Neuropsychiatrie : recherche epidemiologique et clinique

Rapport Hcéres

agence d'évaluation de la recherche
et de l'enseignement supérieur

Department for the evaluation of research units

AERES report on unit:

Neuropsychiatry: Epidemiological and Clinical Research

Under the supervision of the following institutions and research bodies:

Nouvelle Université de Montpellier

Institut National de la Santé Et de la Recherche Médicale - INSERM

January 2014

agence d'évaluation de la recherche
et de l'enseignement supérieur

Department for the evaluation of research units

On behalf of AERES, pursuant to the Decree of 3 november 2006[1]*,*

- Mr. Didier HOUSSIN, president
- Mr. Pierre GLAUDES, head of the evaluation of research units department

On behalf of the expert committee,

- Mr Pierre PHILIP, chair of the committee

[1] The AERES President "signs [...], the evaluation reports, [...] countersigned for each department by the director concerned" (Article 9, paragraph 3 of the Decree n ° 2006-1334 of 3 November 2006, as amended).

Evaluation report

This report is the result of the evaluation by the experts committee, the composition of which is specified below.

The assessment contained herein is the expression of independent and collegial deliberation of the committee.

Unit name:	Neuropsychiatry: Epidemiological and Clinical Research
Unit acronym:	
Label requested:	UMR_S
Present no.:	UMR_S 1061
Name of Director (2013-2014):	Ms Karen RITCHIE
Name of Project Leader (2015-2019):	Ms Karen RITCHIE

Expert committee members

Chair:	Mr Pierre PHILIP, Université Bordeaux
Experts:	Mr Bruno AOUIZERATE, Université Bordeaux
	Ms Catherine BARTHELEMY, Inserm, CHRU de Tours (representative of CSS INSERM)
	Mr Michel CLANET, CHU de Toulouse (representative of CNU)
	Mr Klaus EBMEIER, University of Oxford, United Kingdom

Scientific delegate representing the AERES:

Ms Christel PROTIERE

Representatives of the unit's supervising institutions and bodies:

Ms Martine DAUJAT-CHAVANIEU (representative of the director of the CBS2 Doctoral School)

Mr Jacques MERCIER, Nouvelle Université de Montpellier

Ms Anne ROCHAT, INSERM

1 • Introduction

History and geographical location of the unit

The research group U 1061 was established in 2003 (E 361 then U 888) within La Colombière University Psychiatric Hospital thus facilitating collaboration between Inserm researchers, engineers and technicians with clinicians and academic staff from the university departments of Psychiatry, Neurology, Neuroradiology and Biochemistry in order to develop neuropsychiatric research in the Montpellier region. U 1061 is housed within a separate pavilion in the hospital grounds within easy access to all psychiatric departments and the nearby neurology hospital Gui de Chauliac, where the unit has a clinical suite for examinations carried out in the context of population studies.

Management team

The direction of the unit and its mode of functioning are determined by the director in collaboration with the unit Advisory Council, comprising the director and administrative assistant, leaders of each research theme, a representative of the technical/engineering staff, the health and hygiene officer, and a student representative. Following discussion by the unit's scientific Council, two associate directors will be appointed for the next five years; Dr Marie-Laure ANCELIN (DR2 Inserm) and Pr Sebastien GUILLAUME (PUPH, Department of Psychiatry).

AERES nomenclature

SVE1_LS5

Unit workforce

Unit workforce	Number as at 30/06/2013	Number as at 01/01/2015
N1: Permanent professors and similar positions	5	5
N2: Permanent researchers from Institutions and similar positions	6	6
N3: Other permanent staff (without research duties)	9	8
N4: Other professors (Emeritus Professor, on-contract Professor, etc.)		1
N5: Other researchers from Institutions (Emeritus Research Director, Postdoctoral students, visitors, etc.)	9	7
N6: Other contractual staff (without research duties)	14	12
TOTAL N1 to N6	**43**	**39**

Unit workforce	Number as at 30/06/2013	Number as at 01/01/2015
Doctoral students	7	
Theses defended	7	
Postdoctoral students having spent at least 12 months in the unit	1	
Number of Research Supervisor Qualifications (HDR) taken	2	
Qualified research supervisors (with an HDR) or similar positions	8	10

2 • Assessment of the unit

Global assessment of the unit

The unit, located in a hospital is composed of a single very productive team divided into 4 subthemes interacting in a very attractive mode. The combination of physicians trained in the unit and INSERM researchers give a lot of coherence to the project, as well as to the established connections with both psychiatric and neurological hospitals. The support from the university is obvious and very probably related to their outstanding and original scientifc production. The main themes (affective disorders, suicide, ageing cognitive disorders, sleep) are treated with a translational approach from cohorts to clinical trials. The research strategy is very original and give a unique national and international dimension to the unit.

Strengths and opportunities related to the context

The unit provides a multidisciplinary and synergistic approach to important neuropsychiatric health problems in an ageing society (i.e. depression, suicide, dementia, sleep disorders). Rather than just concentrating on descriptive and epidemiological methodology, the unit engages in truly translational research, providing the skills and knowledge to translate biological and epidemiological findings into improvements in health and social care. The unit impresses by its high international competitiveness and its academic excellence.

Weaknesses and threats related to the context

This ambitious program relies on a steady supply of data from long-term high quality cohorts. Retirement vacancies, if unfilled, may weaken the technical support of the unit in the near future.

The unit lacks engineers and research assistants.

Recommendation

Reinforce links with neuroimaging (post-processing of data) and biology (perhaps by creating a CRB in the hospital and university). Promote the emergence of new teams (ATIP or AVENIR) to anticipate retirement of researchers. Focus on main fields of expertise: late life depression, cognitive impairment and sleep disorders. This may require access to younger cohorts, as causes of late life ill-health may be found in early to mid-life.

