INT - Institut des neurosciences de la Timone

Rapport Hcéres

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

Section des Unités de recherche

AERES report on the research unit

Institut de Neurosciences de la Timone (INT)

From the

Université Aix-Marseille 2

CNRS

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Le Président de l'AERES

Didier Houssin

Section des unités de recherche

Le Directeur

Pierre Glorieux

February 2011

Research Unit

Name of the research unit: Institut de Neurosciences de la Timone (INT)

Requested label: UMR CNRS

N° in the case of renewal: Creation

Name of the director: Mr. Guillaume MASSON

Members of the review committee

Committee chairman:

Mr. Philippe VERNIER, CNRS, Gif-sur-Yvette, France

Other committee members:

Mr. Pascal BELIN, University of Glasgow, Glasgow, UK

Mrs. Caterina BENDOTTI, Inst. Mario Negri, Milan, Italy

Mr. Jean-Marie CABELGUEN, University of Bordeaux, France (CNU)

Mr. Abdel El MANIRA, Karolinska Inst., Stockholm, Sweden

Mr. Martin GIURFA, University Paul Sabatier Toulouse, France (CoNRS)

Mr. Michael GOLDBERG, University of Columbia, New York, USA

Mrs. Linda GREENSMITH, University College London, UK

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Mr. Klaus-Peter LESCH, University of Würzburg, Germany

Mr. Dai STEPHENS, University of Sussex, Brighton, UK

Observers

AERES scientific advisor:

Mr. Bruno BONTEMPI

University, School and Research Organization representatives

Mr. Bernard POULAIN, CNRS

Mr. Jean-Louis MEGE, Faculty of Medicine of Marseille

Mr. Younis HERMES, CNRS

Mrs. Hélène OTZENBERGER, CNRS, ITA representative

Report

1 • Introduction

- Date and execution of the visit

The site visit took place the 14-15 February 2011 at the INT (Institute of Neuroscience de la Timone) building, in Marseille. The candidate Director presented the principles guiding the creation of the new research Unit, its general organization and the research policy, in the presence of all the members of the Unit. Then, the committee listened to 20-30 min presentations by each candidate group leader, followed by 20-25 min questions. These evaluations of the teams were conducted in the presence of the members of each team. The committee had the opportunity to discuss with the team members at coffee breaks and lunch time, and to visit the future building, which should house the Unit at the end of 2011, as well as some of the existing technical facilities. Subgroups from the committee had meetings with the students, scientists with permanent positions, and technical staff. The committee had also an exchange with representatives of the CNRS and Université de la Méditerranée (Marseille) to which the INT will be affiliated (CNRS: Bernard Poulain from the INSB Direction, Younis Hermès, representative from the Regional Delegation; Université de la Méditerranée : Jean-Louis Mege, in charge of Research at the Faculty of Medicine).

- History and geographical localization of the research unit, and brief presentation of its field and scientific activities

The INT is scheduled to be created in January 2012 and Guillaume Masson is presented as the future Director. The INT is composed of eight teams (BAUNEZ, BLIN, DERUELLE, DURAND, HAASE, MASSON, and RIEHLE, VINAY) and hosts technical platforms for Information Technologies, Brain Imaging and Animal Facilities. The teams forming the new Institute derive from five former structures located in Marseille or Nice. It represents a major outcome of the remodelling of the Neuroscience research Institutes in Marseille, a result of 8 years of reorganization. A strong voluntary impetus led to the proposal of the creation of the INT. The teams of the Institute have chosen not to be divided into departments to facilitate integration and interactions between the research teams. The research axes encompass a rather large spectrum including motoneuron diseases, locomotion and motor control, integrative approaches of visual perception, neurophysiology of reward and addiction, and finally cognitive disorders in human and animal models. The coherence of this broad organization is provided by overlapping research themes and collaborations between groups, as well as the use of common technologies and animal models, both the use of primates as prominent experimental models and a trend towards a system level of analysis of cell processes and brain functions

Currently, most of the INT teams are located on the Joseph AIGUIER Campus, in the south of Marseille, but they will all join a new building on the campus of the La Timone Hospital, the largest neurological hospital in the Marseille area. Strong links with clinical services already exist and they should be reinforced by the new project.

- Management team

The new Institute (Research Unit) will be directed by Guillaume Masson. A deputy director, Laurent VINAY, has been appointed for two years only, in order to allow the younger group leader to acquire a necessary experience of laboratory administration. It has been decided that the director could be re-appointed only once. The Institute will comprise 8 teams, each headed by a group leader. Although the research topics covered by these groups are rather widespread, it has been chosen not to make Departments in order to favor a common dynamic since most groups did not work together previously. To decide and carry out the scientific policy of the Institute, the Director will take the opinion and advice of the of the group leaders, without a more formal structure. The INT scientific policy benefits from recommendation from an international Scientific Advisory Board made of highly recognized scientific personalities. The Steering Committee of the Institute, also comprising representatives of the personnel will convene 2-3 times a year to discuss and organize the life of the Unit.

- Staff members

Since the Research Unit is an entirely new structure, past staff is impossible to define and meaningless. Thus, only the newly planned personnel is given below.

N1: Number of researchers with teaching duties (Form 2.1 of the application file)	19
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	29
N3: Number of other researchers including postdoctoral fellows (Forms 2.2, 2.4 and 2.7 of the application file)	15
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	23
N5: Number engineers, technicians and administrative staff without a tenured position (Form 2.6 of the application file)	4
N6: Number of Ph.D. students (Form 2.8 of the application file)	23
N7: Number of staff members with a HDR or a similar grade	27

2 • Overall appreciation on the research unit

- Summary

The INT brings together 8 teams with a strong expertise in a broad range of research topics from cellular neurobiology to integrative and computational neuroscience. It is an entirely new research structure, although it stems primarily from the previous "Institut des Neurosciences Cognitives de la Méditerranée". The INT will be an internationally competitive Institute, made of both strong senior groups and of smaller, generally younger groups, the whole with a great potential of producing original innovative and high-quality science in integrative and cognitive neuroscience. Several core facilities (in particular a Primate facility, and a fMRI Centre) and technical platforms (mechanics, optical imaging, informatics…) is a nice complement to the efficiency of the structure.

- Strenghts and opportunities

The INT provides a high quality scientific environment formed by the combination of groups with a wide range of expertise, in general complementary. There is a clear impetus and a positive dynamics among the group leaders and members to go one step further toward excellence in neuroscience. There is already significant degree of interaction and collaboration and a generally high level of scientific skills and production (see details below).

- The planned development of interface with both the clinicians and theoreticians will be strongly facilitated by the new structure, and this represents an exciting challenge for most of the teams.

