# *JPND Clinical Research Workshop: Paris, 4 March 2011*

# *Final Report*

## 1. Introduction and background to the JPND

The EU Joint Programme on Neurodegenerative Disease Research (JPND), in particular Alzheimer's disease, has been established by 23 European countries to address the growing societal challenge presented by age-related neurodegeneration. This initiative spans the biomedical, healthcare and social science agendas, and seeks to improve the scientific understanding of neurodegenerative disorders, provide new approaches for their prevention, diagnosis and treatment, and ensure effective provision of health and social care and support, so that individuals can receive optimum care at all stages of their illness.

The first goal of the initiative is to establish a joint 'Strategic Research Agenda' to guide research activity and investment over the coming decade. To provide a basis for this, three thematic meetings were held with academic opinion leaders in neurodegeneration (ND) research during March 2011, with the aim of providing a Europe-wide view of the research opportunities and needs of the field, and highlight priorities for action in the near and longer term. The outputs of the thematic meetings will be further developed through consultation with key stakeholder groups, for example industry and organisations representing patient/carer groups and healthcare professionals, and integrated to provide a holistic view of the research landscape and a roadmap for future research activity. This will be achieved through a further opinion leader workshop in June, spanning the three themes, and continued consultation with stakeholder groups and policy makers. The JPND Strategic Research Agenda will be published at the end of 2011.

## 2. Aim and output of the Clinical Research scientific workshop

This report provides a summary of the key outputs from a workshop held in Paris on 4 March 2011 with academic opinion leaders in clinical research pertinent to neurodegeneration. The following sections provide a brief overview of the current 'state of play' in this research domain, and highlight the consensus view of research opportunities as well as the key requirements for progress, leading to some recommendations to be considered under the JPND strategic research agenda. Information on the 'state of play' for clinical research into neurodegenerative diseases was supplied by the workshop 'theme leaders' (see Annex) and integrated with the gaps identified during the workshop. For the sections on 'Opportunities' and 'Needs', points identified during the workshop were integrated and context added by the theme leaders where appropriate.

## 3. State of play and gaps in our knowledge

### Introduction

It is widely recognised that neurodegenerative diseases (NDD) represent one of the major societal challenges of the next decades. The effects of symptomatic treatments, if available, are usually limited and despite intense research efforts in the past, not a single disease modifying treatment of proven efficacy exists in the entire NDD field.

Therefore, in order to reduce human suffering as well as economic and social costs, new and better research strategies are urgently needed to improve understanding of the underlying disease mechanisms and to develop better means for diagnosis, treatment and prevention.

**Overview**

Whilst significant progress has been made in recent years through the application of technological advances in fields such as genetics, molecular biology and neuroimaging to the clinical arena, a number of important gaps remain in our knowledge regarding the clinical progression of neurodegenerative disorders which will need to be addressed if real progress is to be made. At the most basic level, we are far from a full understanding of causality in the different NDD and have yet to identify the full range of risk factors for NDD and their differential effects at different life stages. Given that existing data is drawn from the population born in the first half of the 20th century the effect of relatively recent changes in lifestyle on disease prevalence and risk must be taken into consideration. Secondly, dissection of the mechanisms and processes involved in neuronal dysfunction, degeneration and neuropathology at a cellular level is essential to provide a basis for effective strategies for prevention, diagnosis and treatment.

Insights are emerging however, and genetic studies have made significant progress in identifying genetic subgroups of many diseases, as well as factors which correlate with age of onset, severity and disease progression. Gene expression profiling (transcriptomics) has begun to identify specific gene expression signatures for subgroups of patients and has considerable potential in subclassification of neurodegenerative diseases, an essential step in optimisation of neuroprotective therapy development. Gene expression profiling, followed by protein based and functional assays has also begun to unravel the complex biochemical pathways underlying neurodegeneration and to identify potential targets for therapeutic intervention. Similarly, the imaging techniques that have emerged to date have an important role to play in investigating neurodegenerative pathology. Magnetic Resonance Imaging (MRI) provides rich structural information allowing longitudinal analysis of regional changes, while Positron Electron Tomography (PET) provides molecular information that may antedate such changes by decades. Functional measures provided by fMRI and neurophysiology may bridge the gap by showing the earliest impact of molecular pathology on brain function.