3 • Detailed assessments

Assessment of scientific quality and outputs

The scientific production of the Inserm unit is outstanding with 737 papers published in the last 5 years, 38 of them in journals with impact factors above 10, and 154 above 5. The main findings of the unit are:

1) late onset depression and anxiety disorders constitute separate clinical sub-types;

2) adult suicidal behaviour is mediated by genetic vulnerability, childhood trauma exposure and impaired decision making;

3) risk factors for dementia are gender specific;

4) excessive daytime sleepiness and hypersomnia are related to high mental health risks.

The overall assessment of the unit programme is excellent in both quality and volume of production.

Assessment of the unit's academic reputation and appeal

The unit and several of its researchers have close interactions with the Royal College, the University of Melbourne or the University of Stanford. Researchers are members of the following advisory boards: Institut National de Veille Sanitaire, Haute Autorité de la Santé, MRC UK. 10 national and international conferences have been organised by researchers of the unit.

The unit director is a Member of the MRC steering committee on Biomedical Research and the MRC Lifelong Health unit (London UK), a Member of the Scientific Advisory Board of the Alzheimer's Research Trust, UK, as well as of the Institut de Veille Sanitaire

One researcher is co-chair of the consortium EURECA (EUropean REsearch CArtel – Suicide) for genetic research on suicidal behaviour and the suicide network promoted by the European College of Neuropsychopharmacology (ECNP)

Three researchers are members of the suicide task force of the World Federation of Societies of Biological Psychiatry.

One researcher is a Member of the national committee of Registries Inserm- Invs (2003-2013), a member of the scientific advisory board of the Institut National de Veille Sanitaire (Invs), president of the commission on Chronic Diseases of the High Council in Public Health (HCSP, Ministry of Health), and piloted the evaluation of a national health strategic plan.

A European Narcolepsy Network was also established in 2008. One researcher is a member of the board of EU-NN.

Since 2007, one researcher has been a member of the scientific board of the French Sleep Medicine and Research Society, a member of the European Sleep Research Society, International REM sleep behaviour study group, and of the American Academy of Sleep Medicine

Several researchers are member of editorial boards of scientific journals.

Many post docs have been hosted by the unit and several researchers participated in FP 7 grants demonstrating their international impact.

Assessment of the unit's interaction with the social, economic and cultural environment

Many members have participated in radio and TV programs, many articles have been written in French and international newspapers.

Many events have been organized with scientific societies and patient groups (la journée du sommeil, la semaine du cerveau, réunions de prévention du suicide).

Researchers participate in Alzheimer and rare disease plans. Researchers also advise the French drug agency (ANSM) on the risks of vaccination and the occurrence of narcolepsy.

All subtheme leaders have contracts with the pharmaceutical industry to test drugs in neurological and mental disorders. Some of the theme leaders are members of advisory boards of pharmaceutical groups. Projects are about “Sclerostin and DKK-1 on bone formation in anorexia nervosa” and “neuroanatomical bases of moral pain in depression and suicidal behaviour”, about “Psycho-education in bipolar disorder” and about sleep research. Subtheme leader also participate to clinical trials with various pharmaceutical companies.

Assessment of the unit's organisation and life

The unit is based on strong interactions between epidemiological and clinical research with a transverse structure (biostatistical platform) to help interactions between groups and interface between university hospital medical staff and researchers. It also combines two major themes integrating psychiatric and neurological disorders (depression, suicidal behaviours, cognition, ageing, sleep). We noticed a strong collegiality between members regarding decisions but also intense scientific interactions when conducting projects. There are strong exchanges between the hospitals and the research unit and many professors running the clinical departments have being trained and work also in the unit as researchers.

The direction of the unit and its operating mode are determined by the director in collaboration with the unit advisory council, comprising the director and administrative assistant, leaders of each research theme, a representative of the technical/engineering staff, the health and hygiene officer and a student representative. Scientific or interpersonal difficulties experienced by individual members of the unit are discussed firstly with a member of the council and, if unresolved, are brought to the next council meeting (approximately every three months). Two-monthly unit meetings are followed by a scientific presentation, alternating regional, national and international speakers. All doctoral and post-doctoral students are required to present their work to the unit at least once before submission. The council requires all doctoral students and their supervisors to sign and adhere to a doctoral supervision agreement in order to assure an optimal environment for post-graduate study.

Assessment of the unit's involvement in training through research

The unit, which is mainly attached to the graduate school CBS2 n°168, organizes frequent seminars covering the different themes of the unit. The summer school helps training students in research methods in psychiatry. Researchers participate to teaching in the context of national diplomas (diplômes inter-universitaires). Members of the unit participate to training courses abroad (Switzerland, Australia).

Many physicans did their PhD in the unit and then becam professor of medicine will help significantly the transfert of training from the unit to the medical school.

Assessment of the strategy and the five-year plan

The project is clearly based on translational and synergistic approaches combining both epidemiological and clinical research. By using such a strategy, physiopathology is a relevant step to design new tests and interventional techniques, thereby improving health in depression, suicidal behaviours and neurological/cognitive disorders. The combination of genetic, biological and environmental risk factors to explain neuropsychiatric disorders opens very promising perspectives. Increasing the age range of the population and subjects studied is also a key element to interpret time or life experience components to explain risk factors. The relationship with sleep research will bring new insights in the role of sleep and sleep disorders in the occurrence of mental and neurological disorders. It is also worth noticing a strong involvement of both hospital and university in the setup of the research programmes.