- The INT is a unique place for research using primates as models, including neurophysiology, imaging and behaviors, and studies of related cognitive functions. Although the scope of the research topics is very large, grouping these diverse themes in the same location had positive and original impacts on each area of research. Cellular approaches could acquire a functional meaning and cognitive neuroscience integrates lower-level constraints.

- The technical platforms are remarkable (state-of-the art) including, fMRI center, newly established photonics platform, center for mechanics, center for informatics and computing, facilities for housing non human primates and performing surgery, headed by a veterinarian, a real added-value.

- The building of the imaging facility, close the Unit, will be a nice added value for a large part of the proposed projects of the Unit and it will prompt more collaborations with the other local teams working in the field of Integrative Neurosciences.

- The rate of success for grant application, especially from the European Community and the French ANR, has been very good. Most of these grants have been coordinated by ITN group leaders. This has allowed the scientists to perform expensive experiments and to recruit good post-docs and technical staff.

- The opening of the new building is an exciting opportunity and the plans for the space allocation and practical organization are impressively accurate and clever. There will be space available in the new building, which makes possible the recruitment of one or two new teams. This will allow to fill-in some of the gaps between the three main research topics.

- The atmosphere is both studious and friendly, all the researchers and technical staff seem highly dedicated to their work. The INT houses several foreign scientists, including students and postdocs, and English is widely used as a working language. Altogether this will help the Unit to fit with international standards.

- Weaknesses and threats

Overall, the INT project exhibits only few weaknesses.

- The rather large range of topics tackled by the eight research team bears in itself the risk of a too large divergence, which may render, in the long run, the situation of some groups in the Unit somewhat problematic. This is currently not the case, each team being -or tending to be- strongly anchored to others, with meaningful collaboration and clear and real synergies. This should be worked out in the near future, to make the new structure a real Unit.

- The proposal of calls for interacting transversal project among teams is a good idea. It will certainly promote collaboration, a clear necessity in the Institute. However, the current proposals remain a bit vague, without clear plan for their implementation. Although necessary, such transverse projects should also not be developed at the expense of the main projects of the teams.

- The replacement of the 3T Magnetic Resonance Imaging system is still awaited, and this will be crucial for the experiments carried out and for interaction between teams of the INT and clinical service upon which depend several projects of the Unit.

- To be more internationally recognized, the teams of the INT have still too little foreign students and post-docs. The use of English for the internal seminars and presentations should be generalized. Participation to international networks (such as FACETS or IMI) should also be generalized

- The INT is currently a bit short of technical staff, although this latter seems to be highly skilled and motivated. An obvious and clever choice has been made to gather most of the technicians and engineers in the platforms and facilities. However, the absence of technical staff in many groups could make the temporal continuity of techniques and projects difficult sometimes to achieve.

- Recommendations

As this has be well noticed in the written INT Project document, the proposed director seems to be fully aware of the major potential problems and weaknesses of the future institute. For most of them, the following recommendations have already been anticipated and taken into account. Certainly, practical implemantation of these advices could be more difficult than anticipated.

- There is some degree of heterogeneity among the size, history and scientific forces of the research groups. Although diversity can be fruitful, attention should be paid to canalize the evolution of the teams toward a more homogenous ensemble, not so much in term of research topics but in term of scientific quality and dynamics.

- A good balance should be kept between the two main axes, cellular and integrative neuroscience on the one hand, and on the other hand, cognitive neuroscience. Recruitment of new groups should take this into account.

- Attention should be paid to maintain the currently high motivation of the technical staff, by keeping the recruitment at a reasonable level and professionally promoting the personnel.

- Efforts should be devoted to build an image and a reputation of the INT as a whole more visible from abroad. Recruitments of students and post-docs through international training grants (HFSP, EMBO…etc) or specific measures toward this goal are strongly encouraged. Participation to international networks (such as FACETS or IMI) should also be generalized.

- Production results

A1: Number of permanent researchers with teaching duties (recorded in N1) who are active in research	19
A2: Number of permanent researchers without teaching duties (recorded in N2) who are active in research	27
A3: Ratio of members who are active in research among staff members [(A1 + A2)/(N1 + N2)]	0.96
A4: Number of HDR granted during the past 4 years (Form 2.10 of the application file)	7
A5: Number of PhD granted during the past 4 years (Form 2.9 of the application file)	32

3 • Specific comments

- Appreciation on the results

The research carried out by the teams which will constitute the INT falls within well defined but separate research areas: pathophysiological mechanisms of Amyotrophic Lateral Sclerosis (ALS) and Spinal Cord Injury (SCI), neurophysiology of motor control at different levels, visual information processing and integration, neurophysiology of motivations and addiction, other aspects of social cognition and the consequence of stress on emotional control, a major vulnerability factor for several psychiatric diseases. In all these fields, the INT research teams have made significant contributions (see Results team by team below) and they are well known and respected at the international level, although very few of them can be considered as world leaders in their field.

Since the INT is a new structure, there is no past production of the Institute as such. However, from 2006 to December 2010 the groups that will join the INT have been productive since they have published more than 300 original articles and 50 review articles. A reasonable number of papers have been published in high-rank journals (PNAS, Curr). Biol., Nature Med., Lancet, J. Neurosci., etc…), although the vast majority of papers are published in good specialty journals (3<IF<7), with the usual limitation of bibliometry. During the site visit, a few additional manuscripts accepted for publication were presented.

Since 2007, more than 30 master students have joined the future INT groups for short or long training periods, and they have also trained up to 26 students who obtained a PhD, which is above the average in France.

The future Institute will organize its scientific activity around several state-of-the-art methodological platforms and core facilities, which are a real strength and opportunity to conduct high-level and original research. In particular, the Primate core facility, headed by a veterinarian, is instrumental for the several teams investigating higher brain functions and emotional/motivational processes. Access to the fMRI is a great opportunity to support demanding translational approaches and collaboration with clinicians,an absolute necessity for some of the research programs planned by INT groups. Optical imaging platform and related technologies (optogenetics) and informatics implementation will be also enlarged and optimized to include both morphological and functional techniques, another major development for INT. Finally, the arrival of new groups working at the cellular levels will enlarge the pool of available technical approaches such as different kinds of cell cultures, cell sorting, biochemical and molecular methods.

The strong existing link with clinicians must be reinforced, putting the Institute in an ideal situation to develop translational research, a priority highlighted by Research Policy makers from the French national Agencies.

- Appreciation on the impact, the attractiveness of the research unit and of the quality of its links with international, national and local partners

Researchers of the INT have been recognized by prestigious prizes of honors yet, but most of them are still early in their carrier. The senior researchers and team leaders are highly regarded in their fields. Their works are all very well cited and the details will be found in the individual team evaluations.

