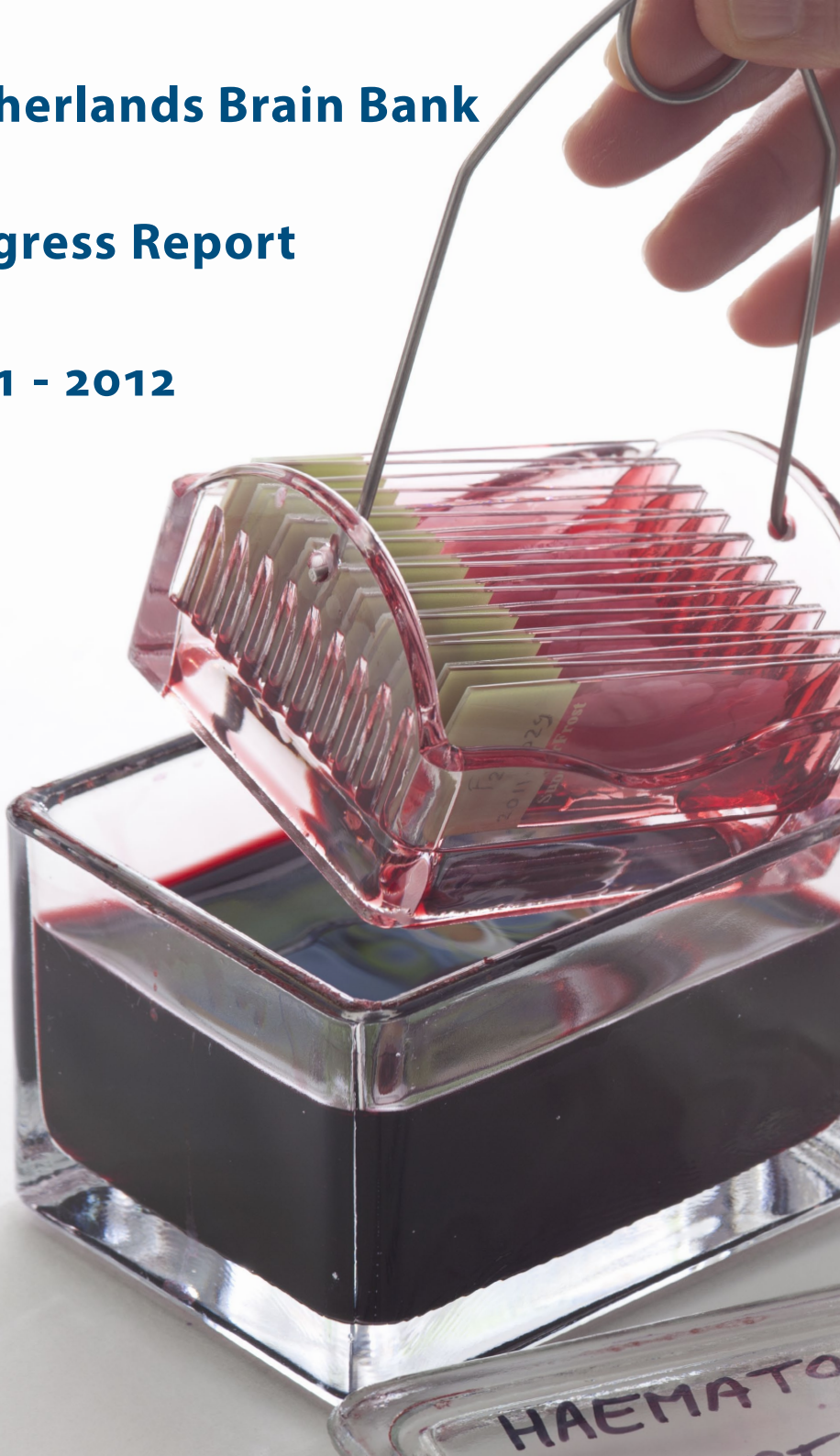


# Netherlands Brain Bank

## Progress Report

2011 - 2012



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# Introduction

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<sup>1</sup>. 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.

