EUROPEAN NETWORK OF BIPOLAR RESEARCH EXPERT CENTRES
ENBREC

Final Report

Grant Agreement number: 223102

Project acronym: ENBREC

Project title: European Network of Bipolar Research Expert Centres

Funding Scheme: Support Action

Period covered: from July, 1st 2009 to June, 30th 2011

Chantal Henry, Professor, INSERM-Université Paris XII

Tel: +33 (0)1 49 81 32 90
E-mail: Chantal.henry@inserm.fr
Project website address: www.enbrec.eu

Table of contents

1. Final publishable summary report

1.1. Executive summary

Bipolar disorders (BP) are characterized by recurrent manic and depressive episodes that affect 1-3% of the population. According to the World Health Organization study, BP are ranked 6th amongst the most disabling illnesses in working age adults worldwide. The pathophysiology of BP is not yet clearly established, with barriers to delineation including the heterogeneity of the clinical presentation and the complex interaction between genetic and environmental factors. The nature and complexity of BP mean that successful translational research requires the integration of clinical and basic science pathways. However, improving research in the field of severe and complex disorders, also requires the development of a critical mass of expertise through collaborative networks and multi-centre projects to increase the recruitment of large clinical cohorts that reflect the heterogeneity of the disorder. Following our successful application to the **'Support Action'** call of the European FP7 programme, we have developed **the infrastructure** for an European Network of Bipolar Research Expert Centre (ENBREC) designed to facilitate EU-wide studies. It provides an EU-integrated facility for research on the mechanism of disease and on clinical research. Six European countries are currently involved in the network (France, Germany, Italy, Norway, Spain and the United Kingdom).

All centres are adopting the same standardized clinical assessment package that explores all potential aspects of BP that influence the course and outcome of the disorder. The measures provide a high quality structured evaluation that can inform clinical decision making, but are also relevant for research purposes. Valid and reliable established observer and self-ratings scales were prioritized, assessment tools were translated into other languages and validation studies have been undertaken when appropriate. A web-based application, e-ENBREC©, an electronic healthcare record system has been developed to collate data for clinical monitoring and research purposes. Protocols to conduct multicentre observational studies for acute episodes and for prophylactic treatment have been developed.

After a review of the literature and a meta-analyses a specific test-battery for cognitive assessment for large cohort of bipolar patients was chosen to be performed in the network. In addition, we have established procedures to set up joint studies on biomarkers and genetics and the development of a secure infrastructure for conducting analyses of pooled brain imaging data is in progress. In parallel, a survey and a pilot study were performed to develop strategies for implementing innovative and effective care (psycho-education) in routine practice.

This network offers a 'proof of principle' that expert centres across Europe can undertake collaborative studies that use shared assessment protocols. The purpose of this network is to improve the quality and efficiency of research in a neglected priority area.

1.2. Summary description of project context and objectives

Bipolar disorders (BP) are characterized by recurrent manic and depressive episodes that usually commence in early adulthood that affect 1-3% of the general population. According to the World Health Organization study on global burden of disease, BP are ranked 6th amongst the most disabling illnesses in working age adults worldwide[1] (above schizophrenia which is ranked 8th). Despite the high prevalence, BP is often unrecognized or mis-diagnosed leading to inappropriate or delayed treatments[2], with significant and devastating health and social consequences. Even when the diagnosis is established, it is clear that the management of BP is a major challenge and surveys confirm that sub-optimal treatments are common concerns in Europe[3]. As a consequence, the significant disease burden attributable solely to BP is amplified by additional and multiple psychiatric and physical comorbidities, and premature mortality from associated medical disorders or by suicide; the estimated rates of completed suicide are between 11-19%[4].

From a research perspective, the pathophysiology of BP is not yet clearly established, with barriers to delineation including the heterogeneity of the clinical presentation (phase of illness, BP subtype, comorbidities) and the complex interaction between genetic and environmental factors. The nature and complexity of BP mean that successful translational research requires the integration of clinical and basic science pathways to develop more BP-specific targeted treatments. However, improving research in the field of severe and complex disorders, also requires the development of a critical mass of expertise through collaborative networks. In addition, multi-centre projects increase the likelihood of recruitment of large clinical cohorts that reflect the heterogeneity of the disorder and facilitate the conduct of cross-national epidemiological studies- this is only usually achievable through the development and implementation of shared research protocols.

In this context, in order to disseminate systematic clinical assessment and high quality treatment protocols and to foster research to improve the management of BP and to develop a better understanding of the mechanisms underlying this complex condition, we have developed a **network of bipolar expert centre at a European level**: ENBREC (European Network of Bipolar Research Expert Centre, www.enbrec.eu).

[1] Murray and Lopez, 1996, Harvard University Press.
[2] Hirschfeld et al., 2003, J Clin Psychiatry. Baca-Garcia et al., 2007, Acta Psychiatr Scand.
[3] Scott et al., 2006, B J Psych. Henry et al., 2010, J Affect Disord.
[4] Goodwin and Jamison, 2007, Oxford University Press.

Resources and missions

Following our successful application to the **'Support Action'** call of the European FP7 programme, in 2009 we start to set about developing **the infrastructure** for ENBREC designed to foster collaboration between centres. ENBREC is designed to facilitate EU-wide studies. It provides an EU-integrated facility for research on the mechanism of disease and on clinical research in order to improve diagnostic and management of the disease. In addition, it will help implement innovative strategies in the healthcare for such a strongly disabling illness.

For Europe, **the added value of ENBREC** is that expertise in different research fields (eg epidemiology, genetics, clinical trial design) is shared across centres and leading researchers in the field of BP immediately gain access to large patient cohorts, improving the clinical representativeness of research participants and enhancing the statistical power of proposed studies. A core goal of ENBREC is to establish connections between leaders in the field and to foster the construction of national networks, which would then link together at a European level

The European network ENBREC includes among its objectives:

- to bring together researchers particularly interested in bipolar research
- to pool the relevant resources, including access to patients, offered by the various centres of the network
- to define diagnostic criteria common to all members of the network, to perform common systematic assessment for clinical, cognitive and brain imaging studies
- To share biomaterial for biomarkers and genetic studies
- to create a common computerized database
- to use their expertise to design and conduct research protocols
- to foster research programmes on specific topics
- to produce consensus papers and dissemination of clinical and basic research
- to translate research into improved healthcare

Participants and organization

Six European countries are currently involved in the network (France, Germany, Italy, Norway, Spain and the United Kingdom).

The work is divided in work-packages organized by a leader.

- WP1: Management of the project (Chantal Henry, INSERM and University of Paris-Est, Paris, France)
- WP2: Developing common tools for diagnosis and multinational cohort follow-up (Eduard Vieta, Fundacio Privada Clinic per a la Recerca Biomedica, Spain)
- WP3: Developing common tools for cognitive assessment (Guy Goodwin, The University of Oxford, UK)
- WP4: Assessment of common biomarkers and genetic markers (Marion Leboyer, INSERM and University of Paris-Est, Paris, France)
- WP5: Development of standards for imaging (Ole Andreassen, University of Oslo, Norway)
- WP6: Treatment optimisation, definition of subgroups of responders (Michael Bauer, Technische Universität Dresden, Germany)
- WP7: Supporting multinational clinical research and data management (Jacques Demotes, ECRIN, INSERM, France)
- WP8: Education, information, dissemination, translation of research outcomes into healthcare (Angelo Barbato, Istituto di Ricerche Farmacologiche Mario Negri)
- WP9: Extension to new countries and within the countries (Jacques Demotes, ECRIN, INSERM, France)
-

The **coordinator** (Chantal Henry) undertook the day-to-day management of the project, whilst the ENBREC steering committee, composed of one representative for each country, steer the overall direction and work of the network. The **steering committee** hold monthly teleconferences, supplement with 2 committee meetings each year. Overall, the coordinators and the ENBREC committee jointly oversee the prioritization and coordination of activities at each centre, including quality control, financial probity, and the management of outputs from each work package.

1.3. Description of the main S&T results/foregrounds

1.3.1. WP2: Developing common tools for diagnosis and multinational cohort follow-up

WP2 commitment was to create a systematic assessment for diagnosis and follow-up using common tools in the network of expert centres in order to facilitate multinational clinical research on bipolar disorders. Another objective was the coordination and support of the translation and validation of the common tools into the official languages of the countries involved in the Network.