In contrast to PhD students, the INT groups have not attracted many post-docs (currently only 5 post docs based on available documents), and this is a rather low number that should be improved. They come mostly from France, but also from other countries.

The INT groups have been able to raise about 1 to 1.5 M€ per year of external competitive funding (approx. 10% from various grants, 30% from ANR, and 60% from European Community). This is remarkable, in comparison to the about 300 K€ provided by CNRS (based on previous funding of the different teams) and University de la Méditerranée, of course excluding the salaries for permanent positions.

Most INT groups have stable and active collaborations with laboratories not only in Marseille and other places in France, but also in Europe or overseas (USA, UK, Germany, Switzerland, Spain, Italy...etc). Most group leaders are regularly invited to international conferences, although with significant differences between them.

Link with the local biotech companies are strong for two of the teams and interesting translational therapeutic programs are on the right track.

- Appreciation on the management and life of the research unit

The committee felt that the choice of the candidate director was really sound and wise. Not only the director is an excellent neuroscientist who has made important scientific contributions, but his truly remarkable organizational and managing capacities are attested by the creation and evolution of the INT. He has conducted the local reorganization and restructuration of the teams during the past few years. He has clearly the skills and capacity to head the INT and to conduct its further improvement. The proposed deputy director is also perfectly suited to his task since he is an experienced scientist, and represents the other main research axis of the research topics. His complementarity to the director is obvious and this well-balanced directorship should be conserved in the future. Indeed, it is proposed that the deputy director will change every two years, to allow younger leaders to gain more experience.

The directors will also directly interact with the team leader board, which should have the strongest weight in the strategic decision of the Institute. The resources in terms of workforce and funding will apparently be managed in a concerted way, with collective decisions for the use of CNRS funds, and some common contribution from the the other projects. The other committees will be the necessary Council of the Unit, to discuss with the representative of the personnel the strategic decisions and an Ethic Committee, also an important component of research strategy, given the concern raised world-wide on Primate and mammalien research overall.

Regular (weekly) internal seminars are planned, in addition to invited conferences and other initiative for scientific animation, which seems to be generally excellent. This will be important to maintain since the Institute will gather many teams with no use of working together and at the same place.

Call for collaborative projects have been made (call for ideas), to foster collaboration between teams, and although this proposal is still a bit vague in the written document, this appeared to be a real concern of the directors and of the group leaders during the visit.

INT leaders and staff are involved in many local, regional, national and international collaborations and networks. They are thus strongly connected locally and nationally, most of them internationally also. All the group leaders are members of local scientific and university committees, members of scientific boards of foundations or journals, and regularly contribute to review papers or grants.

- Appreciation on the scientific strategy and the project

The research topics covered by the INT groups are large and diverse in the Neuroscience field. All the teams, although they are working on rather different topics, have converged on common interests with at least one of the other group, putting the range of topics within a continuum rather than juxtaposed research themes. It is possible however to consider some general trends and interests that should be underlined here and should be probably reinforced in the future. It is clear that the INT has very strong expertise in integrated neurosciences, with an interest focused on the dynamics of neural networks. Neuronal pathway and integrated networks of motor, emotional/motivational and visual systems and processes are mostly studied. Finally, most of these approaches tend to be applied to human and non human primates, at some point. The interest for investigating primate nervous system and behaviors and corresponding expertise is of utmost importance for Neuroscience and should be strongly supported by the French Institutions. Integration of physiological investigations with behavioral studies is beneficial and will continue to generate numerous applications useful for various fields.

Similarly, the teams working on motor neurons and motor control have succeeded in nicely mixing in vivo electrophysiology with behavioral analysis, fine anatomical and functional analyses. These kinds of integrations will help interfacing with clinicians and the development of efficient translational research, which is currently more often a wishful thinking than a reality. Implementation of computational and theoretical approaches within several research projects is also going in the right direction to match current challenges in neuroscience.

Overall, there is a good balance between strong and solid projects and ambitious risky ones among the groups making the Institute. It should be emphasized that the efforts to develop high level methodological facilities, at all levels of experimentation, now put the INT at a top level position at the national level.

Nevertheless, the diversity of interests and topics within the Institute requires a specific strategy for the institute as a whole, which has been taken very seriously by the directorial staff. The call for new transversal projects is a good start, although they have to be carefully chosen to avoid impairing the development of the main projects of the teams. The same remarks hold true for the recruitment of new teams, clearly the occasion to tighten up the scientific cohesion and enhance overall research quality in the Institute.

An effort to increase the international visibility of the Institute as a whole should be undertaken, and the clear definition of major research axes and the recruitment of more foreign students, post-docs or researchers will certainly help.

The diversity of technical skills and scientific expertise among the INT members, either researchers or technical staff, is impressive, and together with the excellent organization of the technical platforms and core facilities, it represents a major asset of the Institute on which the future can be further elaborated.

The choice of dedicating most of the technician and engineers to these platforms and core facility is certainly the best strategy at present that should be a strong factor of attraction for future groups. The corresponding scarcity of technical staff in the teams may be a threat on the long run.

As a drawback, there is a general lack of technical support dedicated to individual teams, which may be deleterious to some long-term technically highly demanding projects. For the future, some effort for more balanced distribution of technical personnel between facilities and teams should be discussed. In this respect, the reinforced link with the University de la Méditérranée may be translated in a larger support from this Institution to the INT.

The research unit staff members contribute a lot to teaching, and education and training is a clear priority of the INT. In this respect, it should have a prominent position within the universitary landscape, both from its biological and medical side.

Twenty-four INT scientists have primary University positions either Professors (mostly PU-PH) and assistant professors (MdC or MCU-PH). Most scientists with CNRS or other academic positions are active in teaching, either organizing courses for Master students or participating in Master teaching at Marseille university and at French or foreign universities. The development of a specific PhD program in Integrative, Clinical and Computational Neuroscience is a very good idea that should be strongly encouraged and supported.

4 • Appreciation team by team

Team 1: Motor Neuron Disease Modeling and Therapy (MoMoThe)

Team Leader: M. Georg HAASE

- Staff members

	Past	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)		0
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)		1
N3: Number of other researchers including postdoctoral fellows (Forms 2.2, 2.4 and 2.7 of the application file)		2*
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)		
N5: Number engineers, technicians and administrative staff without a tenured position (Form 2.6 of the application file)		2
N6: Number of Ph.D. students (Form 2.8 of the application file)		1
N7: Number of staff members with a HDR or a similar grade		

*OP: open positions

- Appreciation on the results

The team is a rather small but recently formed one as highlighted by the fact that all publications of the last four years, except one, carry only the name of the team leader among the authors. So the comments can only be related to the activity of the team leader rather than to the other members.