## **25<sup>th</sup> 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 25<sup>th</sup> 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

1 Samarasekera, N., R. Al-Shahi Salman, et al. Brain Banking for Neurological Disorders. *Lancet Neurology* (in press).



Figure 1 Announcement for the "Depression and Happiness" symposium

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 25<sup>th</sup> 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

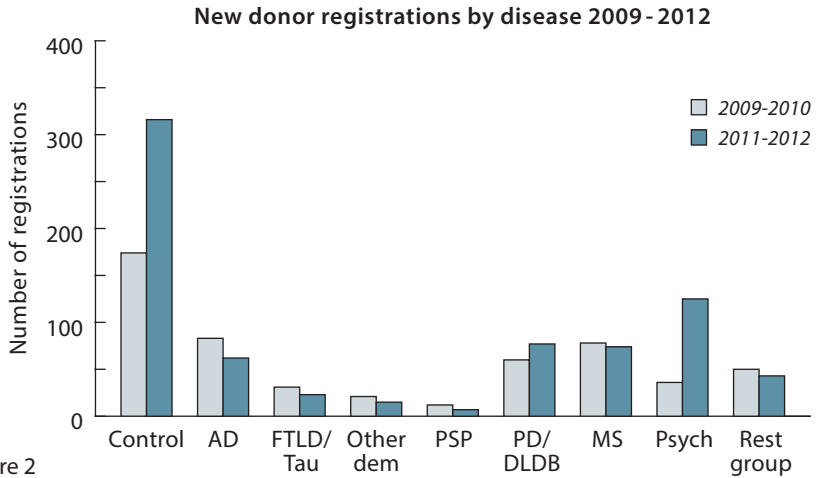


Figure 2

related to the NBB's 25<sup>th</sup> 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

Diagnosis	New registrations
Attention deficit hyperactivity disorder	7
Autism spectrum disorders	3
Bipolar disorder	23
Depression	76
Obsessive-compulsive disorder	2
Post-traumatic stress disorder	6
Schizophrenia	8
<i>Total</i>	<i>125</i>

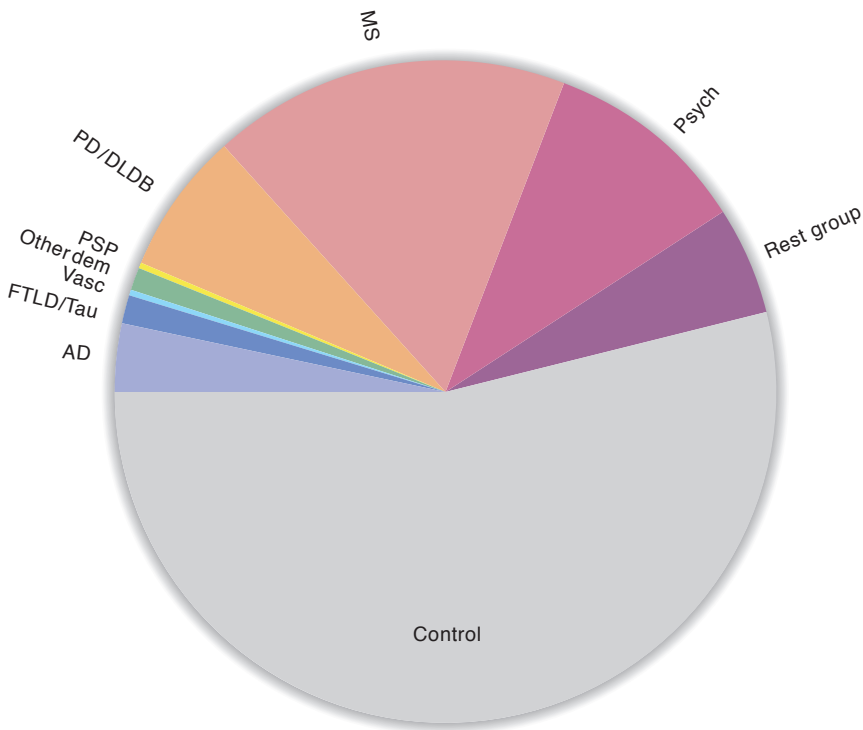


Figure 3 Breakdown of all registered donors by disease (total = 2702 on December 31, 2012)

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 25<sup>th</sup> 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](http://www.donorvoorlichting.nl)).

