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

Research Units Department

AERES report on unit:

Pathophysiology and cognitive pathopsychology of
schizophrenia

INSERM U666

Under the supervision of the following
institutions and research bodies:

INSERM

Université de Strasbourg

February 2012



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

Research Units Department

President of AERES

Didier Houssin

Research Units Department

Department Head

Pierre Glaudes



Unit

Name of unit:	Pathophysiology and cognitive pathopsychology of schizophrenia
Acronym of unit:	
Label requested:	INSERM/UDS (University of Strasbourg)
Present no.:	INSERM U666
Name of Director (2009-2012):	Mr Jean Marie DANION
Name of project leader (2013-2017):	Ms Anne GIERSCH

Members of the committee of experts

Chair:	Mr Philippe COURTET, Montpellier
Experts:	Mr Paul ALLEN, London, UK Mr Jean-François DEMONET, Lausanne, Switzerland (INSERM CSS representative) Mr Jean Louis GUILLOU, Bordeaux (CNU representative) Mr Tilo KIRCHER, Marburg, Germany Mr Pierre THOMAS, Lille Mr Peter UHLHAAS, Frankfurt, Germany

Representatives present during the visit

Scientific Delegate representing AERES:

Mr Christian GIAUME

Representatives of the unit's supervising institutions and bodies:

Ms Catherine LABBE-JULIE, INSERM

Mr Bernard POULAIN, CNRS

Mr Eric WESTHOF, University of Strasbourg



Report

1 • Introduction

Date and conduct of visit:

The on-site visit lasted one day on February 16, 2012. It started at 9 a.m. and ended the same day at 5:30 p.m. In the morning, committee members listened and questioned the head of the laboratory. Then, the committee members listened and questioned the researcher in charge of the theme “Autobiographical memory and the self” and, later, the researcher in charge of the theme “Organization of events in time” and then on “Deep Brain Stimulation in animal models”. After lunch, the committee members and the AERES representative had a closed-door meeting with the “tutelles” representatives (Mrs G EILLER of university of Strasbourg, faculty of medicine and INSERM). This was followed by a short presentation by two young post-doc researchers. Then, the committee members separated in three groups. The first group met PhD students and postdoctoral fellows, the second with engineers, technicians and administrative assistants, and the third one with researchers having a permanent position.

There was a closed door final meeting (2 hours) with the committee members and AERES representative to gather the final opinion of the reviewers on the different criteria of evaluation as mentioned by the AERES report document. During this closed door meeting the committee has interviewed the director of the unit on specific points in relation with the presentations of the day.

History and geographical location of the unit, and overall description of its field and activities:

The actual proposal is a continuation of the laboratory initially headed by JM DANION who has been a pioneer in cognitive research in schizophrenia, particularly in France and this unit is one of the few research units dedicated to Psychiatry in France. The team has a recognized expertise regarding cognitions and schizophrenia. Since 1994, the team headed by JM DANION, has been able to explain the mechanisms of the cognitive disorders observed in schizophrenia, and to identify two series of cognitive disorders that help to characterize schizophrenia better: an abnormal segmentation of events in time, and abnormalities in the organization of recollections in autobiographical memory. The research unit is completely integrated into the activities of the psychiatric academic department of the University of Strasbourg and the Academic Hospital (CHU). Specifically the unit is located in the CHU, in the same building as the clinical departments and close to the brain imaging facilities. The laboratory for animal research is located in the faculty of medicine (5 minutes by foot from the clinical department). The translational research program associates clinical studies aiming to provide new tools for cognitive remediation, which would be tested more widely and implemented within a national network of “expert centres” (FondaMental Foundation), and animal studies developed from an innovative proof of concept model for the interest of deep brain stimulation.

Management team:

This project is headed by A. GIERSCH who has a good visibility in the field of schizophrenia. A. GIERSCH is psychiatrist and INSERM Research Director (DR2 since 1st december 2011). A. GIERSCH will be the director of the Unit for the next five years. The project unit will be a single theme Unit with different research axis centred on Cognitive Neuropsychology and Pathophysiology of Schizophrenia with the following sub-projects: 1)) Autobiographical memory and the self by Jean-Marie DANION, in collaboration with two new members of the laboratory for neuropsychology and brain imaging aspects, and in collaboration with other colleagues for implementing cognitive remediation ; 2) Organization of events in time by the director, supervising also the Cross-cutting project “time- autobiographical memory“ ; and 3) Deep Brain Stimulation in animal models.