The team leader has an excellent background in the field of neurobiology of motor neurons during development and in pathological conditions. Moreover, the team is focused on developing new technical approaches for neurobiological analyses and this may have a high impact on the integration with other groups of the INT that do not have specific expertise in neurobiology. In fact, some collaboration with other teams has been already planned.

The quality of research evaluated on the basis of the preliminary results presented as well as on the competence and the past productivity of the project leader is of high quality even if is not among the very best groups working on the development and pathology of motor neurons. Since there is another team working on ALS and MND at the INT using complementary approaches, i.e. electrophysiology and morphology of motor neurons (PPM), the research program in this field would gain in quality from the collaborations of the two groups.

The team leader has a significant number of publications made in collaborations with groups from other institutions, which demonstrates his attitude to easily participate to scientific networks and to establish stable partnerships. Most of these publications are in journals with a high impact factor.

- Appreciation on the impact, the attractiveness of the team and of the quality of its links with international, national and local partners

The team leader has a good record for invited talks by international and national institutions. Moreover he has a good ability to raise funds both at national and international level. This may contribute to the attractiveness of the team, which at the moment is difficult to judge in term of quality of members since the group has been formed recently, and it is still growing.

The impact of research activity proposed for the next 4 years will be good especially with regard to the development of new technological approaches for studying the neurobiology of motor neurons in animal models and patients which can provide a valid example of an experimental paradigm exportable to other research projects of other team groups at the INT.

A good impact is expected also from the motor neuron disease modeling as paradigms to study the role of Golgi alterations in the pathogenesis of ALS while the impact in terms of therapeutics development and validation in mouse models is less obvious.

- Appreciation on the scientific strategy and the project

Two major approaches characterize the ongoing research activity of the team:

- One is aimed to investigate the pathological mechanisms associated with motor neuron disorders and to develop new experimental therapies, in particular, the focus is on studying the role of abnormalities in Golgi apparatus (GA) network, in the mechanism of motor neuron dysfunction and/or death induced by some gene mutations associated with familial ALS or in a model of motor neuronopathy induced by recessive mutation in TBCE. Although the hypothesis that GA plays a role in the pathogenesis of ALS is not novel, the research plan proposed here of a systematic comparative study of different experimental paradigms from animals and human is original and sound.

- The other more original and of higher impact in the integrative approach that characterizes this new research institute is the development of innovative technical approaches to obtain specific primary cell cultures from mouse models using the FACS technology, to develop a high throughput screening assay in genetically modified cell lines for the detection of potential therapeutics and to obtain cultured neural cell from iPSC lines of healthy individuals and patients. The latter is considered a cutting edge project, although risky, which may lead to an extremely important step forward in understanding and eventually treating neurodegenerative, neurological and psychiatric disorders. In this perspective, the ongoing integrative approach with other teams of INT is crucial.

- Conclusion

  - Summary

This will be a newly established group at the INT. The specific research project aimed to investigate the pathological mechanisms associated with motor neuron disorders and to develop new experimental therapies. They have found an attractive scientific “niche“by studying the involvement of the GA in the pathophysiological processes. The project will extend to use of iPSC cells to access an experimental material as close as possible to the human situation. This team will certainly cumulate technological experiences in neurobiology paradigms from animal models and human that will be of great value also for other teams.

  - Strengths and opportunities

The project is well focused and it certainly will give relevant information on the Golgi and other organelle related mechanism in the motor neuron death at the end of the 4 years project.

The strategies proposed for the immediate future with respect to motor neuron modeling are quite clearly formulated, and considering that the group is expanding and the team has a good ability to attract funds no major problems are expected in the feasibility of long-term project.

- Weaknesses and threats

Since it is now clear that ALS involves many cell populations and multi-systems, studying only the motor neurons in isolation may hardly end up with effective therapies. Focusing on the GA mostly could appear to be a too narrow window on the multifactorial nature of the disease.

The team is joining a new place where the main technical facilities and scientific environment are a bit different from the current needs of the team.

- Recommendations

More emphasis should be given in validating the results in a more complex in vitro paradigm and in in vivo in animal models, an aspect that seems not highly emphasized in the proposed project.

Despite the difference in background and history, collaborating with the other team (PPM) that deals with the pathophysiology of motor neurons using complementary approaches such as electrophysiology and morphology of the motor neurons in in vivo in animal models of MND could make the results of all these studies of high profile and very competitive in this field.

Team 2: Physiopathology of Motoneurones in mice and humans

Team Leader: M. Jacques DURAND

- Staff members

	Past	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)		2
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)		3
N3: Number of other researchers including postdoctoral fellows (Forms 2.2, 2.4 and 2.7 of the application file)		1
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)		0.5
N5: Number engineers, technicians and administrative staff without a tenured position (Form 2.6 of the application file)		0
N6: Number of Ph.D. students (Form 2.8 of the application file)		2
N7: Number of staff members with a HDR or a similar grade		5

- Appreciation on the results

The work from the group on the morphological and electrophysiological properties of motoneurons in SO1 mice has made a significant impact to the field of ALS and on the understanding of the underlying pathophysiology of ALS. The previous output of the clinical members of this team has been largely of a clinical nature, with no evidence of previous research studies on Post-Polio Syndrome (PPS) patients.

The most significant papers have come from the studies on the properties of SOD1 motoneurons. Over the 5 years period between 2006 and 2010, this work has resulted in 4 good publications in international journals, in particular the 2010 publication in J. Neuroscience. However, overall the research output of the entire team has been modest, with the majority of publications appearing in relatively low impact journals. Indeed, some researchers of the team have a particularly poor publication record with 3 or less publications over a 5 years period.

This relatively modest publication rate may be a reflection of the nature of the some of the work undertaken by this team that is labour intensive and not high throughput. For example the electrophysiological studies on motoneurons are particularly time consuming and technically challenging.

- Appreciation on the impact, the attractiveness of the team and of the quality of its links with international, national and local partners

The team has a modest record in training graduate students with only 4 PhD students supervised since 2008.

Members of the team have attended a good number of international conferences and given a number of presentations and talks. However there is no evidence of participation in international networks or international collaborations. The research team appears to consist of French nationals, so there is no evidence of their ability to attract high-level scientists from abroad.

Only 5 relatively minor grants have been awarded to this group since 2003 and among these, only one with a value of 10K€, was an international grant. The total grant income is only 204K€, indicating that this group has a poor record in obtaining competitive funding for their work.