A common database for clinical assessment

All centres are adopting the same **standardized assessment package**. This is a wide-ranging psycho-bio-social assessment that systematically explores all potential aspects of BP including clinical presentation, personal history and exploration of factors that influence the course and outcome of the disorder. The measures provide a high quality structured evaluation that can inform clinical decision making, but are also relevant for research purposes. Valid and reliable established observer and self-ratings scales were prioritized over idiosyncratic or untested measures. Where appropriate, assessment tools were translated into other languages and validation studies have been undertaken where appropriate

A web-based application, e-ENBREC©, an **electronic healthcare record system** has been developed to collate assessment data for clinical monitoring and research purposes. Access to the system is carefully regulated and approval has to be obtained from the committee in charge of the safety of computerized databases in each country. To optimize data entry and retrieval, free text input has been minimized, and drop down lists and other approaches leading to standardized inputs have been chosen when possible. The XML format is used to transfer data from e-ENBREC© into an anonymous common database for research purpose.

Tools for the psychiatric diagnosis

A version paper of the CRF can be provided in the language of each country

For the psychiatric diagnosis, the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I) (Spitzer et al, 1990) or the Mini-International Neuropsychiatric Interview (M.I.N.I.) (Sheehan et al, 1998) can be used, as both provide a DSM-IV diagnosis.

Life time characteristics of bipolar disorders, first episode and comorbidity

The information about initial clinical presentation includes: the age of onset of first symptoms, age of onset and polarity of first mood episode, age of first psychotropic treatment and age at first hospitalization. Details of the total number of manic and total number of depressive episodes, number of hospitalizations, the presence or absence of rapid cycling, and occurrence of any post-partum episodes are also recorded. It the patient is in a current mood episode at the time of assessment, the polarity, duration and severity are carefully evaluated. However, even those patients who do not meet criteria for a full episode are assessed to establish the nature and range of any sub-syndromal manic or depressive symptoms. Psychiatric and medical comorbidities are also recorded. As are any history of suicide attempts and family history of mental disorders.

Pharmacological and Non-Pharmacological Treatments

Past and current pharmacological treatment with psychotropic drugs is documented in the evaluation, with class of drug, dosage and duration of each treatment. The global adherence to treatment (ranked as good, moderate or poor) is also recorded, as well as the degree of improvement with contemporary treatment (see next section).

Non-pharmacological treatments (used over the lifetime of the patient) are noted, including: Physical treatments, eg electroconvulsive therapy (ECT), Transcranial Magnetic Stimulation (TMS), and psychological interventions, eg cognitive-behavioral therapy, interpersonal therapy, individual or family psychoeducation, etc.

Severity of symptoms and functioning

Several observer-rated instruments are used to assess the severity of the disorder, residual symptoms and the level of functioning:

Clinical Global Impression-Bipolar Version- Modified (CGI-BP-M; Vieta et al, 2002), is a user-friendly scale for the assessment of manic, hypomanic, depressive or mixed symptoms and long-term outcome of BP. It takes only a few minutes to complete and it has been proven useful in the assessment of the short and long-term efficacy of several treatments.

Functioning is assessed using a generic rating, the Global Assessment of Functioning Scale (GAF; ref) and a more BP-specific measure, the Functioning Assessment Short Test, (FAST; Rosa et al, 2007). The FAST is a brief, simple instrument, easy to apply measure that

evaluates the range and level of difficulties in psychosocial functioning experienced by patients.

The Montgomery-Åsberg Depression Rating Scale (MADRS; Montgomery and Åsberg, 1979), is one of the most commonly-used rating scale that assess the range and severity of symptoms that are most frequently observed in patients with depressive episodes. It has a wider range of scores for each item, making it useful as a more sensitive measure of change in clinical treatment studies.

The Young Mania Rating Scale (YMRS; Young et al, 1978) is an 11-item instrument used to assess the severity of mania in patients with a diagnosis of BP.

Development of a new tool: Dimensional Assessment of Mental Nosology for DSM (DAMN DSM).

The development of a multimodular standardized system for the diagnosis and assessment of subjects with bipolar illness has been completed which is called Dimensional Assessment of Mental Nosology for DSM. It covers 13 dimensions: psychotic symptoms, negative symptoms, manic symptoms, depressive symptoms, cognitive impairment, anxiety, obsessive compulsive symptoms, substance misuse, impulsivity, suicidality, eating problems, sleeping problems and sexual problems which are rated following a CGI-based severity score. So far, the questionnaire exists in English and Spanish. The next step will be the translation and validation in several languages, including German, Italian, French and Norwegian to be administered and implemented in each country. In Spain 100 patients have been evaluated with the Dimensional Assessment of Mental Nosology for DSM.

Self-rating scales

Three self-rating scales have been selected: the short form of the State-Trait Anxiety Inventory (STAI-SF; Marteau & Bekker, 1992), the Altman Self-Rating Scale for Mania (ASRM; Altman et al, 1997) and the Quick Inventory of Depressive Symptomatology (QIDS-SR16;Rush et al, 2003).

Physical and biological parameters

Since bipolar disorders is associated with highly prevalent medical comorbidities a monitoring of physical and biological parameters is performed (height, weight, abdominal perimeter, blood pressure, cardiac frequency, blood test.

1.3.2. WP3: Cognitive assessment

The scope of work for Work Package 3 was to review the literature with regard to cognitive performance in patients with bipolar disorder and subsequently to select a core and reliable battery of such neuropsychological tests across the key cognitive domains. This "ENBREC test-battery" would then form a minimum level of cognitive assessment across ENBREC sites for further research into: the aetiology of cognitive deficits in bipolar disorder; the potential for a cognitive biomarker or endophenotype for bipolar disorder; and as a potential outcome measure in clinical trials (for either psychological or pharmacological treatments).

Several existing reviews and meta-analyses were reviewed as part of Work Package 3. In summary, evidence exists to suggest a link between bipolar disorder and cognitive impairment across a range of cognitive domains. However, the most striking finding of our review was that, although considerable research has considered cognitive deficits in bipolar disorder, this research has been spread across a plethora of different neuropsychological tests (even within a specific cognitive domain), has often used relatively small sample sizes, has often not controlled for key confounds (such as age, current mood, treatment effects), and these studies have inconsistent definitions of euthymia.

Therefore, in order to attempt to address these shortcomings, we undertook a re-analysis of the available data. This work is completed and has culminated in a presentation of the findings at the 9th International Conference on Bipolar Disorder in Pittsburgh, USA in June 2011 and in a manuscript[6] that is due to be submitted to a leading peer-reviewed journal for publication by end July 2011.

Following completion of the literature review, we have managed to combine existing cognitive performance data on 4 key neuropsychological tests (11 outcome measures) in some 1,948 bipolar patients and healthy controls across 25 different sites. This data has been re-analysed with the intention of answering four key questions:

(i) Do the reported cognitive deficits in bipolar patients remain after controlling for potential confounds (e.g. age, gender, IQ, mood) and site effects?;

(ii) What is the variance explained by site effects? Initial analyses suggest this is relatively large and re-enforces the need for a standardised protocol and/or automated data collection system across sites;

(iii) What drug effects (if any) are present in the patient group? Current literature is ambiguous on this point[5,6] (or has ignored it entirely); and

(iv) Which illness severity factors best correlate with cognitive performance?

The results of this re-analysis have been presented at the 9th International Conference on Bipolar Disorder in Pittsburgh, USA in June 2011 and have been written-up as a scientific article. The manuscript is due to be circulated to co-authors for approval before submission to a leading international peer-review scientific journal for publication. Submission is expected before end July 2011.

Additionally, we developed a computer system (NPTB) to automate and standardise the stimuli presentation and data collection associated with the recommended tests. This system will link with the data management system recommended under Work Package 2 to allow the analysis of neuropsychological data to be conducted with the associated clinical and demographic variables. Following final testing of the system, the system will be introduced into each of the sites within ENBREC.

[5] Goswami, U., Sharma, A., Varma, A., et al. (2009). The neurocognitive performance of drug-free and medicated euthymic patients do not differ. *Acta Psychiatrica Scandinavica, 120*, 456-463.
[6] Jamrozinski, K., Gruber, O., Kemmer, C., Falkai, P., & Scherk, H. (2009). Neurocognitive functions in euthymic bipolar patients. *Acta Psychiatrica Scandinavica, 119,* 365-374.

1.3.3. WP4: Biomarker – genetic studies

ENBREC WP4 aims at defining the procedures and tools that would facilitate studies based on genetic and environmental data collected in different countries. Existing procedures already enables ENBREC partners to perform genetic studies exchanging biological material. The Material Transfer Agreement (MTA) has already been used to this purpose by ENBREC partners. But other difficulties than the legal authorization for exchanging biological material hinder the performance of multinational genetic studies, as well as a lack of standardization in DNA collection or the high cost for equipping a centre with the latest technology. This is why ENBREC has been developing links with the Biobanking and Biomolecular Resources Research Infrastructure (BBMRI), a European infrastructure about to be able to provide solutions to academic centres in order to enable them to benefit from the latest technology and to implement a harmonization of the genetic data collection. These up-stream contacts with BBMRI will facilitate cooperation once the infrastructure will be operational.