4 • Theme-by-theme analysis

Theme 1: Affective disorders: bio-environmental risk factors and resilience

Manager's name: Ms Marie-Laure ANCELIN and Ms Anne-Marie DUPUY

Workforce

Theme workforce in Full Time Equivalents	As at 30/06/2013	As at 01/01/2015
FTE for permanent professors	0,50	0,50
FTE for permanent EPST or EPIC researchers	2,70	2,70
FTE of other permanent staff without research duties (IR, IE, PRAG, etc.)	2,80	3,80
FTE for other professors (PREM, ECC, etc.)		
FTE for postdoctoral students having spent at least 12 months in the unit	1	
FTE for other EPST or EPIC researchers (DREM, etc.) excluding postdoctoral students	2	2,50
FTE for other contractual staff without research duties	1,25	1
FTE for doctoral students	2	
TOTAL	**12,25**	**10,50**

• Detailed assessments

Assessment of scientific quality and outputs

The present theme aims at better understanding the role of various contributing factors related to gene malfunctions primarily based on gene-gene or gene-environment interactions that are supposed to be play a major role in either deregulation of the hypothalamic-pituitary-adrenal axis (HPA axis) or disruption of neurogenesis, neuroprotection in affective disorders of the elderly patients. This topic is of great interest regarding the high prevalence of mood disorders in the general elderly population, who has been exposed to negative life events across their life span. Relationships with other potentially significant markers centred on sleep and brain morphological disturbances will also be explored. To date, this is the first time that the role of genetic and epigenetic determinants of affective disorders among a large population of aging patients is studied, including the putative link with certain physiological and anatomical impairments, by adopting a promising, innovative and integrative neuroscience approach. Also, there is a piece of translational research carried out in both human and laboratory animal models on the importance of stress-related inflammatory and neuroendocrine markers along with anatomical or functional modifications that are implied in the propensity to develop post-traumatic stress disorder (PTSD) and in the prediction of treatment responses and prognosis, thereby addressing relevant scientific questions, that are still relatively unanswered, although representing a crucial issue in the clinical context.

Researchers working on the present theme have been authors or co-authors of many articles (largely >100) whose 18 in journals with high impact factor ranging from 36 to 8, particularly including Nature Genetics, Lancet

Neurology, Plos Medicine, the American Journal of Psychiatry, etc., while 84 others have been approved for publication in journal of impact factor comprising between 8 and 4. This is perfectly indicative of a sustained and intensive research productivity of very high scientific quality giving important new insights in the understanding of ageing-related pathologies.

Assessment of the theme's academic reputation and appeal

The present research team comprises internationally recognized experts in the field of dementia and affective disorders, who work on large cohorts of elderly patients, with an emphasis on the role of interactions between environmental and biological factors, as mechanisms of vulnerability. They are members of collaborative networks combining national and international research teams. They received numerous financial and institutional supports from ANR, PHRC or AOI, as well as prizes and distinctions, attesting to a leadership position beyond the national level. Finally, the internationally attractive status of the researchers working on the present theme is attested by foreign post-doctoral student (n=1) [financial support from: I) Foundation FondaMental, France (2010); II) the National Health and Medical Research Council (NHMRC), Australia (2011-2015)] or academic colleagues (n=2) who have joined the group for a specified period of time.

Assessment of the theme's interaction with the social, economic and cultural environment

This research team is involved in the organization of symposia/conferences during the French "Semaine du cerveau" or the "Nuit des chercheurs". Researchers have been invited to participate in either television or radio interviews and to write several general articles that summarized major neuroscientific findings and printed in both French and international newspapers with high reader levels.

Assessment of the theme's organisation and life

Beyond the extended international collaborations mentioned previously (cf. overall unit assessment), strong partnerships exist with:

I) theme 2 for the assessment of suicidal behaviours;

II) theme 3 for the determination of structural brain abnormalities;

III) theme 4 for the evaluation of sleep disturbances in the aging population;

IV) the Academic Department of Adult Psychiatry in the "La Colombière" Psychiatric University Hospital for the recruitment of older patients, as target populations for the present theme;

V) the Institute of Functional Genomics in Montpellier.

However, the incorporation of neuroimagers and geneticists within the unit, who would be familiar with the structural/functional neuroimaging and genetics in the specific field of psychiatric disorders respectively, could be of significant benefit by improving even more the projects' progress, data management and analysis.

Assessment of the theme's involvement in training through research

Among the two Ph.D. students who are actually hosted, one is an ophthalmologist occupying the current position of "Chef de Clinique-Assistant" at the interface academic hospital/Montpellier University. He is highly involved in a comprehensive eye examination for the detection of vision impairments in the selected research participants. The other one originating from China recently joined the research theme and participates in the scientific projects that are actually performed in ageing patients. Researchers affiliated to this research ensure a sustained supervision of their respective students during weekly regular meetings within the unit. Otherwise, they are implicated in several teaching programs that have been developed by the unit or organized in collaboration with international and institutional partners.

Assessment of the five-year plan and strategy

The scientific project related to theme 1 primarily aims at identifying genetic, epigenetic, physiological, neuroendocrine and structural markers that are supposed to substantially increase the risk for affective disorders in

ageing patients on the basis of the stress-vulnerability model. Particular attention is paid to the genetic vulnerability with the determination of the candidate genes that could be strongly implicated in disturbances of the major stress response biological system HPA axis in elderly patients. Epigenetic mechanisms related to the methylation of the promoter regions of several genes involved in the glucocorticoid receptor expression, neurogenesis/neuroprotection are also studied. Relationships with either sleep disturbances or brain morphological abnormalities will also be examined. Also, another part of the present project is devoted to:

I) the identification of biological markers of vulnerability for PTSD, course and treatment responses, which are associated with the peripheral metabolism, neuroinflammation or brain functioning;

II) the impact of psychiatric conditions and associated treatments on the mortality and the physical activity in elderly patients.