Unit workforce:

Workforce	Number on 06/30/2011	Number on 01/01/2013	2013-2017 Number of producers **
N1: Professors or assistant professors	7	4	4
N2: EPST or EPIC researchers	5	4	4
N3: Other professors and researchers	1	4	4
N4: Engineers, technicians and administrative staff *on a permanent position	6	4	
N5: Engineers, technicians and administrative staff * on a non-permanent position			
N6: Postdoctoral students having spent at least 12 months in the unit	4		
N7: Doctoral students	11		
N8: PhD defended	12		
N9: Number of Habilitations to Direct Research (HDR) defended	1		
N10: People habilitated to direct research or similar	12	8	
TOTAL N1 to N7	34	16	12

* If different, indicate corresponding FTEs in brackets.

** Number of producers in the 2008-2011 period who will be present in 2013-2017



2 • Assessment of the unit

Overall opinion on the unit:

The Committee considered that the research objectives are important. The major challenge faced by clinicians in treating schizophrenic patients justify that there is a need to explore new therapeutic avenues, including cognitive remediation and innovative neurobiological therapeutics with the help of animal models. Improving the knowledge of the cognitive dysfunctions targeted by the group can help to provide tools of cognitive remediation particularly important for the clinical management of patients with schizophrenia. Of note, the original approach in remediation may have a high impact in clinical transfer as it is targeted and tailor-made to suit individual needs. It was recognized that the current scientific approach is highly original. Indeed, after having extensively studied the deficits in autobiographical memory, the current projects focus on the perception of time and the integration of the two themes is very innovative. The strategies implemented are relevant and appropriate to research issues. The animal research that have been accomplished during the last years offers the opportunity to test hypotheses complementary to clinical areas.

Strengths and opportunities:

The unit has a significant reputation in this field based on nearly 20 years of scientific works of good quality. The future direction of the unit with a new director and the arrival of new researchers specialized in neuropsychology and mood disorders can lead to be optimistic about the new project.

It should be emphasized that the full integration of the research unit into a specialized clinic in the field of schizophrenia is an advantage force, as it allows constant exchanges between clinicians and researchers, both in the cognitive field and in animal research. In addition, membership of the unit and the clinical care unit into the network and Fundamental Foundation is an asset to consider the implementation and impact of projects to clinical practice.

The axis concerning animal research represent another strength of the unit. Indeed, the two researchers involved in these specific domains have strong expertise in the physiology of the cortico-thalamo-cortical system and psychopharmacological techniques; their proposal of an original neuro-developmental model has interesting potentialities. The animal project constitutes an important aspect of the future project, in order to test the role of abnormalities in functional networks that may play a causal role in cognitive disorders in patients with schizophrenia.

Thus, the project of translational research that would contribute to an integrated pathophysiological model and the development of truly innovative treatments should be encouraged, considering the unmet needs in the treatment of schizophrenia.

Weaknesses and risks:

The research project for the future unit is very ambitious, considering its multiple axes, clinical, animal, and translational, and requires full integration and even more of the various researchers around the same central working hypothesis. The risk is that each researcher continues to develop a very specific axis independently, which would not generate the expected benefits of the desired synergy.

Brain imaging is an important element of the project. Also, relationships with the imaging platform that does not belong directly to the unit is an important issue that should be carefully addressed by both the director of the unit, the manager of the imaging platform and the supervising institutions. Facilitated access of the unit staff to imaging facilities should be preserved to warrant feasibility of the corresponding projects. Supervising institutions clearly expressed their commitment to this aim on the day of the visit. It is essential that they meet this commitment.

Recommendations:

Access to MRI facilities needs to be strengthened. This is of particular importance with regards to remediation and may have a high impact in clinical transfer being targeted and tailor-made to suit individual needs. This is because MRI may be able to establish biomarkers that predict treatment response on an individual basis. If this could be done, it would be highly innovative world class research.

