The grants of the Internationaal Parkinson Fonds (International Parkinson Fund; www.parkinsonfonds.nl) cover the costs of a part of the Parkinson autopsies and some donor recruitment activities, which would not be possible without this extra funding.

Funding by the Hersenstichting Nederland (Netherlands Brain Foundation; www.hersenstichting.nl) is used to cover donor recruitment, autopsy and administration costs.

Donations
The “Stichting tot Ondersteuning van de Hersenbank” (Foundation for the Support of the NBB) was founded in 1986 and helps to realize the objectives of the NBB by giving financial support. In 2011 and 2012, we received € 17,700 in donations through this foundation.

Since January 2008, the foundation has been deemed an “Algemeen Nut Beogende Instelling” (Institution for Public Advancement) by the Dutch Tax Authorities. The assets of this Foundation are made up of donations, testamentary dispositions and legacies (Dutch Chamber of Commerce; registration no. 41205869). In the last quarter of 2013, the current Foundation for the Support of the NBB will be converted into the “Stichting Vrienden van het Herseninstituut” (Friends of the Brain Institute). Financial donations remain vital to the continued existence of the NBB and are thus very welcome. If you wish to help, please make your donation to: Stichting Vrienden van het Herseninstituut, account number 2167378 (IBAN: NL76INGB0002167378; BIC: INGBNL2A), mentioning “NBB”. Because the foundation also raises money for
the Netherlands Institute for Neuroscience in general, mentioning “NBB” ensures that your donation reaches us.

We are very grateful for all grants and donations. The work of the NBB would not be possible without the support of numerous foundations, patient organizations, and the enthusiastic dedication of private individuals.
Research Projects 2011-2012

The abstracts can be downloaded from our website by clicking on the names below or by visiting http://www.brainbank.nl/research/projects

National

Anink, J. and Aronica, E. Department of (Neuro)Pathology, Academic Medical Center, Amsterdam. Adenosine hypothesis of Parkinson’s disease.

Bonifati, V. Department of Clinical Genetics, Erasmus MC, Rotterdam. Characterization of the FBXO7 (PARK15) protein.

Bonifati, V. Department of Clinical Genetics, Erasmus MC, Rotterdam. Hereditary Parkinsonism and Dystonia with Hypermanganesemia, Polycythemia and Chronic Liver Disease caused by mutations in the SLC30A10 gene.


Brouwer, N., Boddeke, H.W. et al. Medical Physiology, Department of Neuroscience, University Medical Center Groningen, Groningen. Analysis of age-related changes in gene expression in human microglia.

Bruinsma, I. and De Jong, B. Department of Neurology, Radboud University Medical Center, Nijmegen. Role of miRNAs in the pathology of multiple sclerosis.

Bsibsi, M., Amor, S. et al. Department of Pathology, VU University Medical Center, Amsterdam. Alpha B-crystallin activates an immune-regulatory response of microglia in preactive multiple sclerosis lesions.

Creyghton, M.P. Hubrecht Institute for Developmental Biology and Stem Cell Research, Utrecht. Epigenetic profiling of cis regulatory elements in the brain.

Dijkstra, A.A. and Van de Berg, W.D.J. et al. Department of Anatomy and Neurosciences, section Functional Neuroanatomy and Department of Pathology and Department of Medical genomics, VU University Medical Center, Amsterdam. Identifying molecular mechanism underlying the progression of sporadic Parkinson’s disease using advanced genomic and proteomic techniques.

Doorn, K.J. et al. Department of Anatomy and Neurosciences, VU University Medical Center, Amsterdam. Microglial activation beyond the substantia nigra in Parkinson’s disease.

Drukarch, B. and Wilhelmus, M.M.M. Department of Anatomy and Neurosciences, VU University Medical Center, Amsterdam. Association of tissue transglutaminase and lysyl oxidase with cerebral amyloid angiopathy.

Espitia Pinzón, N. and Van Dam, A.M. Department of Anatomy and Neurosciences, VU University Medical Center, Amsterdam. Tissue Transglutaminase in astrogliosis: towards improved remyelination.
Forstmann, B.U. and Alkemade, A. Cognitive Science Center Amsterdam, University of Amsterdam, Amsterdam. Subdivisions of the Subthalamic Nucleus.

Gao, S.F. et al. Netherlands Institute for Neuroscience, Amsterdam. Decreased NOS1 Expression in the Anterior Cingulate Cortex in Depression.