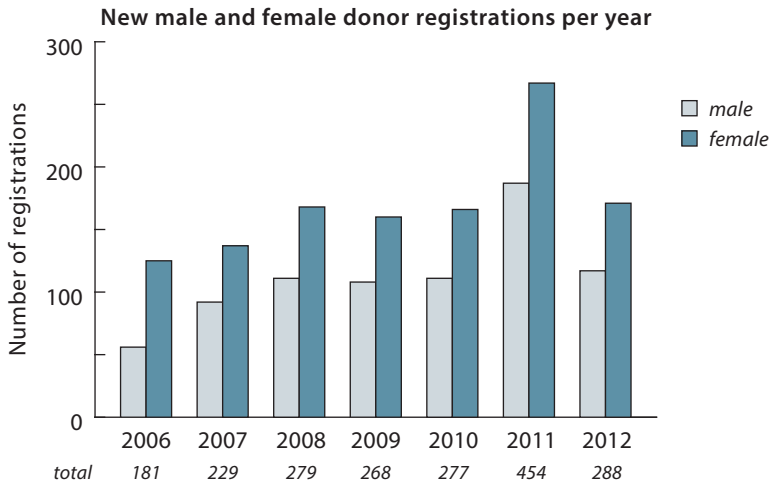


Figure 4

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 2** Public relations activities and articles on the NBB in 2011 and 2012

<b>Date</b>	<b>Title / description</b>	<b>Medium / additional information</b>
2011/01/03	Interview with Inge Huitinga: 'Brain donor shortage'	Alzheimer Actueel (magazine patient organization)
2011/01/05	Interview with Inge Huitinga: 'Fellowship has been the base of my career'	Rondom MS (magazine patient organization)
2011/07/23	Interview with Dick Swaab: 'Living once is enough'	De Telegraaf (newspaper)
2011/07/31	Extensive interview with Dick Swaab including self-selected television fragments illustrating his life	Zomergasten (TV show)
Aug 2011	Articles about the 25th anniversary of the NBB, announcements and reviews of the 2011/09/15 symposium	(websites of) newspapers: De Telegraaf, Spits, De Gooi- en Eemlander, Noordhollands Dagblad, Trouw, De Gelderlander, Het Parool, de Volkskrant. Other websites: NOS News, Medisch Contact artsennet, Dutch Button Works, MSweb. Magazines: Medisch Contact, magazine of KNAW
2011/09/15	Symposium "Depressie & Geluk" (depression and happiness)	On the occasion of the 25th anniversary of the NBB
2011/02/09	Presentation: The role of Vitamin D in Multiple Sclerosis	MS organization Gouda
2011/11/24-25	MS research days	Event of patient organization
Nov 2011 and Oct-Nov 2012	Radio commercial with Inge Huitinga	MS Research (patient organization)
2011/12/01	'Meaningful numbers behind 30 years of MS research'	Brochure MS research Rondom MS (magazine patient organization)
2011/12/01	'Huge shortage of brain tissue for Parkinson research'	Papaver (Magazine of Parkinson patient organization)
2012/01/02	NBB featured in TV show	Labyrint (TV show), episode "Kopzorgen" (head worries).
June-Oct 2012	Press release and articles announcing the grant for developing a psychiatric tissue program (NBB-Psy)	NWO, KNAW, De Telegraaf, nu.nl, nd.nl (news website Nederlands Dagblad), scienceguide.nl, magazine of Rudolf Magnus Institute of Neuroscience
2012/04/10	Prize nomination for using alternatives for laboratory animals	Lef in 't Lab ('courage in the lab') award ceremony; Dutch Society for the Protection of Animals and NKCA
Oct 2012	'Biobanks, defrosting lurks'	Medicines (magazine)
Oct 2012	'NBB expands collection'	AMC Magazine
2012/12/01	'The NBB already has 3500 brains'	Experiment NL, issued by Quest and NOW (magazine)

well, so that our (potential) donors are kept informed about the work of the NBB. The English website of the NBB ([www.brainbank.nl](http://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](http://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.*