- Appreciation on the scientific strategy and the project

This research group brings together two previously separated research teams composed of basic scientists in one case and mainly clinicians in the other.

The overall research program focuses on the normal and pathological function of spinal motoneurons. The group has 3 main established areas of expertise i) investigation of morphological and electrophysiological properties of motoneurons in animal models; ii) motor control studies in humans; iii) motor pathology and rehabilitation in humans.

The proposed research program is divided into 2 main research areas:

- Identification of abnormal properties in motoneurons in the SOD1 mouse model of ALS.
- Identification of early signs of motor dysfunction in patients with Post-Polio Syndrome (PPS).

In addition, the PPM Team report indicates existing interactions with other teams (PICs and spasticity; motor control; cognition and ALS patients) although no details are provided so it is not possible to comment on these collaborative studies.

Overall, from the current plans, there appears to be a feeling that this group is not planning novel, ground breaking studies based on new ideas and new models and unfortunately, the current research plans are not cutting edge.

- Conclusion :

  - Summary

This group is well known for its work on properties of motoneurons in animal models of ALS and on the pathophysiology of ALS. Previous tracking record and attractiveness has been rather poor. It now brings together basic scientists and clinicians, with the ambition to develop related researches on PPS, in addition to ALS.

  - Strengths and opportunities

The combination of basic scientists with expertise in investigating the pathophysiology of motoneurons in animal models, using a highly skilled and challenging approach, together with clinicians with the ability to investigate patients with neuromuscular disorders offers the opportunity to undertake collaborative PPMstudies.

Few groups around the world are undertaking such demanding studies on the electrophysiological properties of motoneurons and this approach is a particular strength of the team, which offers relatively unique training opportunities. By merging with a more clinically oriented team, the PPM team has significant potential to undertake an interesting program of research.

  - Weaknesses and threats

The plans put forward by this group do not appear to optimise the opportunity to undertake correlative studies using mouse models of the neuromuscular diseases that are examined in patients. Thus, the proposed experiments in ALS mice do not involve any parallel studies in ALS patients, and conversely, the studies on PPS will be based on PPS patients with no studies planned in appropriate animal models of PPS – the SOD1 mouse of ALS is not a good model to study the pathophysiological mechanisms that underlie PPS. This team should be encouraged to broaden the animal models they use in their studies (e.g. using aging mice as a basis to model PPS or the SMA mouse as an additional model to examine changes in the electrophysiological properties of degenerating motor neurons). Overall, from the current plans, there appears to be a feeling that this group is not planning novel, ground breaking studies based on new ideas and new models and unfortunately, the current research plans are not cutting edge.

  - Recommendations

A more integrated forward thinking approach by putting together neurobiologists and clinicians may be particularly productive. In addition wider collaborations with other groups in the INT should also be encouraged.

Finally, it should be emphasized that some of the highly skilled approaches used by this group have great potential for the future and should be maintained and promoted among the younger members of the group.

Team 3: Plasticity and physio-pathology of rhythmic motor networks (P_3M)

Team Leader: M. Laurent VINAY

- Staff members

	Past	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)		3
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)		6
N3: Number of other researchers including postdoctoral fellows (Forms 2.2, 2.4 and 2.7 of the application file)		1*
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)		0.5
N5: Number engineers, technicians and administrative staff without a tenured position (Form 2.6 of the application file)		1
N6: Number of Ph.D. students (Form 2.8 of the application file)		3
N7: Number of staff members with a HDR or a similar grade		8

*OP: open positions

- Appreciation on the results

The P_3M is a strong group of scientists with broad expertise in the cellular mechanisms of rhythmic motor control. The main research stream analyzes the contribution of a K+-Cl- co-transporter (KCC2) to modulation of excitability of motor networks, especially after spinal cord injury (SCI). Other aspects of the research encompass the activity-dependent modulation of neurons and spinal networks, including pace-maker properties and rhythmicity, and the dysfunction of motor development with a special emphasis on the role of monoamine systems.

Significant contributions have been made these last few years, in particular the demonstrating that lowered levels of KCC2 is a key mechanism in the hyperexcitability of motor networks of the spinal cord that develops after injury and leads to hyperexcitable stretch reflexes and spasticity. Other important data on the role of ionic fluctuations on the pace-makers activities, either in the brain stem or the spinal cord, have also been obtained, and the research undertaken in the group are generally original and thoroughly carried out.

All permanent members of the group have an excellent neuroscientific background and have well to very well published in good journals of the field (J. Neurosci., Eur. J. Neurosci., J Neurophysiol….) or generalist journal (PNAS, Nature Med., J. Physiol. London). Significant contribution to the history of Neuroscience has been made by an emeritus member of the team.

Researches integrate different techniques from cellular neurobiology, electrophysiology, neuroanatomy and morphology, with original approaches (use of rabies viruses for neuronal tracing, well integrated models of DSCI for in vivo and ex vivo physiology for example).

- Appreciation on the impact, the attractiveness of the team and of the quality of its links with international, national and local partners

The team has trained three PhD students up to their thesis for the past 4 years, which is not much given the size of the group, but 4 PhD students are now in the group. They have attracted good foreign post-docs, and the group leader has been invited 8 times to international conference, attesting of the good recognition of the team.

Collaboration with a local biotech company has been undertaken to look for compounds able to interact with KCC2 and to modulate its activity, with the goal to develop new types of antispastic drugs, and these attempts are certainly promising and have to be encouraged.

Several members of the teams have heavy teaching duty and the contribution to teaching and education in Neuroscience has been strong. This should be even reinforced in the next future.

The group is very well funded from French sources (ANR, and French Foundations), and they also coordinate and international grants they coordinate (Reeve Foundation) attesting that the expertise of the team gained a high recognition at a national and international level.

- Appreciation on the scientific strategy and the project

The different lines of the project are well defined and combine a range of state-of-the-art techniques. More precisely, the investigations focus on the cellular and network mechanisms that underlie the alteration in the balance excitation vs. inhibition following SCI or exposure to environmental/toxicological factors during the prenatal period. The novel and fruitful hypothesis is that these mechanisms result from alteration in the ionic homeostasis of the extracellular medium, especially through a down regulation of the K+-Cl- cotransporter KCC2.

The project is timely and will strengthen the position of this research team as one of the international leaders in motor control. Results from this project will not only provide new insights into the mechanisms of plasticity of neuron properties and motor circuits, but it also has a clear translational and clinical potential.

The research program is well articulated, and there is a clear synergy between the different team members who master complementary technical expertise. The team seems also well organized and well balanced.