Before this next step depending on specific research funding, we developed collaboration in the framework of the network. This preparation has been based on a permanently updated inventory of the genetic collection of each centre, on the participation to international consortia on genetics in psychiatry, and on collaboration between two ENBREC centres in order to perform a study based on the analysis of both environmental and genetic data.

Some ENBREC centres participate to studies leaded by international consortia on genetics as the Psychiatric GWAS Consortium. This consortium aims at conducting meta-analyses of genomewide association study data. A publication of the first results of this consortium activity was published in 2011[7]. Three ENBREC teams were involved in it: the Norwegian one, the German one and the French one.

[7] Cichon S, Mühleisen TW, Degenhardt FA, Mattheisen M, Miró X, Strohmaier J, Steffens M, Meesters C, Herms S, Weingarten M, Priebe L, Haenisch B, Alexander M, Vollmer J, Breuer R, Schmäl C, Tessmann P, Moebus S, Wichmann HE, Schreiber S, Müller-Myhsok B, Lucae S, **Jamain S, Leboyer M, Bellivier F, Etain B, Henry C**, Kahn JP, Heath S; Bipolar Disorder Genome Study (BiGS) Consortium, Hamshere M, O'Donovan MC, Owen MJ, Craddock N, Schwarz M, Vedder H, Kammerer-Ciernioch J, Reif A, Sasse J, **Bauer M**, Hautzinger M, Wright A, Mitchell PB, Schofield PR, Montgomery GW, Medland SE, Gordon SD, Martin NG, **Gustafsson O, Andreassen O, Djurovic S**, Sigurdsson E, Steinberg S, Stefansson H, Stefansson K, Kapur-Pojskic L, Oruc L, Rivas F, Mayoral F, Chuchalin A, Babadjanova G, Tiganov AS, Pantelejeva G, Abramova LI, Grigoroiu-Serbanescu M, Diaconu CC, Czerski PM, Hauser J, Zimmer A, Lathrop M, Schulze TG, Wienker TF, Schumacher J, Maier W, Propping P, Rietschel M, Nöthen MM.
Genome-wide association study identifies genetic variation in neurocan as a susceptibility factor for bipolar disorder. Am J Hum Genet. 2011 Mar 11;88(3):372-81. Epub 2011 Feb 25.

The French and the Norwegian teams implemented a pilot study to assess interaction between genetic and environmental factors. Three main axes of this study are to assess:
-Serotonin transporter gene polymorphism, childhood trauma and cognition in bipolar disorders
- Prevalence of childhood trauma in two samples of patients with bipolar disorder
- Clinical correlates of Childhood trauma in bipolar disorder

The ENBREC teams expect from these studies that they contribute to prepare the network for the development of its own large studies involving genetic, environmental and clinical data collected in a harmonized way in the expert centres of the network.
However, as the genetic side of such paneuropean studies is very complicated, and needs a paneuropean solution, ENBREC teams rely on the coming release of the BBMRI infrastructure to support the genetic collection and storage of data of the expert centres.

Figure 1: collection of bio samples in the ENBREC centres:

The ENBREC genetic material collection Country	**P.I.**	**subjects**	**Nb DNA**	**Nb Cell Lines**	**Nb RNA**	**Nb Serum**
FRANCE	M.Leboyer S.Jamain	BP Relatives controles	546 /377 /215	556 /345/ 217	_	_
GERMANY	T. G. Schulze M. Rietschel M. M. Nöthen	BP Relatives controles	1120/ 570 /1400	-	-	-
NORWAY	O. A. Andreassen	BP Relatives controles	547/450	_	347 / 400	505 /400
SPAIN	Ana G Pinto Carlos Matute	BP Relatives controles	200 /25 /520	_	_	200/ 25 /120

1.3.4. WP5: Neuroimaging

Brain imaging techniques have revolutionized the understanding of the human brain, with subsequent potential to identify brain pathology underlying psychiatric disorders. In addition, it has the potential to become a tool for early identification, subgrouping, disease monitoring and treatment stratification.

The overall aim of this work package is to develop a common Magnetic Resonance Imaging (MRI) protocol which allows pooling of data acquired from different MRI scanners, that can be used in multi-site studies of bipolar disorders.

Structural MRI studies usually provide global estimates of gray or white matter volume changes, or a small number of regions of interest (ROIs). Recent advances in structural imaging now allow for a more comprehensive evaluation of brain changes by providing continuous maps of cortical thickness (figure 1) and surface area, subcortical volumes, and measures of white matter microstructure throughout the brain. Such high-resolution structural MRI for morphometric analyses is now being used for automatic quantification of brain structures. There are reports of cortical abnormalities in bipolar disorder (figure 1).

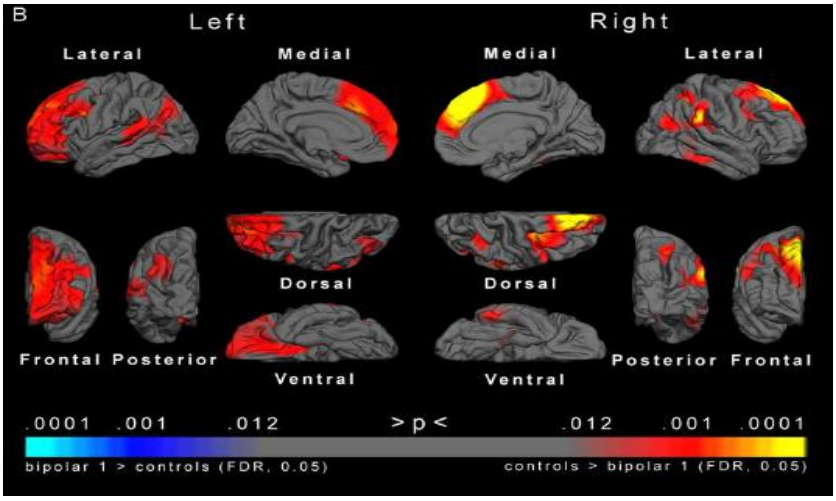

Figure 1. Structural MRI. Statistical maps showing significant differences between bipolar disorder 1 and healthy control subjects Rimol et al 2010.

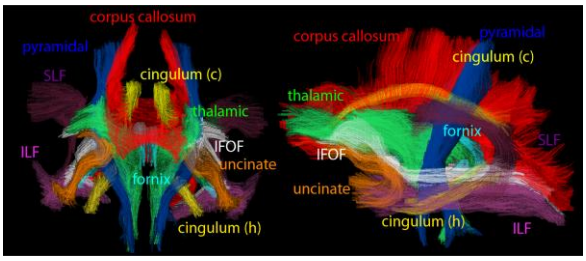

Figure 2. DTI Method. Probabilistic atlas of white matter fibers created by manually labeling fiber tracts in the brains of training subjects, then registering the data into a normalized template.

White matter can now be quantified using *diffusion tensor imaging (DTI*), as shown in figure 2. This MRI variant for quantifying the integrity of white matter structure throughout the brain measures water diffusion and its directionality. The degree of anisotropy of overall motion in a voxel is expressed as an index of the directionality of diffusion (fractional anisotropy; FA). Lower FA values are thought to

reflect factors such as demyelination and axonal injury, and has been used to show white matter abnormalities in bipolar disorder.

The first step was to assess the feasibility of collaborative studies in the framework of the network depending of expertise and equipment.

There are several groups with **extensive expertise and experience** in brain imaging.

Oslo: The TOP study group, *(www.med.uio.no/forskning/ tematisk/top/)*, has long experience in brain MRI imaging, with a series of projects involving structural and functional MRI of psychiatric disorders. The *TOP MRI group* includes Ingrid Agartz (sMRI) and Jimmy Jensen (fMRI), who has expertise in neuroimaging, and a team of scientists, including 3 post docs, 6 PhD students and 2 MD PhD students. The group has one full time MRI technical assistant, as well as a 50% position as research nurse to run MRI studies of patients.

Dresden : The SeSyN group (http://psychiatrie.uniklinikum-dresden.de/0440.html) has excellent experience in functional and structural MRI as well as PET. Projects cover topics related to addiction and affective disorders as well as basic neural, genetic and endocrinological mechanisms in healthy subjects. The group consists of one MRI technical assistant, one physicist, one physician, 3 post docs and 8 PhD students. SesyN is located at the Neuroimaging Center of the Technische Universiät Dresden which is equipped with a 3T MRI exclusively dedicated for research.

Oxford : The Department of Psychiatry has strong links with the Centre for Functional Magnetic Resonance Imaging of the Brain (FMRIB) (www.fmrib.ox.ac.uk) which is generally regarded as a world leading centre for the development and application of MR imaging technology. The physics and analysis groups (headed by Prof Peter Jezzard and Prof Steve Smith respectively) are well used to supporting large-scale clinical research. FMRIB has recently been awarded funds to install new 3T and 7T MRI systems to support and push the boundaries of basic and clinical neuroscience research.