The PHD students did express a desire for better communication between research groups (perhaps in the form of more or better organised lab meetings). There was a feeling amongst students that they did not know much about each others research.



3 • Detailed assessments

Assessment of scientific quality and production:

The scientific production during the four past years is about 150 scientific papers, 22 (15%) in journals whose impact factor is between 4 and 5, and 28 (19%) in journals whose impact factor is above 5. This publications track illustrates the pioneer position of the team in the field and also the quality of animal studies. The researchers involved in the team are well known in this field and considered as references at the international level. They regularly give invited talks.

On the qualitative level, the research carried out is original, risky and its objectives are relevant. The major challenge faced by clinicians in treating schizophrenic patients justify that there is a need to explore novel therapeutic avenues, including cognitive remediation and innovative neurobiological therapeutics with the help of animal models. Improving the knowledge of the cognitive dysfunctions targeted by the group can help to provide tools of cognitive remediation particularly important for the clinical management of patients with schizophrenia. Of note, the original approach in remediation may have a high impact in clinical practice as it is targeted and tailor-made to suit individual needs. It was recognized that the current scientific approach is highly original. Indeed, after having extensively studied the deficits in autobiographical memory, the current projects focus on the perception of time and the integration of the two themes is very innovative. The strategies implemented are relevant and appropriate to research issues. The animal research that has been accomplished during the last years offers the opportunity to test hypotheses complementary to clinical areas.

In addition to activity valorisation as publications, the laboratory created different experimental paradigms with innovative stimuli and designs, with known programming languages and softwares. They allow one to explore visual organization, time perception and memory and have been shared with other laboratories and clinical centers. In the same way, the team created material for remediation, to be shared with other psychiatry centers.

Assessment of the unit's integration into its environment:

The integration of the unit in the environment was considered remarkable. Indeed, it is important that the research unit is located at the interface of clinical services, allowing access to patients for clinical studies. In addition, participation in the national network of Fundamental Foundation allows to test the research hypotheses and more broadly to offer the benefit to the network's members of the expected technological advances in the domain of cognitive remediation. The unit is part of the Strasbourg Federative Institute of Neuroscience Research, an umbrella institute for neuroscience research laboratories and is a member of the Neuro-ex network, a tri-national structure grouping together neuroscience laboratories in Basel, Freiburg and Strasbourg.

It should be emphasized that all the professors of adult psychiatry at the University are involved in this unit.

There are constant interactions between the research team and the university department and similar interactions have been institutionalized with the expert center. The reinforced dialogue between clinician-researchers and animal researchers is particularly relevant in order to facilitate the integration of the translational project. Access to technical support in neuroimaging (3T fMRI, Imaging team LINC-UMR CNRS-ULP 7191) is facilitated and is encouraged by the institutional authorities. As fMRI studies represent an important goal of the project of the unit, this aspect needs to be actively supported by the university and the hospital. The unit participates in scientific events in the community and has a role in the dissemination of scientific themes that deserve to be better known by the public. Finally, the former director of the unit is leading the clinical research of the CHU of Strasbourg.

Assessment of the research unit's reputation and drawing power:

The director of the unit has a good track of publications and communications (including 5 publications with an IF>8 in first or last names since 2009), and has been awarded several times by French institutions. She is the coordinator of several multicentric projects funded at the French or European levels.

The team includes researchers and academics of Psychiatry. It integrates recognized specialists of cognition in schizophrenia, researchers who developed an original model of animal research, and clinicians belonging to a national network allowing to implement innovative tools in cognitive remediation in clinical cohorts. The team has been able to develop international collaborations as well as building up an original contribution in the scientific community in this field of research.

Note also the attractiveness of the unit that should see the arrival of new researchers allowing new ambitious projects to develop.



The reputation of the unit's members in the field of both cognition and schizophrenia and animal models is well established. They are regularly invited to communicate in international events (50 invited talks in the last four years). The recognition of the group's expertise in the areas of cognition in schizophrenia has allowed its members to develop collaborations with several internationally recognized teams, being involved in a European network (COST TimeLy) and organizing specialized scientific meetings of high quality.