Figure 5 New logos of the Netherlands Institute for Neuroscience and the Netherlands Brain Bank



# NBB-Psy The Netherlands Brain Bank for Psychiatry

## 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

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

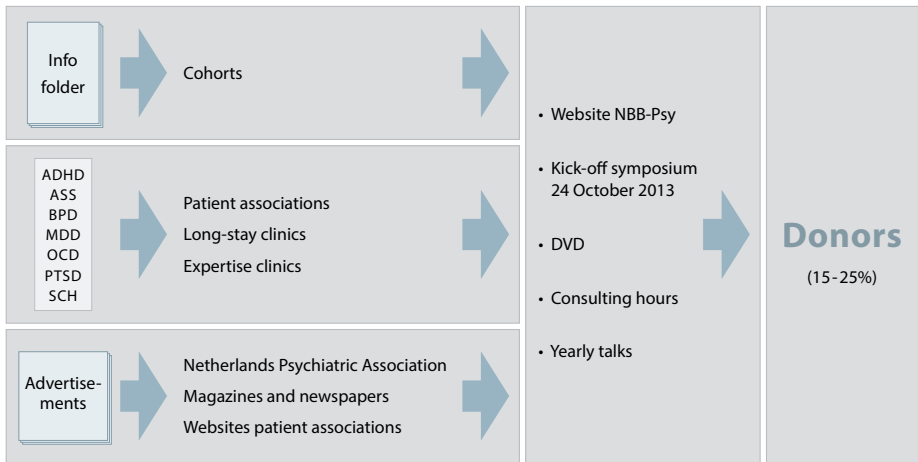


Figure 6 NBB-Psy Donor recruitment activities

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](http://www.nhb-psy.nl)

[www.nbb-psy.nl](http://www.nbb-psy.nl)

 @NHBPsy



# Autopsies & Diagnostics

## 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

	2006		2007		2008		2009		2010		2011		2012	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Contr	11	13%	12	13%	16	15%	17	15%	17	13%	25	20%	22	17%
AD	30	37%	28	31%	29	26%	28	25%	33	26%	39	31%	26	20%
FTLD/tau	3	4%	8	9%	16	15%	15	14%	13	10%	9	7%	5	4%
Other dem	9	11%	7	8%	13	12%	6	5%	13	10%	8	6%	7	5%
PSP	2	2%	3	3%	5	5%	9	8%	7	6%	4	3%	5	4%
MS	8	10%	14	16%	9	8%	11	10%	14	11%	12	10%	1	1%
PD/DLBD	6	7%	7	8%	12	11%	17	15%	18	14%	17	14%	11	9%
Psych	4	5%	2	2%	4	4%	2	2%	3	2%	3	2%	3	2%
Other	9	11%	9	10%	5	5%	5	5%	9	7%	7	6%	9	7%
PANR					1	1%							40*	31%
<i>Total</i>	<b>82</b>		<b>90</b>		<b>110</b>		<b>110</b>		<b>127</b>		<b>124</b>		<b>129</b>	

\* 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.