Hepp, D, Van de Berg, W.D.J. et al. Department of Anatomy and Neurosciences, Department of Neurology and Department of Pathology, VU Medical Center, Amsterdam. The pathological substrate of visual hallucinations in Parkinson's disease patients.

Hondius, D.C., Smit, A.B. et al. Department of Pathology, VU University Medical Center, Amsterdam and Department of Molecular and Cellular Neurobiology, Center for Neurogenomics and Cognitive Research, VU University Amsterdam, Neuroscience Campus Amsterdam. Changes in the human hippocampal proteome during Alzheimer’s disease.

Hoozemans, J., Rozemuller, J.M. and Van der Vies, S. Department of Pathology, VU University Medical Center, Amsterdam. Detection of kinase activity in post mortem cerebrospinal fluid.


Ingrassia, A. and Van de Berg, W.D.J. et al. Department of Anatomy and Neurosciences and Department of Pathology, VU University Medical Center, Amsterdam. Neuroprotection and degeneration in the olfactory bulb of Parkinson patients.


Klaver, R., Geurts, J.J.G. et al. Department of Anatomy & Neuroscience, VU University Medical Center, Amsterdam. Grey matter atrophy in MS.

Kondova, I. Division of Pathology and Microbiology, Department of Animal Science, Biomedical Primate Research Center, Rijswijk. Age-related neurological disorders: comparison of brain tissues from humans, chimpanzees and rhesus macaques and exploring the role of miRNAs and small non-coding RNAs (ncRNAs) in the pathogenesis of neurodegeneration.
Kooij, G. et al. MS Center Amsterdam, Department of Molecular Cell Biology and Immunology, VU University Medical Center, Amsterdam. The blood-cerebrospinal fluid barrier: the primary site for inflammation in multiple sclerosis.


Kuiperij, H.B. and Verbeek, M.M. Department of Neurology, Radboud University Medical Center, Nijmegen. TDP-43 and tau as cerebrospinal fluid biomarkers to discriminate frontotemporal dementia subtypes.

Lopes Soriano, A., Geurts, J.J.G. et al. MS Center Amsterdam, Department of Anatomy & Neuroscience, VU University Medical Center, Amsterdam. Use of quantitative magnetic resonance imaging techniques to stage white matter lesions in multiple sclerosis. MRI-pathology correlation study (pilot).

Lucassen, P.J. SILS-Center for Neuroscience, University of Amsterdam, Amsterdam. Changes in glucocorticoid receptor expression and regulation in human hippocampus, amygdala during depression and dementia.


Müller, M. et al. Department of Neurology, Donders Institute for Brain, Cognition and Behaviour, Radboud University Medical Center, Nijmegen. Differential expression of microRNAs in the hippocampus of Alzheimer’s disease patients.

Nabuurs, R. et al. Departments of Radiology, Pathology and Anatomy, Leiden University Medical Center, Leiden. Histological basis of MRI visualization of AD/CAA in ex vivo human brain tissue.

Nijholt, D.A.T., Scheper, W. et al. Department of Genome Analysis and Department of Neurology, Academic Medical Center and Department of Neuropathology VU University Medical Center, Amsterdam. Activation of the unfolded protein response in neurodegenerative tauopathies.
Peferoen, L.A.N., Vogel, D.A.S. et al. Department of Pathology and Department of Molecular Cell Biology and Immunology, VU University Medical Center, Amsterdam. Do stressed oligodendrocytes trigger microglia activation in pre-active MS lesions?

Prins, M., Van Dam, A. et al. VU University Medical Center, Neuroscience Campus Amsterdam, Amsterdam. Chemokine signalling in the hippocampus of multiple sclerosis patients.

Qi, X.R. et al. Netherlands Institute for Neuroscience, Amsterdam. Aberrant stress hormone receptor balance in the human prefrontal cortex and hypothalamic paraventricular nucleus of depressed patients.


Riese, H., Niezen-Koning, K. et al. University Medical Center Groningen, Groningen. Comparison of methylation and expression of the serotonin reuptake transporter gene in amygdala tissue, cerebrospinal fluid and peripheral blood.


Rozemuller, J.M. et al. Department of Neuropathology, VU University Medical Center, Amsterdam. The pathology distribution of the non-memory phenotype of Alzheimer disease.

Schenk, G.J., Geurts, J.J.G. et al. Department of Anatomy & Neuroscience, VU University Medical Center, Amsterdam. Pathobiology of MS: complex interplay between degeneration and inflammation.