Cohort and population based studies have provided critically important information for our understanding of NDD. In particular they have provided insights into risk factors; early clinical, imaging and biomarker features of the transition from normal aging to clinically manifest disease; the time course of progression; and an assessment of the mixed pathologies associated with aging, cognitive decline and NDDs. Requirements for internationally competitive research – include: a) deeper phenotyping addressing multiple modalities in serial assessments, for example integrating data from genetic, imaging and tissue studies; b) multi-centre studies with networking and alignment of assessments to offer greater power; c) demonstrable translational value (e.g. assessing outcome measures for trials). Particular gaps include studies with pathological confirmation; older cohorts; and methods to ensure compatibility and data integration from different centres and studies. A particular challenge is to maintain stability of data acquisition over several years while adapting to technological advances. The 'state of play' in therapeutic trial designs is for a greater focus on disease-modification particularly in Alzheimer's disease; greater use of biomarkers with a recent trend to incorporate molecular markers of amyloid metabolism and/or PET; and to design 'pre-dementia' trials. Gaps include translating results from animal to human and a lack of non-AD dementia trials and trials of off-patent therapies.

Although several candidate biomarkers have been identified, validated neurochemical markers for early diagnosis, monitoring disease activity, defining prognosis, unravelling key pathophysiological pathways and monitoring therapeutic response are still lacking in the major neurodegenerative disorders. Translation into clinical application has been hindered by small sample numbers, a lack of standardised sampling and analytical procedures, independent cohort validation and a lack of serial assessment in well characterised patient cohorts. Research to date has focused on studies of CNS tissue and CSF, but there is encouraging evidence that peripheral samples such as blood and fibroblasts may provide a useful read-out of changes occurring in the CNS, since many genes and proteins involved in the development of neurodegenerative diseases are ubiquitously expressed in peripheral tissues. Future biomarker discovery may also be aided by techniques that offer the potential to create specific types of neuron and glial cells from patient fibroblasts (through induced pluripotent stem cell technology).

**Prevention**

During the course of the workshop, two key gaps relating to prevention were highlighted. Firstly, the precise time period when modification of risk factors would be most effective must be determined. Significantly, there is more and more evidence that cognitive changes occur years before the impact on daily life is apparent, so intervention at the earliest possible stage must be considered. Secondly, although consensus is growing that certain lifestyles including healthy diet, exercise and control of vascular risk factors may protect against cognitive decline, it is not known how best to stimulate behavioural change at early and mid-life stages, and what public health messaging might have impact.

Biomarker studies will be best placed to identify strategies for prevention of neurodegenerative disease by studying the earliest indices of disease pathophysiology in cellular and presymptomatic animal models and linking findings back to human biosamples. Population-based studies could then be used to assess which modifiable risk factors can have major public health impacts. The establishment of cohorts of 'at risk' individuals (e.g. mutation carriers) would also allow the feasibility of prevention trials to be assessed.

**Diagnosis**

If effective preventative and therapeutic strategies are to be put in place gaps relating to disease classification and diagnosis will need to be addressed. In combination with genetic and environmental risk factors, imaging can play a role in detecting early disease manifestation. However, the time scale for occurrence of early disease features (molecular, functional or structural) and the evolution of the preclinical stages of the various diseases remains unclear and needs to be determined. Cohort studies of preclinical disease subjects offer prospective assessment of the earliest detectable disease features and have the potential to make an important contribution to diagnostic biomarker development. Later in the disease course, cognitive and behavioural changes manifest and certain profiles orient to specific diseases and can thus contribute to diagnosis. However, more work is needed to determine how these clinical and functional changes correlate with other biomarkers before accurate clinical diagnosis can be achieved. Clinical cohorts that follow individuals through the whole disease course do provide the opportunity for pathological confirmation and a (rare) opportunity to assess diagnostic criteria and markers against pathology and ad-mixtures of pathology; how mixed pathologies interact and modulate clinical phenotypes and progression is also unknown.