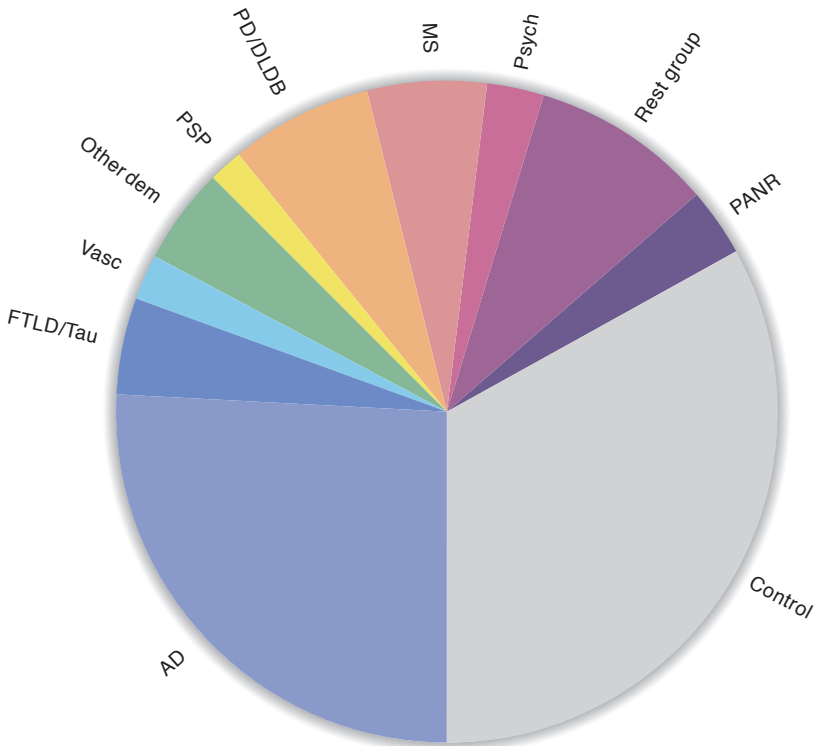


Figure 7 Total number of brain donations since 1985 (3710 on December 31, 2012)

## 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 average 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-

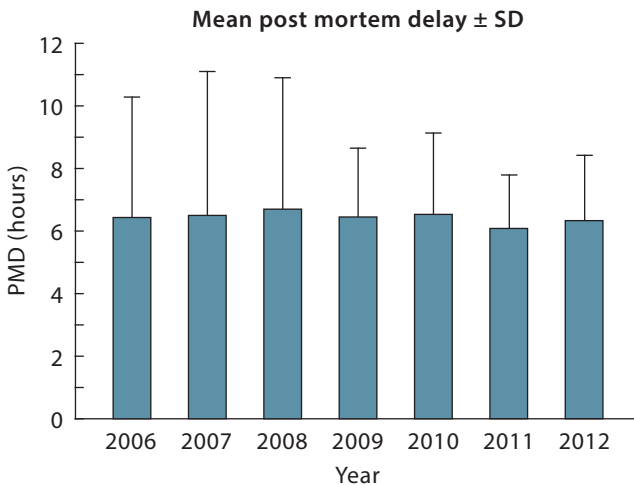


Figure 8

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

Year	PD protocol autopsy	Final diagnosis	n	Diagnosis in PD spectrum
2010	12	PD	1	67%
		PD with dementia	6	
		Alzheimer's disease / Lewy body variant	1	
		Multi-system atrophy	2	
		Cortico-basal degeneration	1	
		Other	1	
		2011	10	
		PD with dementia	3	
2012	19	PD	5	53% (of the finished cases)
		PD with dementia	3	
		Multi-system atrophy	3	
		Progressive supranuclear palsy	1	
		Control with vascular encephalopathy	1	
		Non-Alzheimer dementia	1	
		Other	1	
		PA-report not ready	4	



## 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 glucocorticoid 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  **VRIENDEN  
LOTERIJ**