Schwab, B.C. et al. Applied Analysis and Mathematical Physics and Biomedical Signals and Systems, University of Twente, Enschede. A Possible Role of Neural Gap Junctions in Parkinson’s Disease Pathology.


Smolders, J., Hamann, J. et al. Neuroimmunology Research Group, Netherlands Institute for Neuroscience, Amsterdam and Department of Experimental Immunology, Academic Medical Center, Amsterdam. Characteristics of differentiated CD8+ and CD4+ T cells present in the human brain.


Van Dijk, K.D. and Van de Berg, W.D.J. Department of Anatomy and Neurosciences, section Functional Neuroanatomy and Department of Neurology, Neuroscience Campus Amsterdam, VU University Medical Center, Amsterdam. The expression of clusterin in the entorhinal cortex in Parkinson’s disease: a pilot study.

Van Luijn, M.M., Hintzen, R.Q. et al. Departments of Immunology and Neurology and MS Center ErasMS, Erasmus MC, Rotterdam. Clusterin and chromogranin A expression and localization in white and grey matter brain tissue of multiple sclerosis patients.

Van Nierop, G.P. and Verjans, G.M.G.M. et al. Departments of Viroscience and Neurology and ErasMS center Neurology, Erasmus MC, University Medical Center, Rotterdam. Specificity and phenotype of T cells in MS lesions.

Van Riel, D. et al. Department of Viroscience, Erasmus MC, Rotterdam. The olfactory nerve: A shortcut for influenza viruses into the CNS?

Van der Star, B. and Amor, S. Department of Pathology, VU University Medical Center, Amsterdam.

Van Swieten, J.C. Department of Neurology, Erasmus MC, Rotterdam. Immunohistochemistry and biochemical characterisation of frontotemporal dementia.


Veerhuis, R. and Hoozemans, J. Department of Clinical chemistry and Alzheimer center and department of Pathology, VU University Medical Center, Amsterdam. Analysis of mediators of inflammation in Alzheimer’s disease.


International

Alberio, T. and Fasano, M. Department of Theoretical and Applied Sciences; Laboratory of Biochemistry and functional Proteomics; University of Insubria, Varese, Italy. Analysis of proteasomal and autophagic function in post-mortem Parkinson’s disease tissues.


Bayer, T.A. Department of Psychiatry, University Medicine Goettingen, Goettingen, Germany. Intraneuronal Abeta accumulation in Alzheimer’s disease.


Chung, S. et al. Department of Psychiatry, Asan Medical Center, University of Ulsan College of Medicine. Seoul, South Korea. Relationships between intracellular Na levels and circadian rhythms in SCN2.2 cell.

Cranley, D. And Brophy, P. Centre for Neuroregeneration, University of Edinburgh, Edinburgh, Scotland. Aberrant ion channel expression and nodal disruption within dorsal root ganglia in multiple sclerosis.

Csiba, L. and Farkas, S. Department of Neurology, University of Debrecen, Debrecen, Hungary. A comparative analysis of expressed and functionally active dopamine receptors in the human brain obtained from Parkinson’s disease patients and age matched controls.

Curtis, M.A. and Graham, S. Centre for Brain Research, Auckland University, Auckland, New Zealand. Cannabinoid receptor expression in MS lesions.

Darreh-Shori T. and Unger Lithner, C. Alzheimer Neurobiology Center, Karolinska Institute, Stockholm, Sweden. The pathological mechanisms of β-amyloid in the brain of Alzheimer’s disease and controls.

Delalle, I. et al. Boston University School of Medicine and Harvard NeuroDiscovery Center, USA. Exosomal and cell-class specific miRNA-profiles in bipolar disorder.

Deleersnijder, A., Baekelandt, V. et al. Laboratory of Neurobiology and Gene Therapy, K. U. Leuven, Belgium. Comparative analysis of different peptidyl-prolyl isomerases reveals FK506-binding protein 12 as the most potent enhancer of α-synuclein aggregation.

Duan, S. et al. Department of Neurobiology, Zhejiang University School of Medicine, Hangzhou, China. The protective role of purinergic receptors against the pathogenesis of Alzheimer’s disease.

Fernandez-Ruiz, J. et al. Instituto Universitario de Investigación en Neuroquímica, Department of Biochemistry and Molecular Biology, Faculty of Medicine, Complutense University, Madrid, Spain. Evaluation of the endocannabinoid receptors and enzymes in the postmortem cerebellum of different SCA patients.