Paris : The Cognitive Neuroimaging Laboratory (*INSERM*) is involved in developing new imaging protocols to investigate the neurophysiological basis of cognitive function in both healthy individuals and individuals with certain neuropathologies. As a member of the *NeuroSpin* research unit supported by the French Atomic Energy and Alternative Energies Commission, they have access to NeuroSpin's imaging platform as well as their technical expertise.

Barcelona : The Barcelona group belongs to CIBERSAM which is composed of 26 clinical and basic research groups belonging to different areas in Spain which primarily research mental disorders. Currently, the group is working in collaboration with other groups in different functional imaging studies of bipolar disorder in order to elucidate the neurobiological background of the cognitive abnormalities that have been identified in patients with bipolar disorder. Studies are also been conducted in patients with first episode.

Figure 1: review of the different partners' MRI equipment:

Center	Scanner	Head Coil	Additional Equipment	Phantoms
Albert Chenevier & Henri Mondor Hospitals Créteil, France	Siemens Tim Trio 3T	12-channel 32-channel	Scanner belongs to the Neurospin Imaging Facility who is responsible for every facet of the scanner. Requests must be made to this facility to approve and run protocols.	
Technische Universität Dresden, Dresden, Germany	Siemens Tim Trio 3T	12-channel	Visual & Auditory stim (NNL & Resonance Technology) Various response devices GSR & Pulse (Brain Products) EEG recording (Brain Products)	Non-living x2
University of Oslo, Oslo University Hospital, Norway	GE Signa Hdxt 3T	8-channel	Visual & Auditory Stim (NNL) Response grips (NNL)	Yes
Warneford Hospital Oxford, U.K.	Siemens Tim Trio 3T (OCMR)	12-channel	Projector & auditory stim Response box HR & respiration monitors Infusion pumps	Yes, many
	Siemens Verio 3T (AVIC) (April 2010)	12-Channel		
	Siemens Verio 3T (FMRIB) (April 2010)	12-channel 32-channel		
	Siemens 7T (Autumn 2010)			
CIBERSAM Spain	General Electric 1.5T	8 channels	Auditory Stim, Pulse and EEG recording and Respiration monitors	Yes
	Siemens 3T	12 channels	Visual and Auditory Stim, Pulse and EEG recording and Respiration monitors	Yes

As shown in the table 1, five of the groups have access to state of the art MRI equipment, including scanner and additional equipment and facilities.

We have performed **a test run** to compare magnets and prepare a final protocol for multi-site neuroimaging studies. The MRI center at Oxford and Oslo have tested by scanning the brain of the same person both places. We did not use phantom, because of improved information from a human brain. We ran new tests during spring of 2011 when the equipment used for potential future studies are in place.

The final technical protocol for imaging studies was prepared based on the test runs a soon to be finalized by the Norwegian and German teams. The methods will be compatible across different MR vendors and within an MR vendor product line.

The design of the MRI protocol will be decided by the research questions of each study, but the report will include recommendation about preferred MRI acquisition sequences (Structural MRI, MRI Spectroscopy, Diffusion Tensor Imaging or functional MRI)

The **proposed protocol** will include the following main items :

Morphology

Routine 3D T1-weighted MRI acquisition

DTI

Based on the software tools developed by the partners, DTI data will be analyzed as an automated tool, and with a strict quality control and reliability testing with other research protocols.

A report about need for new equipment or software at different sites to have comparable equipment has been discussed. However, this will strongly rely on the funding situation of new grants, and has not been prioritized much.

Scanning protocol :

- sMRI protocol: 3D T1 (6 min)
- Research data: quantification cortical thickness, area and subcortical structures
- Extended protocol (10min)
  - DTI (white matter), resting state fMRI (connectivity)
  - Functional MRI in special projects

Software:

Image analysis software that will be used is SPM, FreeSurfer, Matlab, BrainVoyager and Nordic ICE, GIFT and PLS. These are available at all sites.

Anders Dale from Oslo has developed an extensive set of methods for performing subcortical segmentation and for reconstructing the cortical sheet based on routine 3D T1-weighted MRI data, and developed a semi-automated, fully 3D whole-brain segmentation procedure for obtaining delineations of different neuroanatomical structures. These methods are publicly available through the FreeSurfer package and used in several studies by the current partners. Dale has also developed a semi-automated method for measuring the thickness of the cerebral cortex, and for generating cross-subject statistics in a coordinate system based on cortical anatomy. Continuous maps of cortical thickness are produced and thickness values are calculated in the numerous ROIs.

Multisite MRI acquisition adjustments:

Similar software and approaches as used in the ADNI multi-center study will be applied.

During the progress of this project, we have also started planning of **large scale meta analyses of already collected Brain imaging data from bipolar disorders**. This is an additional task made available through the current project. We have during the spring of 2011 finished the work of obtainging overview of current datasets :

- Current structural MRI samples:

BIP 235, Controls n=324

  - BIP n=45, Controls n=60, Oxford
  - BIP n=135, Controls n=207, Oslo
  - BIP n=30, Controls n=30, Dresden
  - BIP n=25, controls n=27, Paris

NeuroGrid and potential for pooling imaging datasets

NeuroGrid (PI: J. Geddes) was a UK eScience project funded by the Medical Research Council which investigated and developed potential solutions to the problems inherent in multisite neuroimaging studies. NeuroGrid produced several outputs which may be useful for the ENBREC neuroimaging project:

- a secure infrastructure for conducting analyses of pooled data across geographically disseminated databases. This is achieved by developing a common metadata and federating the individual datasets via flexible and secure middleware.
- a real-time quality assurance tool for ensuring quality of prospectively acquired scans
- a web-based portal to allow analyses across geographically disseminated databases

We are currently working with the Computing Laboratory at the University of Oxford to build on the first of these outputs – the federation of databases – and to extend this across the ENBREC sites. Work is currently underway at the FMRIB centre in Oxford to make the Oxford data remotely before adding in other databases.

Significant results

The main result of the work package will be the common protocol. However, we have also developed a project to investigate morphological brain scans from multiple scanners already collected. The Oslo group has published new findings in brain imaging in bipolar disorder, and this is being followed up with attempts to replicate major findings in Oxford and Dresden datasets.

There are inconclusive brain imaging findings in BP so more knowledge is needed about brain pathology. The ENBREC has developed a short standard MRI protocol that can be used at all sites. The ENBREC team has collected existing imaging data to start doing a mega-analysis across sites. We plan to implement standard MRI protocol in the ENBREC Expert Centers, and use a more specific protocol in future studies.

1.3.5. WP6: Treatment optimization: tools for multinational observational and interventional trials to optimize treatment strategies and to define subpopulations of responders and non-responders

We finalized the document on procedures for long-term follow-up of bipolar patients within ENBREC.Three modules have been developed. The electronic database E-ENBREC was updated following the final revisions. We prepared a manuscript of the ENBREC recommendations for long-term follow-up that is currently circulated in the group for final comments. It will be submitted to the journal “Bipolar Disorders” by July 2011.

To test feasibility of the procedures we suggested a multicentre observational study to analyse the important and not adequately answered question of the impact of treatment with or without adding antidepressants to the psychopharmacological treatment regimen following the patients for 18 months. Frequency of assessment will be every 2 to 6 months. This could potentially deliver results that can be used to plan an interventional study on this issue. The ENBREC group is currently deciding on whether the observational study will be started and on when and at which ENBREC centres.

We defined definitions of resistance to therapy in acute episodes and for prophylactic treatment. Based on a literature search we identified evidence for effective methods to optimize standard treatment strategies that include non-pharmacological, psychotherapeutic and psychoeducational interventions for patients with bipolar disorder who do not adequately respond to standard treatment. We prepared a consensus paper of ENBREC that will be circulated from July 2011. The manuscript is supposed to be submitted for publication in September 2011.

The *third task* of our work package was the identification of predictors of response to pharmacological and non-pharmacological treatments. A literature review on this topic was done. The findings were included into the manuscript prepared for the first task since it was agreed that a combined publication would be helpful. In the context of identifying predictors of response we announced the plan of establishing a clinical registry for bipolar patients to identify predictive factors regarding treatment response. At the Department of Psychiatry and Psychotherapy at Dresden, Germany, and in one of the three other hospitals in Dresden we started to recruit bipolar patients already. The two remaining hospitals will start recruitment in August and October 2011. Within the registry we already use the assessment battery developed in the first task of our working group mentioned above. Within ENBREC a feasibility questionnaire will be circulated to explore the potential of expanding the registry to other cities.