Beyond the relevance of the topic, the quality of collaborative interactions is also one of the strongest points of the project with the participation of transnational research teams (including themes 2, 3 and 4 developed in the unit) that have complementary fields of expertise in perfect alignment with aims and methodological considerations. This is a critical issue that makes the project clearly feasible over the next 5-year contract.

Conclusion

- **Overall opinion of the theme:**

The research theme focused on the determination of clinical, genetic or biological factors implied in the pathophysiology of either late-onset mood disorders or post-traumatic stress disorder, which can be considered as putative markers predicting either the occurrence, relapse/recurrence or treatment responses. This research topic is overall interesting because such pathologies are well known to be highly prevalent in the general population, and therefore considered as serious public health problems. This project could thus increase our current knowledge about the biological substrates known to play a role in late-onset mood disorders or PTSD that might further become target for the development of novel therapeutic strategies in such pathological conditions.

- **Strengths and opportunities:**

- topic related to major depression in the elderly or post traumatic stress disorder, as major public health issues;

- methodological approach combining a wide range of experimental tools for the identification of genetic, biological and anatomic and functional markers of the vulnerability for these pathological conditions;

- large cohorts with the recruitment of patients, which is enabled by the active collaboration with clinicians at the University Hospital in Montpellier;

- active participation in large and international collaborative networks.

- **Weaknesses and threats:**

Absence of neuroimagers or geneticists familiar with the problematic of psychiatric disorders.

- **Recommendations:**

Attraction of neuroimagers or geneticists useful for the management and treatment of genetic or neuroimaging data.

Theme 2: Suicidal behaviour

Manager's name: Mr Philippe COURTET and Mr Alain MALAFOSSE

Workforce

Theme workforce in Full Time Equivalents	As at 30/06/2013	As at 01/01/2015
FTE for permanent professors	1,2	1,5
FTE for permanent EPST or EPIC researchers		
FTE of other permanent staff without research duties (IR, IE, PRAG, etc.)	0,50	0,50
FTE for other professors (PREM, ECC, etc.)		
FTE for postdoctoral students having spent at least 12 months in the unit		
FTE for other EPST or EPIC researchers (DREM, etc.) excluding postdoctoral students	1,50	0,50
FTE for other contractual staff without research duties	3,75	3,75
FTE for doctoral students	2	
TOTAL	**8,95**	**6,25**

• Detailed assessments

Assessment of scientific quality and outputs

The present research theme is focused on the cognitive, emotional and biological markers that are supposed to play a pivotal position in the determination of recurrent suicidal behaviours. This is an important issue in public health because of the high frequency of suicidal attempts that further increase the risk for death from suicide in the general population. This research could also contribute to substantially improve the nature of clinical interventions that could be adopted in order to reduce suicide attempts and therefore to prevent completed suicides. The methodological strategy combining genetic, epigenetic or molecular approaches intending to examine either several gene-gene or gene-environment interactions with the possible role of early life traumatic events is perfectly adapted to the objectives of the present project. Additionally, the use of functional neuroimaging techniques coupled with appropriate instrumental tasks is of particular relevance for assessing the importance of an impairment of decision making, emotional disturbances with the identification of brain regions of interest in suicidal behaviours. To our knowledge, this is the first time that the putative role of interactions genes-genes and gene-environment as well as cognitive and emotional factors are precisely examined with the attempt to better understand the pathophysiology of suicidal behaviours.

Researchers focusing their work on suicidal behaviours have several articles (n=6) in journals with high impact factor (ranging from 16 to 8), such as Plos Medicine, the American Journal of Psychiatry or Biological Psychiatry, as well as numerous articles (n=14) in international journals of lower impact factor (ranging from 8 to 4), while the remaining 76 have been accepted for publication in journal of impact factor below 4. It can therefore be considered that the ongoing research work is characterized by a high scientific quality providing significant new findings useful for improving our current knowledge about the pathophysiological determinants of suicidal behaviours. This is especially important given their high frequency in the general population.

Assessment of the theme's academic reputation and appeal

The clinical researchers who are working on this research topic are well recognized to be highly specialized in the clinical management of patients experiencing suicide attempts. They are widely considered as great experts in the identification of cognitive and genetic determinants for suicidal behaviours. They actively participate in:

I) the consortium EURECA (EUropean REsearch CArtel – Suicide) for genetic research on suicidal behaviour and the suicide network promoted by the European College of NeuropsychoPharmacology (ECNP);

II) the suicide task force of the World Federation of Societies of Biological Psychiatry.

They are financially supported by numerous institutional sources allowing conducting large clinical studies in this research field and are intimately linked to the FondaMental Foundation network along with numerous French clinical academic departments and research teams sharing high expertise levels in the field of suicide. They offer the opportunity to receive foreign post-doctoral students on scientific programs supported at least in part by the FondaMental Foundation grants, thereby illustrating the international reputation and attractiveness of the present research theme.

Assessment of the theme's interaction with the social, economic and cultural environment

There is an active contribution to develop monthly meetings for lay persons and patients' associations. This is paralleled by the participation in radio programs and the written of didactic articles in widely read newspapers on suicidal behaviours and prevention. Finally, there is substantial involvement in the organization of a relatively high frequented meeting every two years designed to inform the lay persons or associations about the ongoing research conducted on the present theme.

Assessment of the theme's organisation and life

Partnerships with:

I) theme 1, with which studies of suicidal behaviours in the elderly are specifically conducted;

II) the academic department of either Adult Psychiatry or neuroimaging at the University Hospital in Montpellier.