The precise characteristics of pathological, clinical and aetiological sub-phenotypes will need to be determined if stratification of patients towards specific therapeutic approaches is to be encouraged. New technologies, such as whole genome sequencing

for genetic analysis, will give rise to new opportunities for subdividing heterogeneous neurodegenerative disease states more accurately, as well as identifying factors which determine the age of onset and rapidity of disease progression.

### Treatment

Adequately powered therapeutic trials are self-evidently essential to assess efficacy of treatment. Key to optimising any potential therapeutic intervention will be a clear understanding of the potential time-window for reversing neuronal dysfunction prior to neuronal death. This in turn will require greater insight into the underlying disease pathophysiology, which should also provide a basis by which patients might be stratified for effective targeting of interventions. Data currently held within the pharmaceutical sector relating to abandoned studies might provide useful insights into disease pathways and subgroup-specific treatment responses, and might provide a valuable resource to academic groups if access could be obtained.

Another gap in our current knowledge is identification of the most appropriate clinical outcomes and measures of disease progression. For example, there is uncertainty about the long-term predictive value of early imaging markers, which precludes their use as accepted surrogate outcomes in clinical trials. Surrogate, or near surrogate, outcome markers that closely predict clinical outcome are necessary as they will facilitate smaller/shorter trials and allow assessment of treatment/therapy effects. Biomarkers to underpin studies of drug safety (e.g. to predict side effects) and for dose finding are also needed. Ideally biomarkers/outcome measures need to enable informed decision-making early in the (treatment) development process as this will help avoid costly late stage failures.

## 4. Opportunities

### Introduction

In the coming years, there will be tremendous opportunities for clinical research in NDD offered by a range of technological advances linking electronic patient records to multi-modal information from multiple systems. Linking longitudinal studies of imaging and biochemical biomarkers to genetic information will allow much richer cohort studies in preclinical and multi-disease populations and should help to determine patterns and risk factors associated with normal vs. pathological ageing as well as specific endophenotypes. Complex issues relating to organisational infrastructure, co-ordination and ethics will have to be addressed and substantial investment will be necessary if landmark studies are to be achieved.

### Disease pathology and aetiology

A number of distinct strategies were put forward in relation to determining the underlying causes of NDD. It was considered important to look for commonalities across, and instructive differences between, the spectrum of neurodegenerative disorders to illuminate mechanisms and factors impacting on vulnerability and resilience. Within this context, cross-reference could also be made to related disorders like multiple sclerosis and stroke which have degenerative components. Studies of normal brain ageing will also need to be undertaken to provide a comparator to the neuropathological process. One area that needs further assessment is the role, and potential treatment, of vascular pathology as a modifier of disease progression. In terms of disease aetiology, the role of genes and environment and their interaction in disease manifestation and protection needs to be dissected. More could be done to look for common denominators of risk through mining/integrating existing data(bases).

An approach that might help inform both aetiology and pathology is to focus on the preclinical stages of disease in 'at risk' individuals and follow early clinical patients through the disease course. Presymptomatic carriers of genetic risk alleles would need to be recruited and patient populations should ideally be enriched to improve power

and homogenise the sample base. However, if this approach is to yield benefits for the wider population it must be determined to what extent findings from the study of genetic disease variants can be applied to sporadic disease. Lastly, if animal models are to be used to inform knowledge of disease processes their relevance to age-related and chronic disease must be improved; currently there is very limited predictiveness outside of a few specific pathologies (i.e. amyloid deposition), and no models have been established with sufficient predictive value for neuronal loss and clinical outcomes. Insights from cellular and animal models of neurodegeneration should be linked into the analysis of human biosamples and *vice versa*.