Last, we and other ENBREC members suggested to use the results of the work packages to plan a study on the very important and dynamically developing issue of early intervention strategies in high-risk subjects for the development of bipolar disorders. At the Department of Psychiatry and Psychotherapy at Dresden, Germany, we currently run a multicentre randomised, controlled clinical trial on early specific cognitive behavioural treatment in those subjects, and results and expertise could be used within ENBREC.

1.3.6. WP7: Supporting multinational clinical research

Centralization of information and tools

Information and tools gathered for facilitating the preparation and the conduct of multinational trials in bipolar disorder within ENBREC are inserted on the ECRIN Campus (http://ecrin.bio-med.ch). The pilot version of the website is currently in test period.

Information common to all Europe and country-specific data for 13 countries are available. ENBREC countries are covered, except for Norway which is not currently connected to ECRIN. The extension to Norway is planned for beginning 2012 which will allow the collection of the relevant information.

The different sections of the public part cover ethical and regulatory aspects, including aspects on data protection and specific populations, information on biosamples including their circulation and storage. Additional aspects, such as insurance, safety monitoring, data management and good clinical practice are also included.

The ethical and regulatory section describes the procedure for regulatory submission and follow-up of a study in the different countries (including flowchart and documents required for the process). Detailed information also includes contact details, timelines and fees. Additional information on regulatory requirements is provided in this section concerning the different type of studies. It covers the various types of interventional and non interventional studies. The definition for these categories is also provided as there can be substantial discrepancies between countries. Depending on the objective of the protocol, the relevant information for a study on bipolar patients will be found in the different parts of this section. The most common types of study in bipolar patients are studies on investigational medicinal product, observational studies, and diagnostic studies.

The last part of this section (i.e. in “other information”) includes information per country on specific population, informed consent and data protection. Different types of populations

can be considered as a vulnerable population depending on national legislation. Thus differences can be found among European countries. A particularity of the studies in bipolar patients is the specific procedure to collect the participants' consent during manic/depressive episodes, however this depends mainly on the appreciation of the investigator.

Data protection in the different countries is the same for the bipolar patients as the other kind of participants in clinical trials.

A specific section on biosamples is also developed, covering the type of biosamples, their circulation and storage.

The pilot version of the website will become publicly accessible after completion of the test period (end of summer 2011).

Pooling the databases for observational studies

For the purpose of observational studies, it was decided to store data collected in a local database, rather than pooling data collected in the centres into a single and common database. Therefore the option chosen has been that **each centre collects and stores data in a local database**. This results in a distributed collection of harmonized data, since collection is made in each country with the same common tools developed by WP 2 and 3.

To this purpose, **ENBREC centres were given E-ENBREC** (described in WP2 report), which enables them to collect in the same way clinical data.

Regarding the collection process of cognitive data, two options were proposed[8], even if they result in both cases in a local storage of data. Centres will be proposed either to collect data with their own computerized version of the common cognitive battery if they have one, either they assess patients with an online access to the NPTB system developed by Partner 3, Oxford University. In this case, the Oxford computer scientists will provide a guarantee that tests performed with a remote access to the NPTB system will send back data created to the centre performing tests, without any way to store it within any database linked to NPTB. Therefore the NPTB system would act as a mirror and doesn't consist in any way in a collection of cognitive data in another country than the one proceeding tests.

The achievement of these objectives enabled us to move forward regarding the possibility to pool ENBREC data collected and stored in each ENBREC centre. This question was discussed at a meeting in Oxford on March 28th 2011. The process would be

the following: a centre foreseeing a study using ENBREC data is required to submit his project to the steering committee, which involves one representative of each partner. The project must precise which variables of the data he wishes to pool, and these variables will be exclusive as the centre won't have authorization to ask for other variables to the centres. Once the centre is authorized to ask for specific variables to other ENBREC centres, he can proceed. This step requires that data are stored in a computerized system that allows computer scientist to extract specific variables easily. Doing so, each centre is able to extract the requested variables and to send them to the centre asking for them. If the analysis of these variables results in a publication, it should mention ENBREC leaders as co-authors, mention that this study was developed with the support of ENBREC, and acknowledge the financial support of the supporting institutions (currently the 7th Framework Program of the European Union).

This procedure was agreed during the final meeting. However, as it is a point requiring specific discussions, the signature of a formal agreement about the use of these data is foreseen in the next months.

The work carried out during the last period of the ENBREC project brings a high added value to the project, as it has consisted in linking the work of three WPs. The result is an agreement about the procedure that would be followed by the ENBREC centres when implementing a study based on ENBREC data. At this point in time the priority will be the collection and storage of data using the common tools developed by WPs 2 and 3. This agreement about the procedure guarantees that centres will have a legal framework to regulate the use of these data, and ensures an actual possibility to perform pan-European studies. The final objective is to perform a pan-European cohort follow-up of bipolar patients.

In contrast, for ***interventional studies*** (ie. for randomized clinical trials that will be designed and conducted by the ENBREC consortium partners, the single data management model proposed by ECRIN will be used. ECRIN has now launched its first call for certification of data centers. These ECRIN-certified data centres for investigator-driven clinical trials will fulfill a set of criteria ensuring high quality, GCP and 21CFR11 compliant data management for multinational clinical trials.

1.3.7. WP8: Education, information, dissemination

The objectives were to develop, implement and evaluate tools and strategies for education, information, dissemination, translation of research outcomes into healthcare in relation to bipolar disorders.

The first step was to review the current evidence on effective strategies for patient psychoeducation and health information to the lay public related to bipolar disorders.
The review has been completed (see article in preparation). The review conclusions were that many patients with bipolar disorders do not achieve a clinical remission and even less a functional recovery, even with good pharmacotherapy compliance. The influence of patients' attitudes, behavior, subjective state and interpersonal environment on course of the disorder points out the importance of psychosocial interventions and patients' active role to improve outcome. Evidence from research findings supports the efficacy and likely effectiveness of a number of psychosocial treatments: Individual and group psychoeducation, family-focused therapy, interpersonal and social rhythm therapy, cognitive behavior therapy. Enhancement of self-help strategies and patients empowerment, as well as the adaptation of models from research to everyday practice are a priority to improve the outcome of bipolar disorders in real world. A report on this issue has been presented at the European Psychiatric Association congress in Vienna on March 15, 2011.

The second step was to develop, in consultation with a sample of users associations, strategies and tools for patient psychoeducation and health information to the lay public.
As a result of the previous review and an examination of consumers' associations views, it appeared (based on lower cost and potential ease of dissemination) that groups of psychoeducation should be a first-line approach, in comparison to more complex interventions, requiring highly specialized skills, reserved to selected subgroups of patients. The elements to be included in a basic psychoeducation package were identified as follows: information about the disorder and available treatment options, identification of early warning signs, encouragement of structured routines and healthy lifestyles, use of a mood diary and life-event charting to monitor mood patterns and effectiveness of intervention, improvement of communication skills, emotional self-regulation and social skills, reduction of self-stigmatization, stabilization of sleep/wake cycles, awareness of medication effects

and improvement of decision-making skills on drug treatment in a collaborative way, acquisition of balanced attitudes towards the self in relation to the illness.

A survey was realized to assess to what extent evidence-based psychosocial interventions are used in mainstream mental health services. The first step concerned three departments of mental health in Milan, serving a catchment area of 867,000 population, the second step the whole Lombardy region. Data were extracted from the Lombardy region psychiatric information system to get information on treatment received by bipolar patients. The information system in Lombardy is implemented at region-wide level, covering an adult population of 8,436,000 in 2009. As a psychiatric case register, it gathers information from all public mental health services and from private day care and residential facilities. It covers the whole region since 1999 and it allows a full description of services activities, monitoring also the treatments provided to patients. The system collects demographic information and ICD-10 diagnoses on any citizen in contact with mental health services and records all patients' care episodes in any treatment setting, i.e. outpatient and home contacts, day care attendances, admissions to general hospital and residential facilities (Lora, Barbato, Cerati et al. , 2011). The full survey results have been presented at the ENBREC Italian conference held in Milan on February 22, 2011.
In 2009, 8,573 (7.1%), out of about 120,000 patients with at least one contact with mental services, received an ICD-10 diagnosis of bipolar disorders (codes F30, F31, F34.0). This corresponds to an 1-year treated prevalence rate on adult population of 1.01‰. True prevalence drawn from recent general population surveys in Western Europe ranges between 3 and 8‰ (Ferrari, Baxter and Whiteford, 2010). Therefore, the results showed that there is probably a 65-85% treatment gap for bipolar disorders, due to a combination of under-recognition, under-diagnosis and lack of access to specialist services. Moreover, as shown in Tables 1 and 2, although most patients were treated by community services with low inpatient services utilization, only a tiny percentage received psychosocial interventions. Low intensity of interventions raises serious doubts about their quality.