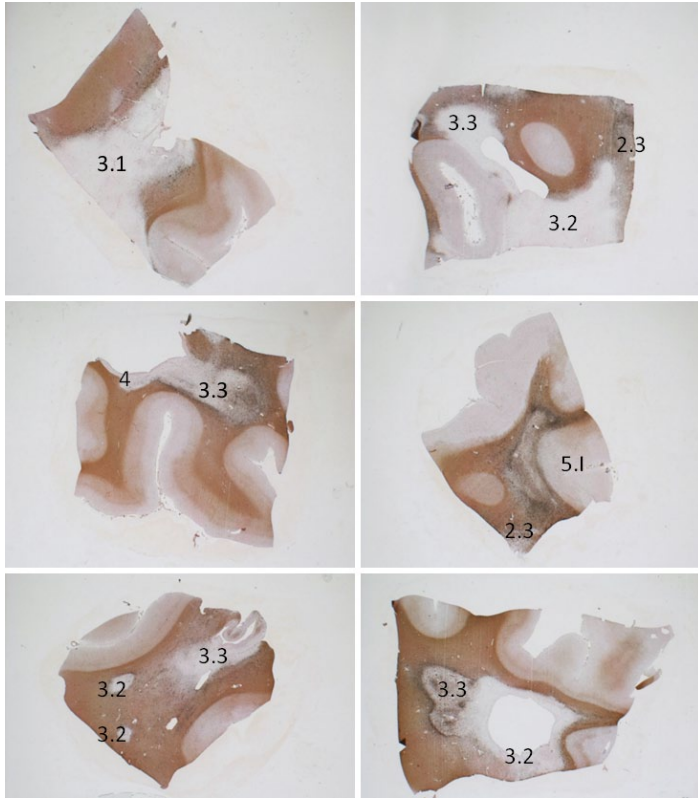


Figure 9 Photographs of MS lesion characterization.

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.

# Tissue Supply

## **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](http://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;

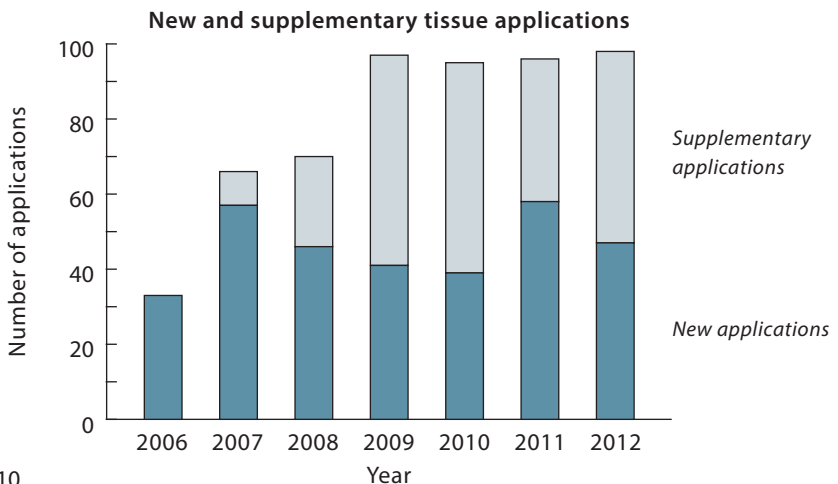


Figure 10

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.

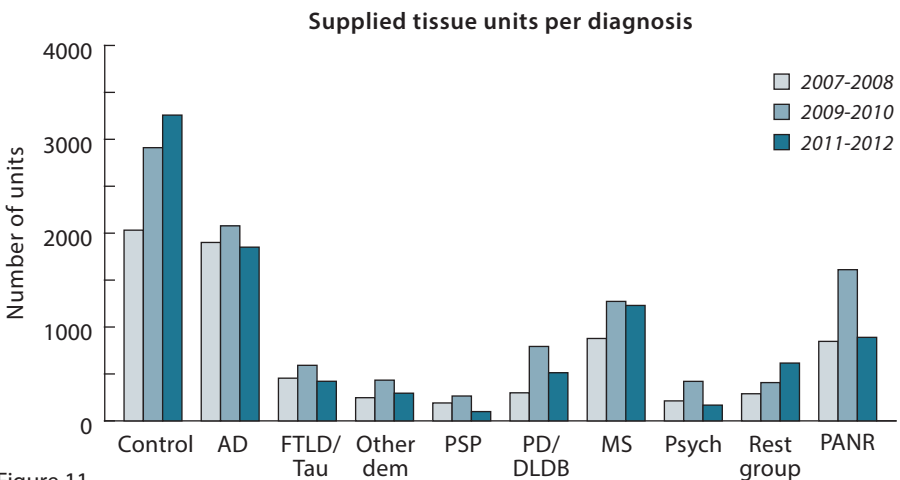


Figure 11

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.