- Conclusion

  - Summary

The group has made significant advances these last few years, and the degree of achievements as well the thorough design of the project is impressive. The discovery of new role for the KCC2 transporter opens new avenues of investigations in other structures than the spinal cord. The specific aims are of interest to both fundamental aspects of neuronal excitability and plasticity, and application to pathology, including drug screening.

  - Strengths and opportunities

The project is timely and will strengthen the position this research team as one of the international leaders in motor rhythmic control.

Extension of the strategy to respiratory systems and the studies of the activity-dependent modulation of neurons and spinal networks, and of the dysfunction of motor development, are also potentially very fruitful.

Results from this project will not only provide new insights into the mechanisms of plasticity of neuron properties and motor circuits, but it also has a clear translational and clinical potential.

  - Weaknesses and threats

Integration of new members and extension of the approaches to other (but related) topics, a too large diversification could weakend the impact of the other aspects of the team's project.

  - Recommendations

Overall, this is an excellent research team with a very strong research program and high quality scientific production. Priority should be given to elaborate on the most exciting recent findings of the group, and extension of the concepts to other models is an exciting perspective. The team has the potential to become a world leader in the field, and it will be a factor of positive dynamics in the Institute. Strong support is recommended.

Team 4: Cognitive Motor Control (CoMCo)

Team Leader: Ms. Alexa RIEHLE

- Staff members

	Past	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)	3	0
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)		5
N3: Number of other researchers including postdoctoral fellows (Forms 2.2, 2.4 and 2.7 of the application file)	2	2
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)		
N5: Number engineers, technicians and administrative staff without a tenured position (Form 2.6 of the application file)		
N6: Number of Ph.D. students (Form 2.8 of the application file)	4	4
N7: Number of staff members with a HDR or a similar grade		

- Appreciation on the results

The CoMCo is a group of scientists with broad expertise in motor control. All five have an excellent background and have published in excellent neuroscience journals (J. Neurosci., Europ. J. Neurosci., J. Neurophysiol., Cerebral Cortex, NeuroImage, PNAS, Neuropsychologia, J. Physiol. London).

Together the members of the group cumulate many scientific fields: biology, psychology, neuropsychology, mathematics and physics. Some of the members have being educated in two of these fields. This is a very good prerequisite for integrated research in Neuroscience.

The members of the group have not yet published together, which indicates that this group is a new consortium with intent of strong interactions between experts. We cannot yet formulate any judgment on the future stability of the group. However, the structure of this group is interesting and promising, with as team leader a scientist with excellent competence, large experience in neurophysiology, in particular recording in awake trained monkeys, with new and elaborate analysis of neuronal activity, and effective collaborations.

- Appreciation on the impact, the attractiveness of the team and of the quality of its links with international, national and local partners

The team leader seems to have always attracted excellent students and postdocs, mostly from abroad. She has productive scientific collaborations with the Bernstein Institute in Freiburg (Germany), the Hebrew University in Israel and the RIKEN in Japan. As expert in motor neurophysiology, she has been and is a member of several organization committees for various conferences and meetings.

The ability to raise funds is not overwhelming. Only the team leader has up to now been able to raise an important international grant and has been largely supported by national grants. This indicates that most of the members are still young and have not yet applied (or received) large grants.

From the five participants of the CoMCo, only three have been involved in teaching at the Master level, but they regularly supervise short-term students.

- Appreciation on the scientific strategy and the project

The submitted scientific strategy and projects have been well thought through and are a clear effort to bring together broad expertise to attack principles of motor control on several levels: behavioral (psychophysics), neuronal, organizational and computational.

Central and common interest of all members is the control of hand and arm movements during manipulation, in particular during grasping, and the learning principles. One basic question for the next research years is the coupling, or coordination, of distal and proximal movements in various manipulations and perturbations, and the influence of predictive mechanisms. This will be investigated at the psychophysical, neuronal and mesoscopic (EEG) levels, using a new exoskeleton robot, the KINARM, which provides well-controlled movements as well as kinetics and kinematics data. Most promising is the contribution of similar tasks in the human experiments and in the chronic recordings in trained monkeys.

Another central aim of the CoMCo is the better understanding of the neural code in various experimental settings, in particular the search for local networks using multi-electrode recordings of single neurons and Low Field Potentials (LFP). Multi-electrodes arrays, which are already implanted in two monkeys, will allow investigating the representation of time and space in the neuronal discharge patterns.

In addition, the team will create collaborations with the clinics and using advanced technology, such as the KINARM, investigate various motor pathologies and putative rehabilitation therapies.

As a cutting edge project, a common effort of the members of the CoMCo is the collaboration in Brain Machine Interface technology for arm and hand, in particular grasping movements.

- Conclusion

  - Summary

The scientific projects submitted by CoMCo are feasible and will, up to 2015, certainly bring interesting new findings. This team cumulates experience in several neuroscience methods and technology, such as EEG, fMRI, single and multi-electrode recordings, analytical software and computer modeling. This new consortium, under the excellent expertise of the team leader, will certainly develop into the intended closely collaborating group of motor system experts.

  - Strengths and opportunities

One of the strength of the CoMCo is per sure the excellence of the strategies to decipher neuronal code, a specialty of the team leader who has very good collaborations with experts in this domain and has published important papers on the subject. Projects on proximo-distal coupling, timing processes and planning of movements and deciphering the neural code of cortical motor control, are quite promising. The collaboration with other members of the team, in particular with the experts in psychophysics, is a most positive development and complement.

  - Weaknesses and threats

Some of the proposed projects are not yet well thoroughly thought through, in particular the learning project which should be better designed in the context of the other collaborative efforts.

With respect to the funding, this team should be able to get more support, in particular for some of the new projects proposed by younger scientists. Applications to national and international grants are strongly encouraged.

  - Recommendations

The potential weaknesses but also strengths are both large and obvious. This is a new team and the committee recommends to give this team a chance and a good support.

Team 5: Inference and Visual Behavior (IViBe)

Team Leader: M. Guillaume MASSON

- Staff members

	Past	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)		2
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)		6
N3: Number of other researchers including postdoctoral fellows (Forms 2.2, 2.4 and 2.7 of the application file)		3 + 4*
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)		8
N5: Number engineers, technicians and administrative staff without a tenured position (Form 2.6 of the application file)		
N6: Number of Ph.D. students (Form 2.8 of the application file)		3
N7: Number of staff members with a HDR or a similar grade		8

*OP: open positions

- Appreciation on the results

Work of the team aims at elucidating the dynamic neural processes, which, in the visual cortex, are used to compute meaningful images, from spatially and temporally segregated features. They use a combination of techniques from unitary neuronal activity to network activity and behavioral response. Questions include the representation of images during visual tracking as a model of sensory integration (visual motion perception and representation) influenced by the context and influencing relevant behavior such as foveal centering of the gaze during eye saccades. Understanding the dynamics of motion integration of natural images, motion illusions or inference and prediction promoted the design of original experimental situation using noisy moving stimuli. Recording are made at unitary or population levels from different cortical areas including V1 by different techniques: voltage sensitive dye imaging or intrinsic signal imaging, fast two-photon imaging, microelectrode recording at multiple sites and even multielectrode recordings. Data obtained at different scales are analyzed by powerful statistical means such as Bayesian probabilistic calculation and sophisticated computational modeling. The team has obtained highly regarded data on motion representation processing these last few years.