Implement the tools, strategies and packages previously developed in a sample of health services

An agreement was reached with the Department of Mental Health of San Carlo Hospital Trust in Milan, an agency providing adult mental health services to a catchment area of 290,000 population. The goal was to implement within the department a pilot study aimed at

evaluating the feasibility of delivering psychoeducation to bipolar patients in real world everyday practice. A study protocol has been drafted and approved by the ethical review board of San Carlo Hospital Trust. The study was designed to assess the rate of referred patients in relation to the total treated population of bipolar patients, the variables related to the referral, the characteristics of referred patients, the rate of patients who successfully completed the intervention, the patients' and clinicians' feedback about their satisfaction with the intervention and their opinion about its value.

The tools included in the ENBREC clinical package were translated into Italian. The validated Italian versions of the rating scales were used. Since a validated Italian version of Functioning Assessment Short Test (FAST) was not available, a validation study of a new Italian version was performed. The Adult Attachment interview was added to the clinical package to assess attachment styles in relation to the establishment of therapeutic alliance. The FAST validation and the addition of Adult Attachment interview were not foreseen in the original ENBREC protocol.

A series of information sheets were prepared to cover the following key aspects:

1. Features of bipolar disorder, 2. Illness and personality, 3. Onset and course, 4. Genetic risk, 5. Gene-environment interaction, 6. Drug treatment, 7. Drugs side effects, 8. Bipolar disorder and the family, 9. Early warning signs of manic and hypomanic episodes, 10. Identification of depression, 11. Stress management 12. Problem solving, 13. Symptoms self-management, 14. Risk reduction and protective factors enhancement, 15. Lifestyle, 16. Eating patterns and exercise, 17. Life events. The Italian translations of the two well-known handbooks were used as a guideline for the development of the psychoeducation package (Miklowitz, 2002; Colom and Vieta, 2006).

A previous survey showed that 218 patients with bipolar disorders have been treated by the department in 2009. In accordance with the review's conclusions, group format was identified as the most suitable way to deliver psychoeducation. All clinicians were informed about evidence supporting psychoeducation and were asked to refer bipolar patients, without exclusion criteria, to psychoeducation program run by the ENBREC Mario Negri team, including a psychologist, a clinical supervisor and a senior researcher. The study started in May 2010. All referred patients were assessed by the ENBREC clinical package and the Adult Attachment Interview. 54 patients have been referred and their progression into the program is shown by the flow-chart presented in Table 3.

Table 3 around here

The planned psychoeducation group characteristics were as follows:

• Size: 8/14 participants

• Lenght: 7/8 months, fortnightly sessions

• Duration: 1 h 30

• Number of sessions: 12 plus three follow-up sessions

• Venue: community mental health centre.

The group model was based on a simplified and flexible version of the already mentioned approaches presented by Miklowitz (2002) and Colom and Vieta (2006). Main focus was on illness information, self-help, enhancement of coping skills, early warning signs and homework. The groups were designed to be responsive to patients' feedback and therefore a feedback questionnaire was administered to all patients to the end of each session.

Information about psychoeducation and feedback about patients' participation was provided to the clinicians of San Carlo Hospital Department of Mental Health throughout the project. In addition, a seminar was organized in Milan on February 22, 2011, with lectures presented by a number of ENBREC experts: Chantal Henry (Paris), Francesc Colom (Barcelona), Jan Scott (Newcastle), Angelo Barbato (Milan). A total of 111 professionals from San Carlo Hospital attended the seminar: 34 psychologists, 31 nurses, 24 psychiatrists, 18 rehabilitation counselors, 4 social workers.

Perform an assessment of the impact of tools, strategies and packages previously Implemented

The impact assessment was performed by using a set of process indicators:

1) Rate of patients with BD treated by San Carlo Hospital department of mental health referred to the psychoeducation program;

2) Rate of attendance to psychoeducation groups

2) Patients' self-reported satisfaction

3) Satisfaction of the referring clinicians.

Referral rate on all eligible patients was 24.8%, rate of patients who refused participation was 20.4% and dropout rate 8.7%. Rates of patients self-reporting high or very high satisfaction, gathered through the feedback questionnaires, ranged between 48% and 82% across the group sessions.

A series of interviews with 12 referring clinicians (psychologists and psychiatrists) showed that 80% found the program very useful for all or most referred patients, observing positive results mainly in areas related to illness insight, treatment adherence and quality of life. Negative effects were observed in 9% of patients.
All clinicians expressed the view that the program should became a permanent service component and the willingness to refer more patients. However, some negative aspects were noted, i.e. the too long delay between the referral and group start in some cases. The need for relatives involvement was pointed out.

On overall, the results show that a simple and flexible version of a psychoeducation program is well accepted by patients and clinicians and it is feasible and easy to implement in a mainstream service where the rate of involvement of bipolar patients in psychosocial interventions is very low.

Table 1
Patients with bipolar disorders in Lombardy in 2009
by treatment setting
(n=8,573)

	N patients	%		
				N Contacts
Outpatient	7689	89,7	Mean Median	15 7
				N Hospital days
Hospital	1459	17	Mean Median	25 13
				N Residence Days
Community Residence	200	2,3	Mean Median	151 92
				N Interventions
Day Center	382	4,5	Mean Median	132 46
				N Interventions
Home	944	11	Mean Median	12,5 4
				N visits
Emergency Room	390	4,5	Mean Median	1,4 1

Table 2
Psychosocial interventions received by bipolar patients in Lombardy in 2009 (n=8,573)

	N patients	%		
				N Interventions
Psychoeducation	180	2,1	Mean Median	3,6 1
				N Interventions
Rehabilitation	1683	19,6	Mean Median	59,9 5
				N Sessions
Individual Psychotherapy	492	5,7	Mean Median	9,3 6,5
				N Sessions
Family Therapy	54	0,6	Mean Median	2,2 1
				N Sessions
Group Therapy	156	1,8	Mean Median	8,5 4

1.3.8. WP9: Extension

The objective of this work package is to pursue the promotion of, and to strengthen the extension of ENBREC to additional centres and networks within the participating countries.

Procedures for extension of national networks and for extension to additional EU member states have been previously developed.The priority has been to strengthen the national networks in the countries partners of the ENBREC project, without increasing the complexity of the management (ie. using a network and hub architecture, with a single contact point in each country,).

In some countries the national network was built during the project (Italy, United-Kingdom).

- Italy: the development of the Italian network leads to the inclusion of Bologna University (Paola Rucci), Siena University (Andrea Fagiolini) and San Carlo Hospital, Milan (Paolo Rigliano). All these centres are associated members of ENBREC.

- Spain: the Basque Foundation for Health Innovation and Research (Ana Gonzalez Pinto) joined the project as associated member. Links has been developed with the CIBERSAM (Centro de Investigación Biomédica en Red de Salud Mental).

- UK: a network is supported by the UK Mental Health Research Network including bipolar experts from different centres. The University of Newcastle (Jan Scott) joined the project as an associated member.

Since the first period of the project and the accession of the associated members to the network, they have been strongly involved in the network activities. The major part of these associated members was part of the ENBREC-IT proposal as full participants (FP7 call Marie Curie Initial Training Network 2011). Specialists from associated members played an active role in working groups, such as the psychoeducation one (meeting in Milan, 21-22 February 2011). Participating to the final meeting of the project, it was clear that associated partners of the network were fully part of it. Would ENBREC receive a new funding, they would be proposed to be full partner of the proposal, as they were for the ENBREC-IT one submitted in January 2011.

In addition procedures were adopted foreseeing the ***enlargement to new countries***, although no specific budget was available to formally support such pan-European expansion in ENBREC. However contacts were made with individual partners in a series of countries, and this will be the basis for further expansion throughout Europe.

Moreover the international visibility of ENBREC is increased by the development of a website (www.enbrec.eu), participation to congresses and publications.

1.4. Impact and dissemination

This network offers a 'proof of principle' that expert centres across Europe can undertake collaborative studies that use shared assessment protocols.
We live in a globally competitive environment and it will be fundamental for Europe's success, that high level of research is a priority. It will demand joint responses and collaboration from member states to benefit from shared expertise and experience.
The purpose of this network is to improve the quality and efficiency of research in a neglected priority area – mental health and specifically mood disorder –
This type of collaborative projects would have a positive impact on attitudes and gather people who actively look for collaborative projects. This project will foster existing collaborations and help to create new ones.