The integration of the unit in a local, national and international network gives access to technical platforms and the necessary methodological and theoretical expertise (through the European network COST TimeLy). Also, the team has received several fundings from national and European highly competitive calls. High level academic researchers are joining the lab for the next four years, bringing important skills in clinical and imaging research, which will be major assets for project success.

The unit demonstrated during the last years its capacity to recruit postdocs and high-level students, in particular from abroad. PhD students or postdoc who stayed at the laboratories now occupy academic or scientific positions. The forthcoming organization of the unit makes a place to a large number (10) of PhD students and the "cross-cutting project" interfacing the two main clinical axes (time- autobiographical memory) will be driven by a postdoc who joined the team in October 2011.

Assessment of the unit's governance and life:

From the on-site visit, the Committee noted the consistency of the project from the research community of the unit, and that the laboratory project has been developed collectively, and each researcher has drawn up his/her own research program in line with the overall project, taking account of the human and financial resources available.

The lab is well structured for decision making through meetings between the director and theme leaders and downstream all members of the lab including engineers and technicians. Scientific meetings are also organized to promote scientific exchanges within the laboratory. The visiting committee has acknowledged the existence of good relationship and conviviality between team members, which creates an environment that fosters exchange of scientific views that can help develop new projects. This is the case for projects potentially synergistic clinical study groups, those between it and the group remediation, and with the group of animal studies.

Team members are involved in local educational/teaching and European activities. Moreover they sit in different master committees and decision-making boards of the university / Hospital.

Assessment of the strategy and 5-year project:

The cognitive neuropsychology approach, which consists in identifying which cognitive processes are disturbed and understanding the mechanisms underlying these disturbances with reference to explicit and detailed theoretical cognition models is very original. Indeed, this strategy differs from the traditional approach based on the use of neuropsychological batteries. This gives to the team a pioneering role in the field and is likely to propose several innovative pathophysiological hypotheses.

Original project based on new techniques like the SenseCam remediation technique are also to be encouraged. Such techniques will make it easier to explore interactions between the organization of information in perception and memory. The nature of the laboratory team, with its specialists in both fields, perception and memory, makes it in an ideal position to develop such new methods.

Financially, the laboratory activities are planned to be covered by INSERM credits, as well as external funding sources (ANR 2010).

The project submitted by the unit for years to come lies in the continuity of the work achieved so far in the field of autobiographical memory (an important pillar in the history of the unit), and in the field the perception of time developed by the director in recent years. The team now proposes to test hypotheses in an integrative manner. The translational project presents an important added value where the development of innovative animal models should offer original perspectives on the molecular neuroanatomy of the processes at work in these cognitive dysfunctions.

The committee deemed that both the research hypotheses and the strategies employed, supported by the results obtained by the group were very original. However, the pursued synergy should be more focused to provide a working hypothesis even clearer, suggesting an even more promising benefit expected from this work.



Assessment of the unit's involvement in training:

Research training is strongly present within the laboratory, in the form of student supervision from the last degree year to the post-doctoral fellowship. Eight permanent researchers are accredited to supervise research (maximal rate is 4 PhD students per accredited researcher), 12 PhD have been completed between 2007 and 2011, 3 post-doctoral students made a stay in the lab, and all now occupy a scientific or hospital position.

The members of the laboratory are largely involved in teaching activities, in psychology, life sciences and psychiatry. More precisely, the laboratory is involved in several masters organized within the Strasbourg university's life and health doctoral school (Integrated and Cellular Neurosciences, Neurosciences and Cognitive Psychology, Cognitive and Clinical Neuropsychology, Sciences of the Drug), in a joint master in neurosciences with the universities of Basel and Freiburg, in the biological imaging masters (doctoral school of mathematics, information and engineering sciences).

All people met during the on site visit recognized that they have the opportunity to attend trainings as needed.



4 • Grading

Once the visits for the 2011-2012 evaluation campaign had been completed, the chairpersons of the expert committees, who met per disciplinary group, proceeded to attribute a score to the research units in their group (and, when necessary, for these units' in-house teams).

This score (A+, A, B, C) concerned each of the four criteria defined by the AERES and was given along with an overall assessment.