They have had a very good publication record in a number of important journals. The group has published 44 papers and 3 reviews, many in the best journals of the field (Science, J. Neurophysiol., Vision Res., J. Neurosci., NeuroImage, Cereb. Cortex…etc), although none of them in a major journal yet.

- Appreciation on the impact, the attractiveness of the team and of the quality of its links with international, national and local partners

The group has attracted many students for short and mid-term training in the laboratory. Several PhD students have also been trained and 5 of them are still working there, several of them being from foreign countries, attesting of the international attractiveness of the group. Two French post-docs have also recently joined the team.

Implication of the group members in teaching is really high despite the fact that none of them have university position except the physician associated to the group. They have organized several excellent specific courses at the Master level, which is important for the future of the field, and to establish the Marseille groups as leaders in cognitive neuroscience on the long run.

They have been very successful in raising funds from different highly competitive sources (French ANR -5 grants- and European programs -4 grants-), providing the group with the means to conduct the research they have planed on the sage side. These research programs have fostered numerous international collaborations with excellent groups in USA, Germany, Israel, UK, Spain, Italy and also in France of course.

Collaboration with clinicians both in Marseille and Paris should be acknowledged and encouraged. The projects are exciting in this respect and should lead to important, exemplary translational research of great interest and fruitful outcome.

- Appreciation on the scientific strategy and the project

The project plans to explore several important aspect of movement representation in the visual cortex. Analysis of motion representation in visual areas is using both simple and complex stimuli (motion clouds) and multi-scale recordings, which are at the leading edge of cognitive and computational neuroscience. Especially creative is the project studying synergy between gaze stabilization and saccade during fixation, which brings the oculomotor system into the state concept.

Another part of the project includes inference, diffusion of information within the cortical sheet and prediction for motion integration. It studies motion integration from a number of standpoints: Comparing motion prediction signals in the V1 area with current theoretical models, applying likelihood statistics to ocular following, using inference to understand human oculomotor choices. In addition, the team will look at the balance between saccades and pursuit in visual tracking, which is an interesting problem. They will use Bayesian inference to understand motion processing that leads to smooth pursuit, and then applying new neural network analysis methods to the data.

Still another important challenge in the project will be the link with clinical visual neurosciences. Implanting photosensing arrays into the retinas of humans blind from AMD or retinitis pigmentosa is thought to be a possible way to cure retinal blindness. The group proposes to study, in non-human primates, the neural effects of retinal prostheses. This is an excellent project and one which seems to be doing the brain-machine-interface problem right.

Some technical developments are also proposed, and the group proposes developing two-photon Ca++ imaging in awake monkeys, in collaboration with a well-known group in Israel, which is an excellent idea to strengthen the cellular approaches in the group. Their other project is to use multieletrode arrays, which will bring a missing link in the levels of integration analyzed in the group.

- Conclusion

  - Summary

The IViBe team is a very strong group, including several young and highly talented neuroscientists. The group leader is an internationally respected vision scientist who has done important work in both the visual and oculomotor systems. The potential to make cutting edge science is there. The approaches, from single unit record and optical imaging to brain-machine-interface are broad, but the different approaches should provide for a large amount of cross-fertilization.

  - Strenghts and opportunities

The group first strength lies in the broad range of techniques that they use: single unit recording, 3D 2 photon microscopy, optical imaging with voltage sensitive dyes.

The second strength is a strong theoretical framework in which to use these techniques. The idea of brain states is particularly interesting, extending beyond stimulus-evoked activity to the baseline activity of neurons, using trajectories in phase space to analyze data in a new way.

The team has a great potential as a whole, due to the complementary skills of the researchers. They show a communicative enthusiasm, a good sign of the positive dynamics of the group.

- Weaknesses and threats

There is a general weakness in that some of the research proposals are extremely broad, especially as far as inference and prediction for the visual integration of motion is concerned. However, there will be enough focus to be successful, especially since the interaction among the sub-projects is excellent. The committee was wondering why the omnipause neurons have been chosen instead of the rostral colliculus as the source of his supression of saccades. Also the investigators do not seem to distinguish between the open and closed loop segments of pursuit.

Although recent data are of high interest in the field, the group has not recently published in top journals.

- Recommendations

The group is strong, young, with a lot of enthusiasm, a very positive dynamics and an excellent research project. This should be acknowledged and worthy of taking the risk to support it as described. Effort should be made to publish more in high-ranked journals. The group would nevertheless score quite well in the international competition.

Team 6: Basal Ganglia, Motivation and Reward (BaGaMoRe)

Team Leader: Ms. Christelle BAUNEZ

- Staff members

	Past	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)		1
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)		3
N3: Number of other researchers including postdoctoral fellows (Forms 2.2, 2.4 and 2.7 of the application file)		3
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)		1
N5: Number of engineers, technicians and administrative staff without a tenured position (Form 2.6 of the application file)		
N6: Number of Ph.D. students (Form 2.8 of the application file)		3 + 3*
N7: Number of staff members with a HDR or a similar grade		3

*OP: open positions

- Appreciation on the results

The general aim of this group is to elucidate the role of basal ganglia substructures in behavioral integration. A statement is "to use a translational approach from rodents, monkeys to PD patients to better understand the role of the basal ganglia in motivation and reward-related behaviours, and their dysregulation such as addiction and impulse control disorders". The team members have analyzed the functional anatomical basis of motivational processes including addiction, with a strong emphasis on the role of the subthalamic nucleus (STN). They have obtained ground-breaking results based on deep brain stimulation and STN lesion to show the key role of this structure in processing selective addiction features. Implications of these data for therapeutic approaches of addiction but also Parkinson's disease are large and important. Studies are also undertaken to better understand the neural basis of incentive learning and motivated behaviors in the different striatal components. These researches are of course also applied to models of Parkinson's disease in rodents and primates, and they will be extended to human in the proposed project.

The group has a solid record of publications in good-to-excellent journals. They have published 32 papers and 9 reviews (PNAS, Lancet Neurol, TINS, Brain, J. Neurosci., J Neurophysiol, Neuro-psychopharmacology, etc).