This is of utmost importance for psychiatry research. In spite of the major burden of disease for the society, mental health research as a whole (and bipolar research in particular) is currently hampered by:

- a gap in structuring, due to its cross-disciplinary nature, encompassing a broad range of disciplines from psychology to molecular biology
- a gap in funding, as a result of the poor structuring of mental health research at the national and European level

In 2009, the EU resolution on Mental Health (EU parliament A6-0034-2009) emphasized the need to develop comprehensive and integrated mental health strategies in Europe, such as cohort studies. This strategy acknowledges that the only way to diminish the cost and burden of mental disorders in the long-term is to invest resources in research to improve early diagnosis, develop innovative treatment and ultimately to begin to identify those at high risk of disorders with the goal of implementing prevention strategies. There is an evident need for a coordinated approach to building cohorts of one of the disorders representing the major mental health challenges in the modern day through an integrated research programme incorporating clinical, epidemiological and cognitive data with biological studies (brain imaging, genetics, neurobiology…).

Expert centres provide a unified setting for care and research. We believe that building cohort studies embedded within the expert centres network we have created provides the most efficient

approach to obtaining cross-sectional and longitudinal information about bipolar disorder. Our links to clinical settings will allow speedy implementation of improved diagnostic, assessment and therapeutic strategies.
The ultimate clinical aim is to develop stratified medicine, aspiring to assessing each patient with a broader focus of behavioural and neurobiological measures in order to define the best therapeutic strategies relevant to a particular profile of the disorder. Implementing prevention, early diagnosis, and personalized interventions, we will provide ways to improve personal and economic components of mental health care.

Currently, a deeper knowledge of the pathophysiology of mental health is required to improve the management of diseases and the development of new molecules. The programme will strengthen translational research delivering a new broad comprehensive understanding from basic science to biomedical research.

Research topics that can take advantage of such a network

The likelihood of developing bipolar disorders depends in large part on the combined, small effects of variations in many different genes in the brain. Currently, none of them has been found to be powerful enough to cause the disease by itself. An important issue in genetics research is that findings correlating specific genes with specific diseases in one population may not apply to other populations. Thus, genetic studies must be coupled with an accurate phenotype analysis, associating follow up data and data on response to treatment. Moreover, to be able to take into account interactions between genes and environment, there is a need to have access to large cohort.

It is also necessary to identify neural correlates of clinical and functional presentations of BP, to improve diagnostic and prognostic evaluation. Neuroimaging is a particularly promising approach since tremendous progress has recently been made in the neuroimaging of BP. New imaging techniques and analysis methods are being developed and existing techniques refined (high-strength magnetic fields, diffusion tensor imaging and tractography algorithms, event-related fMRI, analyses of functional connectivity...) A network can trigger some collaborations between teams using these sophisticated techniques. However, a network is well adapted to promote the combined use of genetics and neuroimaging and/or cognitive studies with simple structural approaches (MRI) but on large cohort of patients. Moreover from large and well-characterized

samples of patients, it is possible to recruit more homogenous sub-groups of patients including for example first episode cases that can help the process of determination of cause and effect.
The chronic and frequently progressive course of under-treated or inappropriately-treated BP, and its inherent variability with multiple subtypes, calls for comprehensive, flexible assessment methods to deal effectively with the heterogeneous clinical presentations. Fundamental to the understanding of recurrences is an adequate description of the clinical phenomenology and a systematic evaluation of its acute and long-term treatment response. Only long-term follow-up can improve the understanding of the evolution of this pathology taking into account its heterogeneity. Naturalistic cohort follow-up studies may improve our understanding of predictors and moderators of poor outcome, and on this basis we can develop secondary and tertiary preventive strategies. Also, like many other severe and complex disorders, it is known that up to 80% BP patients are ineligible for clinical trials because of their comorbid physical or mental disorders, lack of insight and/or risk of suicide. In mood disorders research, industry-funded randomized trials in depression have generally excluded those with BP. It is increasingly recognized that there is a need for effectiveness and generic outcome data regarding treatment outcomes in day to day practice. Such studies are often seen as the 'second element' of translational research, which bridges the gap between research efficacy trials and clinical effectiveness of proposed treatments through the development and dissemination of guidelines.

Although cognitive dysfunctions in psychosis have classically been associated with schizophrenia, there is clinical evidence that some bipolar patients show cognitive disturbances either during acute phases or in remission periods. Changes in the fluency of thought and speech, learning and memory impairment, and disturbances in attention processes are as fundamental to depression and mania as changes in mood and behaviour. Moreover, a significant number of BP patients show persistent cognitive deficits during remission from affective symptoms. However, there are several methodological pitfalls in most studies such as unclear remission criteria, diagnostic heterogeneity, small sample sizes, lack of longitudinal assessment, practice effects and poor control for the potential influence of pharmacological treatment[9].

The episodic and chronic nature of BP usually requires long-term treatment in all patients. There is an unmed need to develop stratified therapeutic strategies as a function of more homogeneous

[9] Harmer et al., 2006, Biol Psychiatry.

phenotypes and profile of tolerance defined by clinical research in order to optimize available pharmacological treatment.

Pre-marketing clinical trials do not address issues related to possible toxicities due to drug interactions or comorbid illnesses. Moreover, clinical trials are short and not appropriate for diseases requiring life-time treatment. Only large cohort follow-up studies can help detect rare side-effects, assess safety and efficacy in the long term for new drugs.

The network can also be considered as a hub for pharmaceutical industry to give access to large cohort of patients facilitating patient recruitment to conduct clinical trials. Although pharmacotherapy is the mainstay of treatment strategies for BP, research over the last 5 years suggests that combining psychological interventions with drug treatment increases overall effectiveness, mostly by further protecting from relapse or recurrence. Further research should focus on determining the therapeutic value of each ingredient of the tested psychological interventions and examining differential benefits of different treatments for manic or depressive poles. To do this requires multiple centres, expertise in a range of psychological therapies for BP and strategies that can be shared, developed and evaluated- all of which is more likely to be achieved if the research is undertaken across expert centres.

Currently, there is no equivalent multi-site collaboration in the field of psychiatry in Europe able to conduct research within an organized disease-oriented network, including multidisciplinary and trans-cultural approaches and with a long lasting perspective.

The network will provide useful clinical data from a European sample of patients and one strength of the network is its capacity to develop research from basic science to psychosocial research programmes.

Sustainability of the network: links maintained beyond initial phase of ENBREC

By the time FP7 funding ends (June 2011), ENBREC members will be engaged in several joint research projects at a Europe-wide level. The sustainability of the network is secured since the centres involved in the collaboration are all clinically active, offering expert care and treatment of BP. Resources are provided within each country to ensure continuity of clinical care. The common clinical and cognitive assessment and the follow-up protocol chosen for ENBREC represent a basic, but systematic and comprehensive assessment of cases that allows the expert centres to provide high quality advice on diagnosis and treatment to referrers and patients in each participating country. Thus a major potential barrier to cross-national research has been

overcome, allowing easier implementation of new basic science and clinical research in the future and a research group with a strong identity that will be in a position of strength when applying for multicentre research grants and also represent an attractive option to international industrial partners who e.g. wish to plan and execute pilot phase and/or late-stage randomized controlled clinical trials.

Address of the project public website
www.enbrec.eu

Contact:

Pr. Chantal Henry - Scientific coordinator (Chantal.henry@inserm.fr)
Pôle de psychiatrie universitaire-Hôpital A. Chenevier
40 rue de Mesly,
94000 Créteil-FRANCE

2. Use and dissemination of foreground

Section A: scientific publications and dissemination activities

As a support action, the consortium did not result in scientific foreground. However, two publications related to the Support activity of ENBREC are submitted to scientific review:

- Henry C, Andreassen O, Barbato A, Demotes J, Goodwin G, Leboyer M, Vieta E, Scott J, Bauer M and the ENBREC group. ENBREC: a network to promote innovative system of care and foster research at a European level. Submitted to Eur Neuropsychopharmacol.

- Andrea Pfennig, Philipp Ritter, Eduard Vieta, Chantal Henry, and Michael Bauer and the ENBREC group. The European Network of Bipolar Research Expert Centres (ENBREC) Recommendations for Long-tem Follow-up Assessment of Bipolar Patients in Observational and Interventional Studies. Submitted to Bipolar Disord.

TEMPLATE A1: LIST OF DISSEMINATION ACTIVITIES

NO.	Type of activities	Main leader	Title	Date	Place	Type of audience	Size of audience	Countries addressed
1	Conference	Michael Bauer, Partner 5, and al.	ENBREC: The European Network of Bipolar Research Expert Centres	September, 25 2009	Dresden, Germany	Scientific community	100	International
2	Conference	Chantal Henry , Coordinator	European Network of Bipolar Research Expert Centres	October, 30th 2009	Madrid, Spain	Scientific community	100	International
3	Conference	Guy Goodwin, partner 3, and al.	ECNP supported European network for research in bipolar disorder: can we identify a consensus for future research directions?	August, 29th 2010	Amsterdam, The Netherlands	Scientific community	50	International
4	Conference	Michael Bauer, Partner 5, and al.	The new European Network of Bipolar Research Expert Centres (ENBREC): Missions and Visions	March, 14th, 2011	Viena, Austria	Scientific community	100	Europe
5	Conference	Chantal Henry, Coordinator, and al.	European and United States Consortia	June, 11th 2011	Pittsburgh, USA	Scientific community	100	International
6	Conference	Chantal Henry, Coordinator, and al.	First results of the European Network of Bipolar Expert Centres (ENBREC)	September, 4th 2011	Paris, France	Scientific Community	100	International

Section B: Type of exploitable foreground

As a Support Action, ENBREC did not result in clear exploitable foreground. Nevertheless the strengthening of collaboration potential through the development of common assessment tools is a foreground which benefits should appear in a near future, by pan-European large scales studies on Bipolar disorders.