**Diagnosis and biomarkers**

A critical requirement for progress in the area of NDD is to identify and validate new state and trait biomarkers that can be used across large populations; biomarkers from peripheral compartments such as blood, fibroblasts and saliva may be the easiest (and cheapest) to implement widely. Robust biomarkers of therapeutic response are also needed, an area where partnership with the pharmaceutical sector should be encouraged.

Imaging could potentially provide earlier and more specific diagnostic information allowing disease progression to be monitored and better disease stratification; different imaging methodologies could be exploited to provide combined biomarker approaches. Complementary to imaging, cognitive, behavioural, affective and functional assessment tools could be refined to better reflect clinical phenotypes, help subtype cohorts and identify early disease stages; tests should be designed so that they allow monitoring of symptomatic treatments across disease categories. Lastly, the use of more in-depth neurophysiological phenotyping (e.g. EEG, sleep-studies) should be explored.

**Treatment**

In the absence of effective treatments one approach might be to initially concentrate on slowing decline after onset of the disease. One additional benefit is that this approach might enable diagnostic/disease markers to be back-translated to help identify modifiable risk factors and inform primary prevention. However, new approaches to treat disease pathologies are urgently needed, and one option might be to seek to target the emerging molecular pathways at multiple points, rather than the single target approach currently employed. Though it is important to focus on disease modification, trials of symptomatic treatments should not be neglected. For example, trials to treat non-motor symptoms of PD and related disorders could be implemented relatively rapidly, and would respond to an important therapeutic need.

Gene expression profiling before and after therapeutic intervention may have the potential to provide an early read-out of therapeutic efficacy and illuminate the pathways underlying treatment effects; findings could be correlated with read-outs obtained from cellular and animal models of disease. Imaging could also potentially be used to provide a better means of understanding modes of action and comparison of drug effects across trials and populations

Clinically meaningful readouts and a solid statistical framework are required for future studies. Natural history studies can be used to provide assessment of outcome measures and inclusion criteria for future therapeutic trials. Together with genetic and other 'omic' data, risk information from imaging can be used to stratify patients into treatment groups to enhance the statistical power, but also to provide a surrogate outcome measure if validated properly. To enable better assessment of efficacy and to overcome the limitation that industry-supported trials are generally short-term, long-term follow-up to treatment trials in NDD should also be undertaken.

To improve collaborative studies in the EU, a re-evaluation and validation of current rating scales and tools should be undertaken to enable them to be harmonised and

standardised across countries and cultures. Acceptable clinical endpoints for the major disease manifestations, as well as those often neglected features (e.g. non-motor symptoms in PD), will have to be defined with regulators.

**Cohort and intervention studies**

The principle way to ensure that population-based research is of better quality and more effective is to conduct larger, adequately powered studies with comprehensive assessments including genotyping, multi-modal imaging, cognitive and biomarker assessment and banking of bio-fluids and tissues. In addition to new studies, research effectiveness could be improved by exploiting the potential of existing cohorts, including those from non-NDD, and by utilising nested and add-on studies. Large and long-term cohort studies could enable better assessment of phenotypic variability (including differences in progression) and a means of assessing diagnostic criteria and markers [see 'Diagnosis and biomarkers', above]. Studies of at risk subjects followed comprehensively through to pathology should also be encouraged. For presymptomatic studies, entry criteria will need to be based on standardised surrogate markers of disease and ethical concerns must be taken into consideration. For rarer diseases, multi-centre and multi-national cohorts could provide the power for significant insights but will require greater collaboration and investment to ensure compatibility.

## 5. Needs

In order to address the research questions discussed in the previous sections efficiently and successfully, existing research infrastructures have to be improved upon and novel organisational and technological capacities will have to be developed. Infrastructural requirements were identified throughout the workshop discussions, and have been classified into two sections separating out organisational activity from the suggestions for more direct infrastructural investment to support research. For the latter there was broad consensus that existing patient cohorts and established brain banks represent important European resources that should be built upon.