With respect to this score, the research unit concerned by this report (and, when necessary, its in-house teams) received the overall assessment and the following grades:

Overall assessment of the unit [Pathophysiology and cognitive pathopsychology of schizophrenia]:

Unité dont la production, le rayonnement, l'organisation, l'animation et le projet sont très bons.

Grading table:

C1	C2	C3	C4
Scientific quality and production.	Reputation and drawing power, integration into the environment.	Laboratory life and governance.	Strategy and scientific project.
A	A	A	A



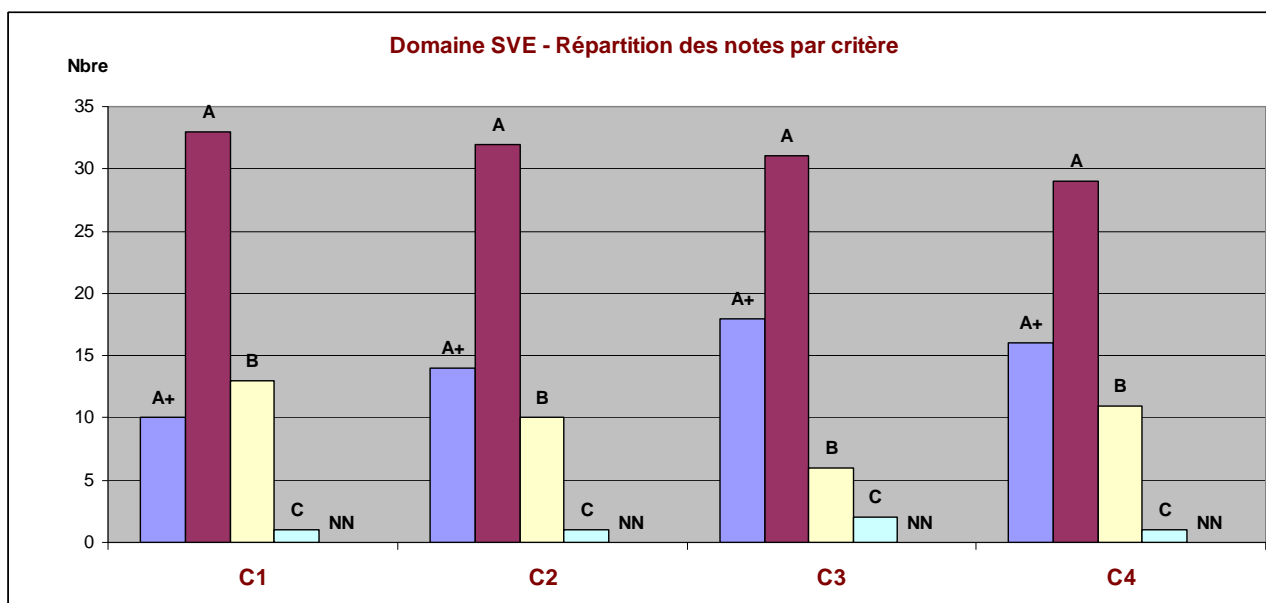
5 • Statistics per field : SVE au 10/05/2012

Notes

Critères	C1	C2	C3	C4
	Scientific quality and production	Reputation and drawing power, integration into the environment	Laboratory life and governance	Strategy and scientific project
A+	10	14	18	16
A	33	32	31	29
B	13	10	6	11
C	1	1	2	1
Non noté	-	-	-	-

Pourcentages

Critères	C1	C2	C3	C4
	Scientific quality and production	Reputation and drawing power, integration into the environment	Laboratory life and governance	Strategy and scientific project
A+	18%	25%	32%	28%
A	58%	56%	54%	51%
B	23%	18%	11%	19%
C	2%	2%	4%	2%
Non noté	-	-	-	-





6 • Supervising bodies' general comments

Monsieur Pierre GLAUDES
Directeur de la Section des Unités de recherche
Agence d'évaluation de la recherche et de
l'enseignement supérieur (AERES)
20 rue Vivienne
75002 PARIS

Alain BERETZ
Président

Strasbourg, le 15 mai 2012

Objet : Rapport d'évaluation de l'UMR_S 666 Neuropsychologie cognitive et physiopathologie de la schizophrénie (réf. S2PUR130004589-RT)
Réf. : AB/EW/N° 2012-245

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Direction de la recherche

Cher collègue,

Je vous remercie pour l'évaluation de l'unité mixte de recherche « Neuropsychologie cognitive et physiopathologie de la schizophrénie » (UMR_S 666 Université de Strasbourg et INSERM) dirigée par Monsieur Jean-Marie Danion, puis par Madame Anne Giersch à compter du 1^{er} janvier 2013.