Fraussen, J. and Somers, V. Hasselt University, Biomedical Research Institute, and Transnationale Universiteit Limburg, School of Life Sciences, Diepenbeek, Belgium. Antibody-independent effects of B cells in multiple sclerosis (MS).

Galter, D. Department of Neuroscience, Karolinska Institutet, Stockholm, Sweden. Expression and quantification of candidate genes of Alzheimer’s disease in brain regions primarily affected by disease.

Grosser, C., Van de Nes, J.A.P. et al. Institute of Human Genetics and Institute of Pathology and Neuropathology, Faculty of Medicine, University Duisburg-Essen, Essen, Germany. Methylation analysis of SST and SSTR4 promoters in the neocortex of Alzheimer’s disease patients.

Hemelsoet, D. et al. Department of Neurology/LCEN3, Ghent University Hospital, Ghent, Belgium. The role of matrix metalloproteinases in excitotoxicity and neuroinflammation in temporal lobe epilepsy.

Höökfelt, T. and Ceccatelli, S. Department of Neuroscience, Karolinska Institute, Stockholm, Sweden. To characterize the expression levels of galanin and its receptors in human pituitary tumors.


Ikemoto, K. et al. Department of Neuropsychiatry, Fukushima Medical University School of Medicine, Fukushima, Japan. DNA methylation status of MAOA and MAOB genes in post-mortem brains of patients with schizophrenia.

Ishunina, T., and Swaab, D.F. Department of Histology, Embryology, Cytology, Kursk State Medical University, Kursk, Russia and Netherlands Institute for Neuroscience, Amsterdam, the Netherlands. Estrogen receptor α splice variants in the human brain.


Kalmar, B., Greensmith, L. and Fisher, E. UCL Institute of Neurology, Queen Square London, United Kingdom. Lower motor neuron pathology in Down’s syndrome.

Kaut, O. et al. Department of Neurology, University of Bonn, Bonn, Germany. Genome-wide DNA methylation analysis of depression in human brain samples.


Ko, E.A. et al. Yonsei University College of Medicine, Seoul, South Korea. Interaction of HMGB1 with α-synuclein and the effect on α-synuclein aggregation.

Köse, M. et al. PharmaCenter Bonn, Pharmaceutical Institute, Pharmaceutical Chemistry I, University of Bonn, Bonn, Germany. GPCR distribution in human brain from patients with Alzheimer’s and Parkinson’s disease.

Leuze, C.W.U., et al. Department of Neurophysics, Max Planck Institute for Human Cognitive and Brain Sciences, Leipzig, Germany. 3D cortical profiles of diffusion MRI data in primary motor (M1) and somatosensory (S1) cortex.

Mikkelsen, J.D. Neurobiology Research Unit, University Hospital Rigshospitalet, Copenhagen, Denmark. Detection of nicotinergic receptors in normal and diseased brain.

Mott, N. and Pak, T.R. Loyola University Chicago, Chicago, USA. Mapping human estrogen receptor beta splice variants in the aged brain.

Nichterwitz, S. et al. Department of Neuroscience, Karolinska Institutet, Stockholm, Sweden. Characterization of human protein expression in motor neuron populations that are resistant or vulnerable to degeneration in Amyotrophic Lateral Sclerosis.

Nielsen, H.M., Wennström, M. et al. Lund University, Dept of Clinical Sciences, Molecular Memory Research Unit, Skåne University Hospital, Malmö, Sweden. Analyses of distribution and activation of NG2-cells in the Alzheimer’s brain.

Niola, F. and De Pietri Tonelli, D. Neuroscience and Brain Technologies department, Fondazione Istituto Italiano di Tecnologia (IIT), Genova, Italy. Somatic 22q11 loss of heterozygosity in psychiatric disorders.

Notter, T. et al. Institute of Pharmacology and Toxicology, University of Zurich, Switzerland. Characterization of Reelin-positive deposits in the human postmortem brain of nondemented subjects and patients with AD.

O’Neill, C. et al. Neurobiology and Alzheimer’s Disease Laboratory, Department of Biochemistry, BioSciences Institute, University College Cork, Cork, Ireland. Examination of the Akt/PTEN signalling system in Alzheimer’s disease and related disorders.

Papanikolopoulou, K. and Skoulakis, E.M.C. Division of Neuroscience, Biomedical Sciences Research Centre “Alexander Fleming”, Vari, Greece. Use of phosphorylated Tau as a biomarker.