The possible weakness of the present theme might be primarily related to the absence of full researchers compared to that of clinical researchers, although clearly engaged in research activities for almost half time. However, this undoubtedly relies on the specific topic of the theme project with clinical research studies enrolling large psychiatric cohorts. The recruitment of neuroimagers familiarized with the anatomical and functional approaches in psychiatric diseases could make access to the neuroimaging equipment, acquisitions, data analysis even easier. Similar initiatives could be encouraged intending to facilitate the manipulation of genetic data beyond the existing interactions with the Institute of Functional Genomics located in Montpellier.

Assessment of the theme's involvement in training through research

Two Ph.D. students who are both psychiatrists are actually receiving training and participate in the ongoing research projects on the assessment of clinical, genetic and anatomic and functional markers of predisposition for suicidal behaviours. They benefit from an intensive supervision by the theme leader and collaborators during weekly regular or informal meetings at either the hospital or the unit. Otherwise, there are clinical researchers who are actively involved in significant teaching activities within:

I) the university Diploma Introduction to cognitive-behavioural therapies (Université Montpellier I – UM1);

II) the university Diploma Advanced cognitive-behavioural therapies (Université Montpellier I – UM1);

III) university Diploma Management of Eating Disorders (Université Montpellier I – UM1, Université de Nantes, universities of Lille), etc.

Assessment of the five-year plan and strategy

The present project is expected to improve current knowledge about environmental, cognitive and biological factors that are assumed to be highly involved in the pathogenesis of suicidal behaviours by using various and appropriate experimental tools derived from genetic, neuropsychology and brain imaging. The 5-year plan and strategy adopted are both in accordance with the primary goals of this scientific project. The development of psychiatric cohorts will be helped by the active intervention of the theme leader within a large collaborative network specifically involved in the evaluation, treatment and prevention of suicide. Additionally, the academic department of Adult Psychiatry directed by the theme leader at Hospital is specialized in the clinical management of suicidal patients who will be easily recruited for the research programs defined in the scientific project. Among future strategies that might be considered, there are the attraction of neuroimagers and geneticists that could possibly be helpful for the collection and treatment of neuroimaging and genetic data, respectively.

Conclusion

- **Overall opinion of the theme:**

The research theme centred on the identification of clinical, genetic and biological factors implied in the determination of vulnerability for suicidal behaviours is particularly relevant because of the high prevalence of suicidal attempts in the general population, thereby representing a serious public health problem. This project could also open new perspectives for the prevention of suicidal acts and recurrences in high-risk subjects.

- **Strengths and opportunities:**

- topic related to suicidal behaviours and related psychiatric disorders, as major public health issues;

- methodological approach combining a wide range of experimental tools for the identification of genetic, biological and anatomic and functional markers of the vulnerability for suicidal behaviours;

- large cohorts with the local recruitment of suicidal patients, which is facilitated by the active collaboration with the Academic Department of Adult Psychiatry at the University Hospital in Montpellier;

- large international and national collaborative networks, particularly including Academic Departments of Psychiatry associated with the FondaMental Foundation.

- **Weaknesses and threats:**

- absence of neuroimagers or geneticists familiarized with the problematic of psychiatric disorders;

- absence of full-time researchers.

- **Recommendations:**

- attraction of neuroimagers or geneticists useful for data collection, analyses.

Theme 3: Ageing-related cognitive disorder

Manager's name: Ms Claudine BERR and Mr Jacques TOUCHON

Workforce

Theme workforce in Full Time Equivalents	As at 30/06/2013	As at 01/01/2015
FTE for permanent professors	0,30	
FTE for permanent EPST or EPIC researchers	3	3
FTE of other permanent staff without research duties (IR, IE, PRAG, etc.)	2	1
FTE for other professors (PREM, ECC, etc.)		0,30
FTE for postdoctoral students having spent at least 12 months in the unit		
FTE for other EPST or EPIC researchers (DREM, etc.) excluding postdoctoral students	1	1
FTE for other contractual staff without research duties	2,20	2
FTE for doctoral students	2	
TOTAL	**10,50**	**7,30**

• Detailed assessments

Assessment of scientific quality and outputs

This group aims to understand the determinants of the inter-individual variability in the ageing process through three different approaches:

I) investigating the causal inference of modifiable risk factors on age-related health outcomes;

II) identifying the MRI Brain morphological and functional biomarkers of cognitive decline and maintenance (cognitive reserve) ;

III) assessing the clinical phenotypes and biomarkers of Alzheimer's disease.

For this purpose they have access to well-defined different cohorts of patients (3 cities, /ESPRIT, White Hall II, Gazel, E3N), CONSTANCES. Two ambitious projects (MORPHODEM,CRESCENDO) are described in the MRI approach which requires a strong collaboration with an imaging group expert in the field of post processing even if they have access to a platform which allows a good acquisition to the data. Some of these MRI biomarkers will be integrated with other imaging markers (PET amyloid tracers), clinical and biological markers into a better definition of clinical subtypes of the disease. This broad-based programme will contribute to a preventive approach through a better identification of risk factors and physiopathological aspects of the heterogeneity of the different phenotypes.

The project "modelling the impact of reversing risk factors for dementia" has shown that dementia incidence over the next decade may be reduced by a third with treatment and prevention of insulin resistance, depression, stroke and improvement of education and diet. This is excellent translational work of eminent practical impact. Similarly, the contribution to identify early biomarkers is of great clinical value, as reflected by multiple publications in highest impact refereed journals (such as Nature Genetics, JAMA, Mol Psych, NEJM). Equally, the participation in scientific networks and activities, the publicly financed institutional contracts, and the interactions with the social, economic and cultural environment are plentiful and of highest quality. Finally, the quantity of

publications is excellent: we count 38 publications for theme 3 members in 2013 alone, three of these with impact factors >10 and a further 13 with impact factors >5.