### i) Organisational requirements

**Networking, collaboration**

Increasing networking, collaboration and data sharing between researchers will be essential if progress is to be made towards producing effective interventions for NDDs. Where studies are conducted at more than one site, motivation, including the provision of regulatory support, must be maintained across the centres involved. Key to producing effective interventions will be improving links between basic scientists and translational researchers, which might be incentivised through enhancing support for centres that deliver such interaction. Similarly, more platforms and expansion of existing networks will be required to underpin clinical collaboration, bio-data exchange and cross-border cohorts [see also 'Centres and repositories' and 'Cohorts and registries']. Development of tools and technologies as well as the identification of new therapeutic targets could be promoted by increasing engagement between researchers and biopharma and diagnostic companies. Lastly, co-ordination of overall research strategy across this field could be provided through a regular forum encouraging innovative discussion and networking of expertise across diseases and approaches.

**Training and education**

To ensure the next generation of researchers and clinicians are sufficiently well equipped to deal with future needs their training must be improved, particularly in the areas of computational modelling, clinical neuroimaging, biosample collection and data analysis (including knowledge of software); enhanced support should also be targeted at clinician-scientists. Research capacity could potentially be increased by promoting greater exchange of students/expertise between research centres and by improving links with, and recruitment of, scientists from engineering and computer science backgrounds. The latter would allow recent technological advances in neurodegeneration research to be better utilised.

One topic that was heavily promoted in the JPND Healthcare Workshop and which recurred here was the need to de-stigmatise individuals with NDD and provide greater education for care givers and health practitioners in order to improve participation and support for the research agenda. Education to improve public awareness and motivation to participate in studies, donate brains etc, will also be needed if research is to be sufficiently resourced in future.

**Standardisation/harmonisation**

A key point that was repeatedly raised during the workshop was that standardisation and harmonisation should be encouraged across all areas of clinical and pre-clinical research. For example, the adoption of common standards and approaches for biosample collection, data collection across specific diseases, diagnostic criteria, imaging and biomarkers, clinical readouts and clinical endpoints would enable studies to be conducted with greater power and facilitate reproducibility thus enabling more definitive conclusions to be drawn.

One challenging area where common guidelines and standards could have significant impact is the field of cognitive function and behaviour, and it was proposed that the creation of a European-wide board could provide a mechanism to i) promote new tests or test batteries; ii) organise the standardisation and validation of scales or tests across European countries (with reference to those adopted in the wider international domain); and iii) advise on protocols to promote multi-site studies.

**ii) Research infrastructures**

**Centres and repositories**

Maximum efficiency of technology development and translational research may be best served by concentrating skills and resources in dedicated centres of excellence. Accordingly, proposals for focussed translational research centres along with technology centres for the development of high-tech apparatus and tools (e.g. imaging hardware and molecular imaging probes) were put forward. Though individual centres could be specialised, networking/sharing across them would ensure collaboration and focus of effort.

To allow researches across the JPND project area access to good quality data with sufficient numbers of samples, databases and repositories should be developed to facilitate access to existing/pooled data and well characterised and appropriately consented samples, particularly for cognitive data, neuroimaging scans, and for biological, tissue and brain material. To achieve major advances it will be necessary to facilitate systematic collection of CNS tissue and peripheral biosamples from well characterised, genetically subclassified and longitudinally followed clinical cohorts of patients. To ensure sufficient sample numbers and lack of duplication of effort, this should be done by a collaborative European neurodegenerative disease network, which facilitates cross-talk between the major disease areas.

**Cohorts and registries**

A number of proposals were put forward to improve the effectiveness of research utilising cohorts and ensure maximum value is obtained from the available resources. Firstly, it was proposed that cohorts might be registered to reduce redundancy. Secondly, embedding standardised measures within studies would allow cross-study calibration (i.e. through common imaging/cognitive test protocols). Thirdly, population-based and phenotyped control data should be built-up and shared across studies. Lastly, open-access data sharing (though with context, appropriate quality-control, and time-limited protection for use by the Principle Investigators) should be promoted and coupled to innovation in e-science/ICT platforms.