Picardi, E. and Eisenberg, E. Istituto di Biomembrane e Bioenergetica del CNR, Bari, Italy. Assessment of global A-to-I RNA editing patterns in Alzheimer’s disease by parallel DNA capturing and sequencing.

Preisner, A. et al. Institute of Neuropathology, University Hospital Münster, Münster, Germany. Functional role for Wnt/β-Catenin for remyelination (failure) in MS.


Qiao, J.P., Zhou, J.N. et al. CAS Key Laboratory of Brain Function and Disease School of Life Sciences, University of Science and Technology of China, Anhui, China. Novel Indanone Derivatives as Potential Imaging Probes for β-Amyloid Plaques in the brain.


Sriram, S. and Seely, E. Vanderbilt Medical Center, Multiple Sclerosis Laboratory, Nashville, USA. MALDI analysis of spinal cord tissue of MS patients and controls.


Szodorai, A. and Nitsch, R.M. Molecular Psychiatry, University of Zurich, Zürich, Switzerland. Analysis of the putative presence of dendritic cells in demented brains.

Szodorai, A. and Nitsch, R.M. Molecular Psychiatry, University of Zurich, Zürich, Switzerland. Reduction of pyroglutamate-Abeta (pEAbeta) containing HC brain cells in AD.

Tiepolt, S. et al. Department of Nuclear Medicine, University of Leipzig, Leipzig, Germany. Validation of 7 Tesla MRI to image β-amyloid plaque associated iron in Alzheimer's disease.

Wang, Y. Institute of Neuroscience, Shanghai Institutes for Biological Sciences, Chinese Academy of Sciences, Shanghai, China. Neuroprotection of TRPC6 channels in Alzheimer's disease.

Wanker, E.E. Max Delbrück Centrum für Molekulare Medizin (MDC), Berlin, Germany. Small molecule AMC3.1 for AD therapy by converting monomeric and oligomeric Aβ to protofibrils.

Wähnert, M. et al. Department of Neurophysics, Max Planck Institute for Human Cognitive and Brain Sciences, Leipzig, Germany. Do cortical layers conform to the Laplace equation?

Webb, S. et al. Institute of Neurosciences, Department of Neurology, Southern General Hospital, Glasgow, Scotland, United Kingdom. A comparison of viral infections in lymph nodes of patients with Multiple Sclerosis and normal controls.

Wennström, M. and Nielsen, H.M. Department of Clinical Sciences, Lund University, Malmö, Sweden. In vitro studies on glial targets in neurodegenerative dementia.

Yoon, S-Y. and Kim, D-H. Department of Anatomy and Cell Biology, University of Ulsan College of Medicine, Seoul, Korea. Search for the key pathogenic molecules in Alzheimer's disease brain.

Zhou, J. Institute of Neuroscience, Shanghai Institutes for Biological Sciences, Chinese Academy of Sciences, Shanghai, China. Verification of αB-crystallin and Hapln2 expression in brain of patients with Parkinson's disease.
Pharmaceutical companies

Asterand UK Ltd.
- Analysis of protein expression in normal and Alzheimer’s Disease human brain.
- Examination of autoradiographic binding of a proprietary radioligand in frozen sections of different brain regions from normal donors and those with Parkinson’s Disease.
- Expression of therapeutic candidate gene in cerebellum from Type 2 Diabetic and control donors.

AstraZeneca
- Identification and validation of transcripts and proteins in brain tissue derived from Alzheimer’s patients with special emphasis on pharmacogenetics.

Bayer Schering Pharma AG
- Interrelationship of activated microglia & reactive astrocytes in AD.
- Characterization of alpha-synuclein binding molecules.
- Characterization of small molecules binding to dementia related pathological targets.

BioFocus DPI BV
- Collaborative research program with CHDI Foundation (Cure Huntington’s Disease Initiative).

Evotec AG
- Identification of small molecules binding to aggregated huntingtin for the development of a PET-ligand.

GlaxoSmithKline
- Identification of potential therapeutic targets for amyotrophic lateral sclerosis and Huntington’s disease.
- Identification and validation of potential therapeutic targets for multiple sclerosis.

London Genetics Limited
- Immunohistochemistry studies in cadaver control (normal) human dorsal root ganglia.

Merck Serono SA
- Inflammation drives axonal pathology in the grey matter of neurodegenerative diseases.