Vous trouverez ci-joint les réponses du porteur du projet d'unité de recherche concernant les erreurs factuelles et les remarques et appréciations du comité d'experts.

Je n'ai pas de remarque particulière à ajouter au nom de l'Université.

Je vous prie d'agréer, Cher Collègue, l'expression de mes sentiments distingués.


Alain BERETZ

P.J. :

- Une première partie corrigeant les erreurs factuelles
- Une seconde partie comprenant les observations de portée générale.



Strasbourg, 23 avril 2012

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We would like to thank the AERES committee for the quality of their report. We are especially grateful for the interest of the reviewers for our project. The description of our activities is accurate and the commentaries are to the point, and will help us fulfilling our project successfully.

Response to the paragraphs 'weaknesses and risks' and 'recommendations' (page 5)

The committee wrote that 'the risk is that each researcher continues to develop a very specific axis independently, which would not generate the expected benefits of the desired synergy' (page 5, paragraph weakness and risks).

It is also noted that 'the PhD students did express desire for better communication between research groups (perhaps in the form of more or better organised lab meetings)'.

As emphasized by the report, our project is translational, and is indeed based on a multidisciplinary expertise (memory, perception and animal models). The committee additionally noted the 'consistency of the project', that 'has been developed collectively' (page 7, paragraph assessment of the unit's governance). The multidisciplinary approach of the project necessarily entails the risk of research divergence, and we agree with the concern of the committee. The project's leader will make sure that the coherence of project is maintained over the years. This follows the recommendations and politics of the University of Strasbourg.

First, the coherence of the project will be reinforced by the already existing projects cutting across researchers' expertise. Second, we will make use of the attractiveness of the unit (emphasized in the paragraph 'assessment of the research unit's reputation and drawing power' page 6) to recruit new researchers and technicians to reinforce our research project.

Third, even if scientific meetings are already organized to promote scientific exchange (page 7 paragraph 'assessment of the unit's governance and life'), direct communication between research groups will be further enhanced with an increased rate of internal presentations of current work during the seminars, especially by students, and by the organization of journal clubs between students (this being a students' initiative). This should help both to answer the recommendation of the committee on communication and to strengthen the coherence of the project.

The report emphasizes also the need for a preserved access to imaging facilities and recommends it to be strengthened (paragraph ‘weaknesses and risks’, and ‘recommendations’ page 5). We realize this point is addressed more to the supervising institutions; we share this concern with the committee and we are grateful for emphasizing this important point, which will help us to address the matter, and to strengthen our imaging studies.

Response to the comment of the committee on the strategy (page 7, paragraph ‘assessment of the strategy and 5-year project’, last lines).

The committee wrote:

‘... the research hypotheses and the strategies employed, supported by the results obtained [are] very original. However, the pursued synergy should be more focused to provide a working hypothesis even clearer, suggesting and even more promising benefit expected from work’.

In our project we aim at developing a more integrated model of the pathophysiology of schizophrenia, and to derive proofs of therapeutic concept from this model.

We consider it is unlikely that a pathology as complex as schizophrenia is explained by a unique perturbation, and our working hypothesis is that it is the conjunction of cognitive disorders that accounts for clinical symptoms. We explore how autobiographical memory and time disorders jointly contribute to the emergence of symptoms like delusions of control. We thus reconcile two conceptions of the pathology that are usually opposed (elementary vs. high-level cognitive disorders).

Therapeutics concepts are elaborated to target both types of disorders. We develop original cognitive remediation methods to address memory disorders. To target more elementary deficits, we develop proofs of therapeutic concept regarding deep brain stimulation in animal. Our long-term goal is to target the disorders evidenced in our laboratory in human, i.e. abnormalities in the organization of events in time, that can be reproduced in animal models.

Dr Anne Giersch