There is also a pressing need to create and support pan-European patient registries of rare diseases, particularly those with a genetic basis, including rare genetic forms of

common NDD (e.g. MND, FTD, FAD, FamPD). Once assembled, patient cohorts should be longitudinally followed.

**Tools and technologies**

Improvements in diagnosis and monitoring of disease are dependent on the development of new research tools. For example, new molecular imaging probes for PET and fMRI and new or improved proximity markers of conversion, including neuroimaging, cognition and neurophysiology, are required. To complement new and existing tools, novel analytic techniques for imaging and neurophysiology will also be needed; potentially they should utilise both computational neuroscience and systems biology. From a patient perspective, technologies that enable monitoring and data capture from home (telemedicine) would help avoid or reduce study visits, thus keeping disruption to a minimum.

## 6. Broad recommendations

In summary, the following clinical topic areas were identified as those where concerted action at a European-wide level would provide real impact over the coming decade:

- **Cohort studies:** Promote large, sustained, integrated and integrateable cohort studies with multimodal data and material collections. Effort should be made to assess comorbidities associated with NDD, and cross reference should also be made to longitudinal studies of normal brain ageing.

- **Build and expand on existing cohorts:** Utilise innovative methodological approaches to link and cross calibrate studies to increase study power, and translate from rare monogenic variants of the diseases sequentially to their common sporadic forms.

- **Biomarker development:** Develop imaging, electrophysiology, proteomics, metabolomics and cognitive approaches as biomarkers for disease progression and monitoring of treatment response, with particular emphasis on measures that can be implemented at the population level.

- **Assessment tools/outcome measurements:** Improve tools to reliably and validly assess cognitive, behavioural, affective and functional outcomes in a transcultural manner and link these outcomes to the genetic, biochemical and imaging markers.

- **Study populations and identification of risk factors:** Promote research across traditional diagnostic categories, integrating new knowledge on underlying disease pathways to identify traits that can be used to help stratify (preclinical) study populations and provide new insights into modifiable risk factors impacting on vulnerability and resilience.

- **Harmonisation:** Harmonise data and sample acquisition across centres, countries and diseases, and facilitate wide access to bio and data repositories.

- **Technological advancement:** Promote computational approaches and systems biology, which will require new hardware (computational hubs), software development and training to increase capacity in bioinformatics and data handling, storage and analysis.

- **Training:** Promote training of translational and clinician-scientists by improving interdisciplinary training programmes and professional perspectives.

*Published 10th September 2011*

# Annex

## Workshop location and agenda

INSERM, Meeting Room 132 (10th floor), 101 rue de Tolbiac, Paris 13ème, Paris.

| Time | Item | Note |
|---|---|---|
| 10.00h | Introduction | *Chair (Bruno Dubois)* |
| 10.10h | JPND and the SRA | *Rob Buckle* |
| 10.20h | EU landscape of neurodegeneration research | *Rob Buckle* |
| 10.40h | Thematic presentations (x4) - 5 minutes | *Theme leads* |
| 11.20h | Introduction to break-out groups (1) | *Chair* |
| 11.30h | Parallel discussion groups (Dimension 1) | *Chaired by theme leads* |
| 12.45h | Report to plenary | *Chaired by theme leads* |
| 13.15h | Lunch | |
| 14.00h | Introduction to break-out groups (2) | *Introduced by chair* |
| 14.10h | Parallel discussion groups (Dimension 2) | *Chaired by theme leads* |
| 15.30h | Break | |
| 15.45h | Report to plenary | *Theme leads* |
| 16.15h | Summary and conclusions | *Discussion lead by chair* |
| 17.00h | End of meeting | |

| **Dimension 1 theme** | **Theme leader** |
|---|---|
| Imaging and neurophysiology | Frederik Barkhof – VU University Medical Center |
| Cognition, function & behaviour | Florence Pasquier – University Hospital Lille |
| Biomarkers – genetics/metabolomics | Pamela Shaw – University of Sheffield |
| Cohorts and trial design | Nick Fox – University College London |
| **Dimension 2 theme** | **Theme leader** |
| Prevention | Laura Fratiglioni – Karolinska Institute |
| Diagnosis | Bruno Dubois – Pitié Salpétrière Hospital |
| Treatment | Thomas Gasser – University of Tübingen & DZNE |