3. Report on societal implications

A General Information *(completed automatically when **Grant Agreement number** is entered.*

Grant Agreement Number:	223102
Title of Project:	ENBREC
Name and Title of Coordinator:	Professor Chantal Henry, MD PhD

B Ethics

1. Did your project undergo an Ethics Review (and/or Screening)? • If Yes: have you described the progress of compliance with the relevant Ethics Review/Screening Requirements in the frame of the periodic/final project reports? Special Reminder: the progress of compliance with the Ethics Review/Screening Requirements should be described in the Period/Final Project Reports under the Section 3.2.2 *'Work Progress and Achievements'*	***No***
2. Please indicate whether your project involved any of the following issues (tick box) :	
RESEARCH ON HUMANS	
• Did the project involve children?	No
• Did the project involve patients?	No
• Did the project involve persons not able to give consent?	No
• Did the project involve adult healthy volunteers?	No
• Did the project involve Human genetic material?	No
• Did the project involve Human biological samples?	No
• Did the project involve Human data collection?	No
RESEARCH ON HUMAN EMBRYO/FOETUS	
• Did the project involve Human Embryos?	No
• Did the project involve Human Foetal Tissue / Cells?	No
• Did the project involve Human Embryonic Stem Cells (hESCs)?	No
• Did the project on human Embryonic Stem Cells involve cells in culture?	No
• Did the project on human Embryonic Stem Cells involve the derivation of cells from Embryos?	No
PRIVACY	
• Did the project involve processing of genetic information or personal data (eg. health, sexual lifestyle, ethnicity, political opinion, religious or philosophical conviction)?	No
• Did the project involve tracking the location or observation of people?	No
RESEARCH ON ANIMALS	
• Did the project involve research on animals?	No
• Were those animals transgenic small laboratory animals?	No
• Were those animals transgenic farm animals?	No
• Were those animals cloned farm animals?	No
• Were those animals non-human primates?	No
RESEARCH INVOLVING DEVELOPING COUNTRIES	
• Did the project involve the use of local resources (genetic, animal, plant etc)?	No
• Was the project of benefit to local community (capacity building, access to healthcare, education etc)?	No

DUAL USE	
• Research having direct military use	No
• Research having the potential for terrorist abuse	No

C Workforce Statistics

3. Workforce statistics for the project: Please indicate in the table below the number of people who worked on the project (on a headcount basis).

Type of Position	Number of Women	Number of Men
Scientific Coordinator	1	
Work package leaders		6
Experienced researchers (i.e. PhD holders)	4	2
PhD Students		1
Other		1

4. How many additional researchers (in companies and universities) were recruited specifically for this project?	**3**
Of which, indicate the number of men:	1

D Gender Aspects

5. Did you carry out specific Gender Equality Actions under the project?

○ Yes
● No

6. Which of the following actions did you carry out and how effective were they?

	Not at all effective				Very effective
❑ Design and implement an equal opportunity policy	○	○	○	○	○
❑ Set targets to achieve a gender balance in the workforce	○	○	○	○	○
❑ Organise conferences and workshops on gender	○	○	○	○	○
❑ Actions to improve work-life balance	○	○	○	○	○

○ Other:

7. Was there a gender dimension associated with the research content – i.e. wherever people were the focus of the research as, for example, consumers, users, patients or in trials, was the issue of gender considered and addressed?

○ Yes- please specify

● No

E Synergies with Science Education

8. Did your project involve working with students and/or school pupils (e.g. open days, participation in science festivals and events, prizes/competitions or joint projects)?

○ Yes- please specify

● No

9. Did the project generate any science education material (e.g. kits, websites, explanatory booklets, DVDs)?

○ Yes- please specify

● No

F Interdisciplinarity

10. Which disciplines are involved in your project?

○ Main discipline: 3.2

○ Associated discipline: 3.1 ○ Associated discipline[Erreur ! Signet non défini.]:

G Engaging with Civil society and policy makers

11a Did your project engage with societal actors beyond the research community? *(if 'No', go to Question 14)*

○ Yes
● No

11b If yes, did you engage with citizens (citizens' panels / juries) or organised civil society (NGOs, patients' groups etc.)?

○ No

○ Yes- in determining what research should be performed

○ Yes - in implementing the research

○ Yes, in communicating /disseminating / using the results of the project

11c In doing so, did your project involve actors whose role is mainly to organise the dialogue with citizens and organised civil society (e.g. professional mediator; communication company, science museums)?	○ ●	Yes No

12. Did you engage with government / public bodies or policy makers (including international organisations)

- ● No
- ○ Yes- in framing the research agenda
- ○ Yes - in implementing the research agenda
- ○ Yes, in communicating /disseminating / using the results of the project

13a Will the project generate outputs (expertise or scientific advice) which could be used by policy makers?

- ○ Yes – as a **primary** objective (please indicate areas below- multiple answers possible)
- ○ Yes – as a **secondary** objective (please indicate areas below - multiple answer possible)
- ● No

13b If Yes, in which fields?

Agriculture		Energy		Human rights	
Audiovisual and Media		Enlargement		Information Society	
Budget		Enterprise		Institutional affairs	
Competition		Environment		Internal Market	
Consumers		External Relations		Justice, freedom and security	
Culture		External Trade		Public Health	
Customs		Fisheries and Maritime Affairs		Regional Policy	
Development Economic and Monetary Affairs		Food Safety		Research and Innovation	
		Foreign and Security Policy		Space	
Education, Training, Youth		Fraud		Taxation	
Employment and Social Affairs		Humanitarian aid		Transport	

13c If Yes, at which level?

- ○ Local / regional levels
- ○ National level
- ○ European level
- ○ International level

H Use and dissemination

14. How many Articles were published/accepted for publication in peer-reviewed journals?	**0**
To how many of these is open access provided?	**0**
How many of these are published in open access journals?	
How many of these are published in open repositories?	
To how many of these is open access not provided?	**0**
Please check all applicable reasons for not providing open access:	
❑ publisher's licensing agreement would not permit publishing in a repository ❑ no suitable repository available ❑ no suitable open access journal available ❑ no funds available to publish in an open access journal ❑ lack of time and resources ❑ lack of information on open access ❑ other: ……	

15. How many new patent applications ('priority filings') have been made? *("Technologically unique": multiple applications for the same invention in different jurisdictions should be counted as just one application of grant).*		**0**
16. Indicate how many of the following Intellectual Property Rights were applied for (give number in each box).	Trademark	**0**
	Registered design	**0**
	Other	**0**
17. How many spin-off companies were created / are planned as a direct result of the project?		**0**
Indicate the approximate number of additional jobs in these companies:		

18. Please indicate whether your project has a potential impact on employment, in comparison with the situation before your project:

❑	Increase in employment, or	❑	In small & medium-sized enterprises
☒	Safeguard employment, or	❑	In large companies
❑	Decrease in employment,	☒	None of the above / not relevant to the project
❑	Difficult to estimate / not possible to quantify		

19. For your project partnership please estimate the employment effect resulting directly from your participation in Full Time Equivalent (*FTE = one person working fulltime for a year*) jobs:	*Indicate figure:* 2
Difficult to estimate / not possible to quantify	❑

I Media and Communication to the general public

20. As part of the project, were any of the beneficiaries professionals in communication or media relations?

○ Yes ● No

21. As part of the project, have any beneficiaries received professional media / communication training / advice to improve communication with the general public?

○ Yes ● No

22 Which of the following have been used to communicate information about your project to the general public, or have resulted from your project?

❑	Press Release	☒	Coverage in specialist press
❑	Media briefing	❑	Coverage in general (non-specialist) press
❑	TV coverage / report	❑	Coverage in national press
❑	Radio coverage / report	❑	Coverage in international press
❑	Brochures /posters / flyers	☒	Website for the general public / internet
❑	DVD /Film /Multimedia	❑	Event targeting general public (festival, conference, exhibition, science café)

23 In which languages are the information products for the general public produced?

☒	Language of the coordinator	☒	English
☒	Other language(s)		