Assessment of the theme's academic reputation and appeal

The theme co-leader is member of the national committee of registries INSERM-Invs, member of the scientific advisory board of the INVS, president of the commission of chronic diseases of the High Council of Public Health. (Ministry of Health). The other co-leader serves in different advisory boards of pharmaceutical companies. The group has obtained different prizes. They have national (Bordeaux, Villejuif, Paris, Toulouse, Grenoble, Lille) and international (Melbourne, Camberra, Sydney, University College London, Columbia University) collaborations.They organise or participate to national and international meetings (National Health registries, Clinical trials in Alzheimer disease).

Assessment of the theme's organisation and life

Partnership with theme 1 for the imaging project and theme 4 (alteration of sleep with aging as risk factor for cognitive decline). Participation to masters diploma, training of residents and students in public health, 2 post doctoral supervision/year.

Assessment of the theme's interaction with the social, economic and cultural environment

Organisation of different events in relation to dementia and *Alzheimer disease*: regional "Science Bar", Workshops on *Alzheimer disease* prevention, (Association France Alzheimer), creation of an *Alzheimer disease* network in Languedoc-Roussillon, informations on *Alzheimer disease* and ageing through media.

Assessment of the theme's involvement in training through research

The theme caters for two to three masters diploma students and two doctoral students per year, trains three residents in public health and two neuropsychologists per year. These appear to be well supported within the theme.

Assessment of the five-year plan and strategy

The comittee was impressed by the width of approach to the theme of cognitive impairment. In particular the broad approach including 'resilience' and frequently allied conditions, such as depression in old age. If cognitive impairment in old age follows the paradigm of cardio-vascular disease (which appears likely), rather than that of Huntington's disease, a painstaking epidemiological strategy with careful evaluation of naturalistic studies, 'natural experiments' (as in the 'pieds noirs' study) and mass interventions (e.g. by change of diets) is indeed the way to go. Theme 3 will provide the sufficiently large critical mass of expertise to analyse such data

Conclusion

- **Overall opinion of the theme:**

This is an excellent theme group that is highly synergic with the overall unit's strategy and is likely to gain in importance in the near future. It is ideally placed in the retirement belt of France to make best use of the growing elderly population, who may be amenable in the future to large scale interventions and attempts to reduce the load of cognitive impairment on the health service in a systematic and rational way. Such interventional studies are being actively prepared by the group's work.

- **Strengths and opportunities:**

The theme group has the critical mass and specialist expertise to make a substantial and international contribution to the epidemiological analysis of cognitive impairment. With access to the Three-City Study, as well as other national and international data sets, such as Whitehall II, Gazel, E3N, CONSTANCES, and the Nurses' Health Study the group has made important contributions to the epidemiology of dementia and depression, with special regard to gender, occupation, diet, metabolic syndrome, adverse life events, modulation by 5- HTTLPR genotype and the chronic effect of solvent exposure. The group has further made a useful contribution to the study of

genetics of dementia and dementia treatment trials as collaborators.The overarching theme of "Modelling the impact of reversing risk factors for dementia" is of particular translational value, as the researchers move on from listing and relational evaluations of risk factors to an interventionist strategy that, in the absence of quick solutions to the treatment of dementia, is likely to be crucial to national health. In addition, the group makes a fulsome contribution to mechanistic research, covering the important fields of neuropsychology, neuroimaging and blood-biomarkers.

- **Weaknesses and threats:**

The quality of such epidemiological research will depend on the availability of new good quality data. The group have been excellent at networking and utilising national and international data sets, but the continued provision of new high quality data will be essential for its success. In particular, the feed-back from the group into new cohort studies would generate added value by generating data useful for analysis. In terms of international competition, new epidemiological studies with an imaging component, using cutting edge methods (Connectome, structural and functional connectivity) would benefit from the epidemiological expertise of the group. The imaging project (conventional and functional MRI) is a wide project which requires a strong collaboration with an imaging team experienced in methodology and post processing analysis.

- **Recommendations:**

The broad approach including 'resilience' and frequently allied conditions, such as depression in old age, are promising and should be pursued in the future.

A painstaking epidemiological strategy with careful evaluation of naturalistic studies, 'natural experiments' (as in the 'pieds noirs' study) and mass interventions (e.g. by change of diets) is the correct way to advance this topic further and should continue into the future.

Theme 3 should as such be preserved with high priority as an integral part of the unit.

Theme 4: Sleep pathologies

Manager's name: Mr Yves DAUVILLIERS

Workforce

Theme workforce in Full Time Equivalents	As at 30/06/2013	As at 01/01/2015
FTE for permanent professors	0,30	0,30
FTE for permanent EPST or EPIC researchers		
FTE of other permanent staff without research duties (IR, IE, PRAG, etc.)	0,50	0,50
FTE for other professors (PREM, ECC, etc.)		
FTE for postdoctoral students having spent at least 12 months in the unit		
FTE for other EPST or EPIC researchers (DREM, etc.) excluding postdoctoral students		
FTE for other contractual staff without research duties	1,50	1,50
FTE for doctoral students	1	
TOTAL	**3,30**	**2,30**

• Detailed assessments

Assessment of scientific quality and outputs

The leader of the Sleep theme is a very well-known researcher working in the field of neurology and sleep disorders. His work continues that of its predecessors, who made of Montpellier hospital one of the world most renowned sleep clinics.