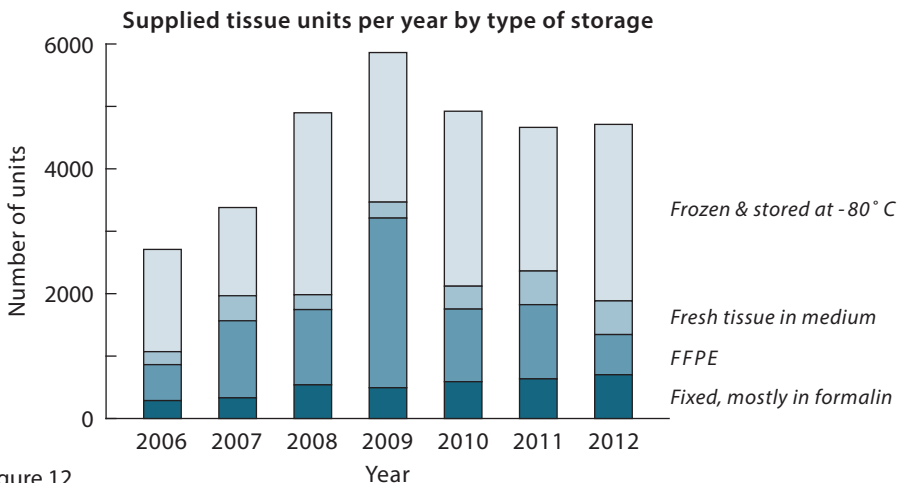
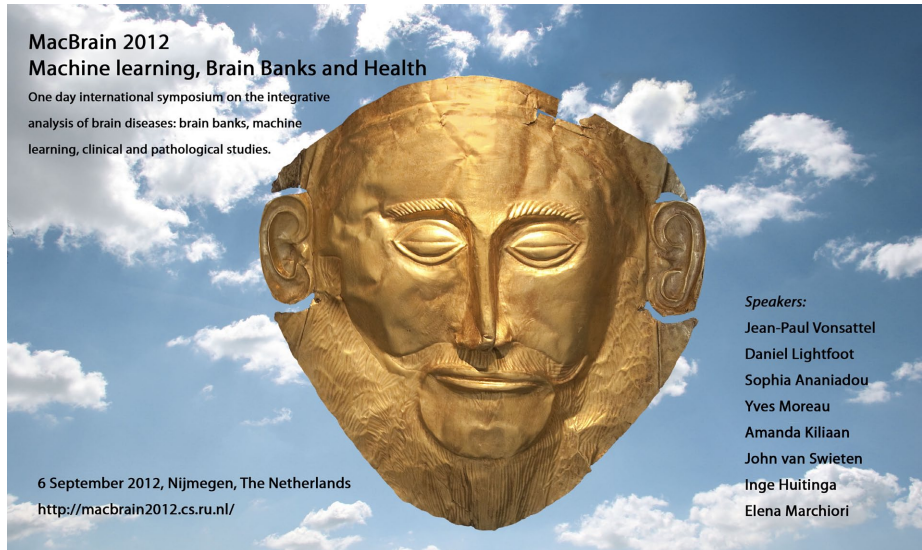


Figure 12

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.



**MacBrain 2012**  
**Machine learning, Brain Banks and Health**

One day international symposium on the integrative analysis of brain diseases: brain banks, machine learning, clinical and pathological studies.