Neurimmune Therapeutics AG
- Characterization of therapeutic antibody candidates with respect to binding of pathological protein deposits, in Alzheimer’s disease, Huntington’s disease and amyotrophic lateral sclerosis.

Neusentis (a Pfizer Ltd. research unit)
- Determining expression of pain-related ion channels in human lumbar spinal cord.

Novartis AG
- Autoradiographic examination of extra- and intracellular markers in Huntington’s disease, with special emphasis on visualization of huntingtin aggregates.
- Autoradiography studies on orexin receptors in the human brain.

Pfizer Ltd.
- Target characterisation and safety de-risking.
Prosensa Therapeutics BV

Polyclonal antibody screening for the detection of the brain dystrophin isoform in muscle of patients with Duchenne Muscular Dystrophy.
Publications 2008-2012

In recent years many articles have been published that report the results of research projects realized with the use of NBB tissue. Table 6 shows the number of publications (2004- September 2012) for which NBB-tissue was used, for different journal impact factors. The impact factor of a scientific journal indicates how often its recently published articles have been cited, on average.

**Table 6** Number of publications resulting from the use of NBB tissue, by impact factor

<table>
<thead>
<tr>
<th>Impact factor</th>
<th>Publications</th>
<th>Publications by NIN research groups</th>
</tr>
</thead>
<tbody>
<tr>
<td>Over 9</td>
<td>56</td>
<td>27 (48%)</td>
</tr>
<tr>
<td>7 - 9</td>
<td>52</td>
<td>12 (19%)</td>
</tr>
<tr>
<td>Under 7</td>
<td>362</td>
<td>128 (35%)</td>
</tr>
<tr>
<td><strong>All journals</strong></td>
<td><strong>470</strong></td>
<td><strong>167 (36%)</strong></td>
</tr>
</tbody>
</table>

The following publications were realized through the use of NBB tissue


Fazio, F. et al. Switch in the Expression of mGlu1 and mGlu5 Metabotropic Glutamate Receptors in the Cerebellum of Mice Developing Experimental Autoimmune Encephalomyelitis and in Autoptic Cerebellar Samples from Patients with Multiple Sclerosis. Neuropharmacology 55.4 (2008): 491–499.


Ikemoto, K. Are D-Neurons and Trace Amine-Associated Receptor, Type 1 Involved in Mesolimbic Dopamine Hyperactivity of Schizophrenia? Medicinal Chemistry (2012).


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We owe special thanks to the autopsy assistants of the Pathological Institute, VUmc, Amsterdam, A. Bakker, P. Kraaijeveld, T. Oldert and R. Vos, and to John and Thomas of Rouwservice Nederland and the undertakers of Uitvaartcentrum Zuid (Unigra) for their dedication to the Netherlands Brain Bank.

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List of Abbreviations

Diagnoses
AD Alzheimer’s disease
Contr Non-demented controls
FTLD/tau Frontotemporal lobar degeneration/Tauopathy
MS Multiple sclerosis
Other dem Other dementia
PANR Pathological report not ready
PD/DLBD Parkinson's disease/Diffuse Lewy body dementia
PSP Progressive supranuclear palsy
Psych Psychiatric disorders
Rest group Other diagnoses
Trans Transsexuality
Vasc Vascular dementia

Organizations
AMC Academic Medical Center
KNAW Koninklijke Nederlandse Akademie van Wetenschappen (Royal Netherlands Academy of Arts and Sciences)
NBB Netherlands Brain Bank
NIN Nederlands Herseninstituut (Netherlands Institute for Neuroscience)
NWO Nederlandse Organisatie voor Wetenschappelijk Onderzoek (Netherlands Organisation for Scientific Research)
NKCA Nationaal Kenniscentrum Alternatieven voor Dierproeven (Netherlands Knowledge Centre on Alternatives to Animal Use)
VUmc VU University medical centre
The application is received by the NBB and the availability is reviewed

The requested material is available

Review of the application by the NBB’s scientific committee

Approved

The MTS and Implementing Letter are signed by the applicant

The applicant receives an invoice for the financial contribution

The material is collected by the researcher or sent by the NBB

Feedback is given to the applicant

Supplementary tissue application for project that has already been reviewed

Approximately 1 week

On average 3 weeks

* 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/organization 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.

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Application new project

Supplementary application within reviewed project

Appendix
Figure 15  Non-hierarchic scheme of the organization of the Netherlands Brain Bank