The group continued to develop top clinical expertise in the Montpellier hospital and significantly increased the number of patients followed by the Gui de Chauliac Sleep Clinic. The center for rare diseases was created in 2007 and coordinates several major sleep centers in Paris and Lyon has a large cohort of hypersomniac patients. In the last 4 years the center received the cerebrospinal fluid samples from narcoleptics and hypersomniac patients from most of the French sleep centers to analyse their orexin levels

The group has demonstrated the association between excessive daytime sleepiness, hypersomnia and health risks (cardiovascular diseases, dementia an depression). This association underline the importance of orexine deficiency in the most severe causes of hypersomnias.

The theme 4 represents one of the best national and European scientific projects on sleep research, it is even surprising to see (according to the size of the group) the very high scientific production of the theme.

The team has a published 102 papers in the last 5 years (2008-2013) with excellent impact factors especailly in Nature genetics (IF 35), Archives of general psychiatry (IF 12), and in neurological journals like annals of neurology, brain, neurology. It as also a strong publication line in sleep journals like sleep, journal of sleep research, sleep medicine or sleep medicine reviews.(IF 3 TO 11.2)

Assessment of the theme's academic reputation and appeal

The group collaborates with top international teams in Lausanne or in Stanford. A very strong effort is made to initiate more work with other national teams in many fields (psychiatry (Attention Deficit Hyperactivity Disorders), obstructive sleep apnea syndrome.

Assessment of the theme's interaction with the social, economic and cultural environment

Promising results in the field of public health (vaccine and aging) have been obtained.

Potential new therapeutics are investigated with a pharmaceuticla company.

There is a good communication on sleep disorders and rare diseases at national level.

There are strong links with many pharmaceutical companies.

There is a limited amount of patents but promising expected results in the field of diagnosis and phenotyping techniques.

Assessment of the theme's organisation and life

The subtheme is mainly centralized on its activities in the sleep clinic of Gui de Chauliac. It interacts in a translational way with the epidemiological groups and it benefits of all the methodological expertise (i.e. statistical analysis) of the unit.

Assessment of the theme's involvement in training through research

The subtheme leader is responsible of the training program of the French sleep research society (DIU veille sommeil). The sleep clinic host students coming for the training of the DIU. In addition fellows working in the clinic do their Phd in the unit to reinforce the translational approach of the project.

Assessment of the five-year plan and strategy

After focusing for many years on narcolepsy, the sleep theme now opens more to excessive daytime sleepiness at large and comorbidities with aging and psychiatric disorders. This approach based on comorbidities of hypersomnia but also collaborative work with epidemiological teams form the INSERM unit make the project very original and promising.

The "sleep" theme does not present as many links with the other themes that one could expect (e.g. no clear links with the PTSD project). Up to now, if the reputation of the U 1061 is very clear in the field of mood and neurodegenerative disorders, the place of sleep was not perceived as promising as it could be.

Conclusion

- **Overall opinion of the theme:**

This project focuses on ageing-related sleep problems within population-based cohorts and on sleep pathologies, notably hypersomnia, using clinical cohorts.

The program on sleep and ageing aims to determine the mechanisms involved in the relationship between sleep disturbances and comorbid disorders.

The study on sleep disorders will investigate the weight of environmental risk factors including vaccine & infection exposures.

This original approach will help to understand mechanisms underlying hypersomnia, sleep fragmentation disorders and to identify novel therapies.

- **Strengths and opportunities:**

- national and international networks;

- grants and platforms;

- cohorts available.

- **Weaknesses and threats:**

The project is alsmost too ambitious considering the few permanent researchers involved and possibly all objectives will not be achieved.

- **Recommendations:**

Reinforced collaboration between clinicians and scientists.

Theme 4 is a bit isolated, and most of its research is based on neurology and hypersomnia. Stronger links with mood disorders and dementias could be reinforced, in particular, with a better definition of phenotyping techniques (ex. use of MSLT in cohort and epidemiological studies). There is room for more researchers to join theme 4, as it is one of the smaller among the four themes in the unit. A stronger explanation of interaction between themes and sub teams could help understand the long term strategy of the unit. Phenotyping strategies deserve to be better explained.

5 • Conduct of the visit

Visit date:

Start:	January 21th 2014, at 08.30 am
End:	January 21th 2014, at 05.00 pm

Visit sites:	Unité 1061 INSERM
Institution:	Hopital la Colombière
Address:	39 avenue Charles Flahaut, Montpellier

Programme of visit:

08.30 am	Welcome to the experts committee
08.45 am	Preliminary meeting of the experts committee (closed hearing)
09.15 am	Presentation of AERES evaluation and of expert committee members
09:25 am	Presentation of the unit project (time includes questions and discussion, nearly half of the time)
10.55 am	Break
11.10 am	Meeting with researchers
11.40 am	Meeting with technicians and meeting with doctoral students and post doctoral fellows
12.10 pm	Meeting with a representative of the graduate school
12.25 pm	Lunch buffet/discussion
01.30 pm	Meeting with representatives of institutions
02.00 pm	Meeting with the unit director
02.30 pm	Deliberation of the experts committee (closed hearing)

6 • Supervising bodies' general comments

Université Montpellier 1

nouvelle université de Montpellier
un projet, une ambition

Monsieur Didier HOUSSIN
Président de l'AERES
Monsieur Pierre GLAUDES
Directeur de la section des unités de recherche
Agence d'Evaluation de la Recherche et de l'Enseignement Supérieur (AERES)
20, rue Vivienne
75002 PARIS

Montpellier, le 31 mars 2014

Référence : K. RITCHIE : S2PUR150008525 Neuropsychiatrie : recherche épidémiologique et clinique. 0342321N

Messieurs,

Je tiens à remercier le comité de visite AERES pour la qualité de son rapport d'évaluation concernant l'unité de recherche « *Neuropsychiatrie : recherche épidémiologique et clinique* » dirigée par Madame Karen RITCHIE.