6 September 2012, Nijmegen, The Netherlands  
<http://macbrain2012.cs.ru.nl/>

*Speakers:*  
Jean-Paul Vonsattel  
Daniel Lightfoot  
Sophia Ananiadou  
Yves Moreau  
Amanda Kiliaan  
John van Swieten  
Inge Huitinga  
Elena Marchiori

Figure 13 Announcement for the MacBrain symposium





# Finances

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.

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

<b>Grant for NBB-Psy</b>	<b>2012-2017</b>
NWO (Netherlands Organisation for Scientific Research)	€ 3,450,000*

\* 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](http://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](http://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](http://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.



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

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## 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 Theurapeutics 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

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

*The following publications were realized through the use of NBB tissue*

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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*

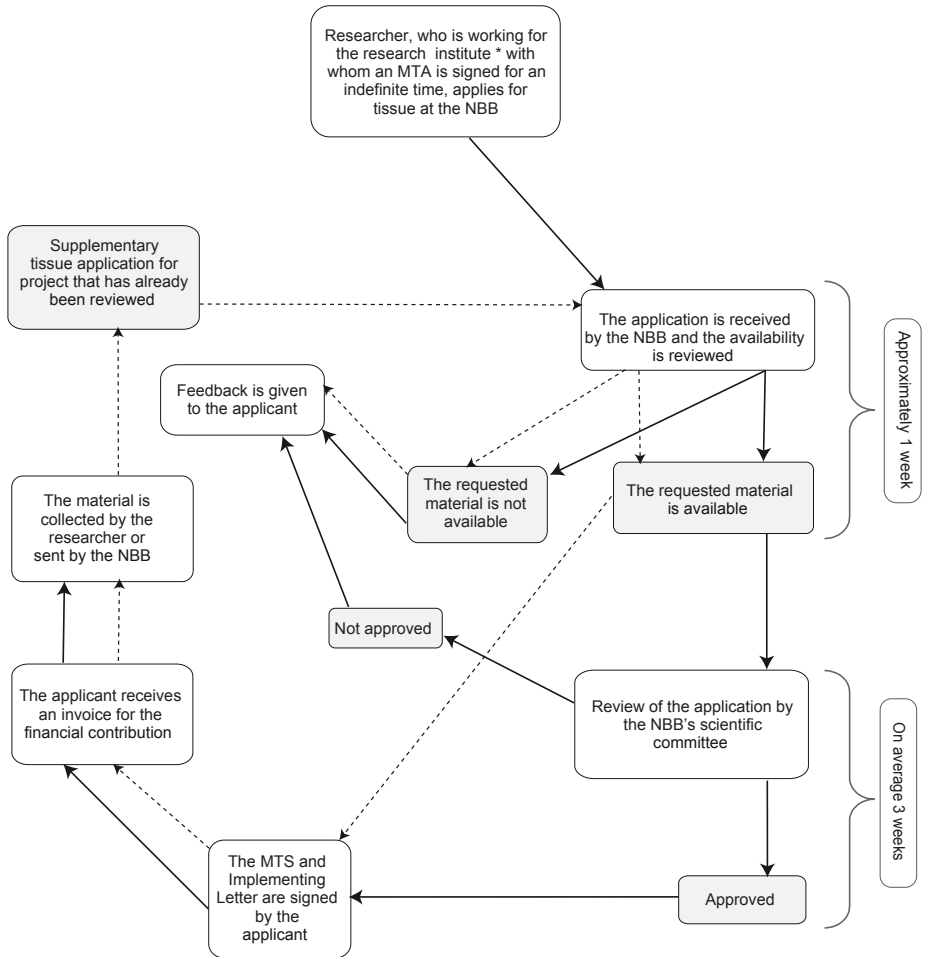
AMC	Academic Medical Center
KNAW	Koninklijke Nederlandse Akademie van Wetenschappen (Royal Netherlands Academy of Arts and Sciences)
NBB	Netherlands Brain Bank
NIN	Nederlands Herseninstituut (Netherlands Institute for Neuroscience)
NWO	Nederlandse Organisatie voor Wetenschappelijk Onderzoek (Netherlands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





# Appendix

Figure 14 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/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.

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

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