## Format

The workshop revolved around two structured discussion sessions, with participants allocated to one of three or four break-out groups. The morning and afternoon discussions addressed different topics, related to methodologies and outcomes, with membership of the break-out groups changing between the two sessions to encourage discussion from different perspectives.

**Meeting attendees**

| | |
|---|---|
| Isabelle Arnulf | Hopital Pitié Salpétrière APHP |
| Alim Louis Benabid | Joseph Fourier University |
| Frederik Barkhof | VU university medical Center |
| Habib Benali | INSERM U678 |
| Kaj Blennow | University of Gothenburg |
| Monique Breteler | Erasmus University Rotterdam and Harvard School of Public Health |
| David Brooks | Clinical Science Centre MRC |
| Patrik Brundin | Wallenberg Neuroscience Centre, Lund University |
| Stefano Cappa | Vita-Salute San Raffaele University |
| Jean-Francois Dartigues | University Victor Segalen Bordeaux 2 |
| Jean François Demonet | INSERM |
| Bruno Dubois | Pitié Salpétrière Hospital, APHP |
| Alexandra Dürr | Pierre and Marie Curie University |
| Charles Duyckaerts | Pitié Salpétrière Hospital, APHP |
| Nick Fox | University College London |
| Laura Fratiglioni | Karolinska Institute |
| Giovanni Frisoni | IRCCS Centro S.Giovanni di Dio |
| Lutz Fröelich | ZI Mannheim Central Institute of Mental health |
| Thomas Gasser | University of Tübingen & DZNE |
| Miia Kivipelto | Karolinska Institute |
| Brian Lawlor | Trinity College Dublin |
| Manuela Neumann | University Hospital Zurich |
| Agneta Nordberg | Karolinska Institute |
| John O'Brien | Newcastle University |
| Wolfgang Oertel | Marburg University Medical Centre |
| Florence Pasquier | University Hospital Lille |
| Philippe Robert | University Hospital Nice |
| Anne Rosser | Cardiff University |

| | |
|---|---|
| Paolo M. Rossini | Associazione Fatebenefratelli per la ricerca (AFaR) |
| Martin Rossor | Dementia Research Centre, UCL Institute of Neurology |
| Nikos Scarmeas | University Columbia |
| Philip Scheltens | VU University Medical Centre |
| Pamela Shaw | University of Sheffield |
| Ingmar Skoog | University of Gothenburg |
| Hilka Soininen | University of Eastern Finland |
| Rick R.C. Vandenberghe | University Hospital Leuven |
| Frans Verhey | Maastricht university |
| Gunhild Waldemar | University of Copenhagen |
| Bengt Winblad | Alzheimer Disease Research Centre, Karolinska Institute |

**JPND staff and observers**

| | |
|---|---|
| Philippe Amouyel | JPND Management Board (Chair), INSERM France |
| Rob Buckle | JPND Management Board, MRC UK |
| Karine Baudin | JPND WP1, INSERM France |
| Stéphanie Le Naour | JPND WP1, INSERM France |
| Ingrid Tamby | JPND WP1, INSERM France |
| Sean Greatbanks | JPND WP2, MRC UK |
| Alexander Pemberton | JPND WP2, MRC UK |
| Micol Zappa | JPND WP2, MIUR Italy |
| Marlies Dorlöchter | JPND WP3, BMBF Germany |
| Petra Pütz | JPND WP3, BMBF Germany |
| Philippe Cupers | European Commission, DG Research and Innovation |