J'ai bien noté les remarques formulées par le comité de visite et je veillerai à ce que celles-ci soient prises en compte par la directrice de cette structure de recherche.

Vous trouverez ci-joint les corrections factuelles et les observations générales formulées par la directrice.

En tant que tutelle Universitaire de cette structure de recherche, je n'ai pas de remarques supplémentaires.

Je vous prie d'agréer, Messieurs, l'expression de mes salutations les plus respectueuses.

Philippe Augé
Président
Université Montpellier 1

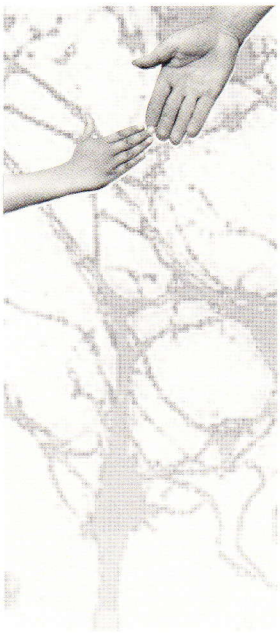
U 1061 Neuropsychiatrie : Recherche épidémiologique et clinique

Directeur : Pr Karen RITCHIE

Instituts thématiques

Inserm

Institut national de la santé et de la recherche médicale



AERES Evaluation – NEUROPSYCHIATRY: EPIDEMIOLOGICAL AND CLINICAL RESEARCH

The report submitted by the AERES expert committee members was received from the University of Montpellier 1 on March 12, 2014 and examined by the unit's Scientific Council on March 18. The report was considered overall to fairly reflect the activities, strengths and weaknesses of the unit and we therefore have no significant disagreement with its contents.

We would, however, like to add some further information not covered during the visit, which may help in the understanding of some of our current needs and limitations. The time-table, which was decided by the president of the committee, only allowed us one and a half hours to cover the overall scientific and administrative situation of the unit (50 members) and the presentation of four thematic groups each with numerous large national and international projects, and a technical platform. The result is that much was omitted although covered in our evaluation report. We would also like to correct some minor omissions/errors in the report.

1. **The committee suggested the creation of a CRB**. A CRB is being certified by the CHU of Montpellier and currently has provisional status. Anne-Marie Dupuy (co-leader of Theme 1) has been responsible since 2006-7 for the Biological Liquids Section of the Montpellier Hospitals, as well as being responsible for ministerial declarations and participating as an associate director of the Scientific Advisory Board of the Technical Committee.

2. **It is recommended that the unit gain access to younger cohorts for studies of cognition; notably with imaging data**. While not only already having privileged access to the younger Gazel and Whitehall data banks, a member of the unit (C Berr, Theme 3) has actively participated in the development of the Constances Cohort (18-70 years), and K Ritchie (Theme 1) is on the Scientific Advisory Board of the U.K. 1946 Cohort (a cohort followed from *in utero* development since 1946) with free access to this unique platform. Both these data banks include imagery. Additionally in collaboration with Imperial College London we have recently begun the first mid-life clinical and biomarker study (including both PET and MRI imaging) of Alzheimer's Disease starting at age 49. http://www.prevent-dementia.org/

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U 1061 Neuropsychiatrie :
Recherche épidémiologique
et clinique

Directeur : Pr Karen RITCHIE

Instituts thématiques

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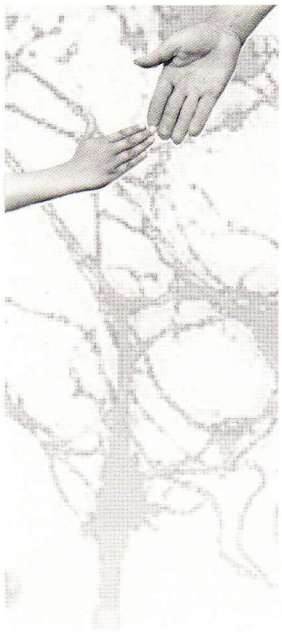
Institut national
de la santé et de la recherche médicale



3. **Assessment of the Unit's Academic Reputation**. Mention is made of our collaboration with the Universities of Melbourne (co-tutelle of PhDs) and Standford, but not more importantly of our European Associated Laboratory (Inserm-King's College, London) which has now existed for over ten years and has been the source of multiple research projects, a combined summer school and numerous student exchanges including a co-tutelle PhD programme.

4. **In relation to Theme 1 it is noted that this team have published over 100 articles**. The group has actually published over 300 articles (345.

5. **Research into resilience** is mentioned in relation to Theme 3, however, no dedicated work has yet been carried out by this group on resilience; this is the area of expertise of Theme 1 who have not only published in the area but have put in place a national research network on psychotrauma and resilience.

6. **The need to attract geneticists** is mentioned at several points in the document. While several members of our unit do have established international reputations in the area of molecular psychiatry (P. Courtet; A. Malafosse Theme 2) we would of course benefit from further reinforcement. J. Ryan (Theme 1) is a geneticist who completed her PhD on neuropsychiatric disorders in our unit and is currently a post-doctorate at Melbourne University. This collaboration continues with work in the epigenetics of depression in two young cohorts, but as yet we have not secured a permanent position for her.

7. **With regard to the five year plan for Theme 4 (sleep pathologies) it is noted there are no clear links with the PTSD project of Theme 1.** I Chaudieu (Theme 1) has in fact designed a multicentric project with members of the psychotrauma network in collaboration with Theme 4 which has, however, not yet been funded.

Montpellier, March 21st, 2014

Karen RITCHIE, Ph.D.
Head, Unit 1061

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