- Appreciation on the impact, the attractiveness of the team and of the quality of its links with international, national and local partners

Three PhD students are currently in the group and a few other have previously completed their PhD, which is reasonably good. They have also attracted two post-docs, which is not much, and should certainly be improved.

Group members are all teaching at some levels, those with university position much more than the others, as it should be. A stronger involvement, for example in the PhD program proposed by the future director of the Institute is encouraged.

The funding is good, with 3 ANR grants, 1 PHRC, several supports from Foundations, and the group members should be careful in maintaining these funding high enough to fulfill the needs of their beautiful project.

Collaboration with excellent-to-outstanding research group in France (Bordeaux, Marseille, Grenoble) and abroad (USA and UK mostly) should be acknowledged.

The international recognition of the group members is good, overall, and excellent for the group leader, who has been often invited to international and national conferences.

- Appreciation on the scientific strategy and the project

A first important aspect of this work is to investigate the consequences of inactivation of the STN on models of motivation to obtain drug. This work follows up on previous publications from the group suggesting that STN stimulation is able to disrupt place preference for cocaine, while actually facilitating it for sucrose rewards. The experiments to follow up these interesting findings are using additional methods from a group in Bordeaux to characterize motivation for cocaine in rat models. This work is supported by collaboration with the Bordeaux group. Although there is increasing interest in the role of the subthalamic nucleus and deep brain stimulation in several disorders, including Parkinson's disease, this group is the foremost worldwide in studying its potential involvement in addictive processes. The ongoing link to a well-known group in Cambridge ensures that the theoretical approach of the group remains at the forefront worldwide.

For motivational and reinforcement learning in non-human primates, electrophysiological analysis of neuronal firing in behaving animals is a currently promising method for understanding integrative function of neuronal systems underlying behavior. Based on current knowledge on dopamine neurons, it is important to know if reward-prediction error neurons are also carried out in striatum. The group is interested in so-called TANS, probable cholinergic interneurons that are apparently not simply time-locked to VTA dopamine neurons. They have a complex pattern of activity which may be related to allocation of attention to informative events. They are presumably the source of cholinergic (nicotinic) inputs into the presynaptic terminals of dopamine neurons, offering a means of pharmacologically influencing their outputs.

Since identification of the cholinergic neurons is based on their electrophysiological properties in rodents, the ongoing work which will seek to confirm this identity in primates is most welcome.

The issue of transition from incentive motivated behaviours to habitual behaviours, and how these interact is currently a hot topic in the addiction area. An understanding of the neuronal organisation that gives rise to such transitions would be of great interest and potential importance. The important question of how striatal neurons communicate to integrate motor and motivational information is fundamental to understanding many neurological and mental disorders. This is a really exciting project, which the group is well equipped to pursue.

Then, understanding motivational processes within the basal ganglia is close to what is currently done in the group with rodents, and this sub-project is very appropriate.

The third area of research has the potential to relate theoretical work of the first two projects to the clinic, and especially to aspects of Parkinson's disease. A first approach proposes to use a task with two variables, level of reward, and difficulty of motor output to gain reward, in an attempt to dissociate these two influences on behavioral output. This is a problem that has faced animal researchers for many years, and without a complete solution. Nevertheless, the proposed experiments will go some way to allowing the dissociation to be made. By recording activity in STN, in patients who have had electrodes implanted for deep brain stimulation, it should be possible to dissociate the two manipulations on activity in this structure. Thus work relates nicely to the work in rodents.

Secondly the effects of deep brain stimulation of STN on motivational processes, and in particular the development of impulse disorders and addictive behavior will be studied. There is an opportunity that is available only to rare groups, such this one, able to integrate surgical techniques such as DBS with adequate psychological analyses.

At the present, the work of this group falls into the successful ongoing work of the separate independent approaches that have come together to form this group. There is a clear desire to integrate these approaches into a cohesive whole, and progress in this direction is already being made. Internal and external collaborations are well planned and are a real synergistic addition to the project.

- Conclusion

  - Summary

The group is excellent and proposes a very exciting, ambitious yet realistic and well-defined project. The way links between basic and clinical research are established is perfectly sound and clever. Although they are tackling problems of neuroscience that lie among the “hot topics” in research, they have the skills and means to stay competitive in the field. The group leader is a highly talented and insightful researcher and she will undoubtedly conduct the team on the right track, with impressive international collaborations and perspectives and a very good productivity.

  - Strenghts and opportunities

The planned studies using electrophysiological and cellular methods to investigate role of STN in reward bring together separated approaches and will benefit of the new grouping. The collaboration with a group in Bordeaux is also a useful addition.

The planned studies on motivational and reinforcement learning in non-human primates is timely, well designed and should strongly benefit of the new grouping.

The proposed approaches of related question in humans are also perfectly sound and very exciting.

The group has a great potential and the new grouping is not only complementary but really synergistic and joining the INT is a bright idea, since the environment appears perfectly appropriate to still increase the impact of current research. Overall, quality and motivation of the group members is impressive.

  - Weaknesses and threats

The potential weaknesses are the other side of any good, ambitious project: since it is rather broad and involve many different aspects and experimental models, making it really efficient is a tremendous task. Nevertheless, the group leader showed awareness of potential weaknesses of the existing findings from the group, and had clear plans on how to address them.

  - Recommendations

Overall, this is an impressive and active group, clearly able to fulfill its mission. They are close to the very best teams in the field. The separate projects have importance and impetus in themselves to justify continuing support. Natural links also suggest themselves with other teams within INT, but the committee recommends that such links should be allowed to grow organically, and not forced prematurely. Common interests, not organizational requirements should be decisive in determining research collaborations.

Team 7: Stress and Vulnerability (SteVe)

Team Leader : M. Olivier BLIN

- Staff members

	Past	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)		6
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)		1
N3: Number of other researchers including postdoctoral fellows (Forms 2.2, 2.4 and 2.7 of the application file)		4
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)		
N5: Number engineers, technicians and administrative staff without a tenured position (Form 2.6 of the application file)		
N6: Number of Ph.D. students (Form 2.8 of the application file)		
N7: Number of staff members with a HDR or a similar grade		4

- Appreciation on the result

The main interest of the team stems on how strong emotional load or stress is processed in the brain and impact on behavior of healthy subjects as well on the course of psychiatric disorders (post-traumatic stress disorders, but also schizophrenia, bipolar disorders, addiction…etc), essentially by using brain imaging technologies and neuropsychological and clinical investigation. A strong emphasis is put on the role of the medial prefrontal cortex and amygdala, well known players in the processing of aversive cues and fear. In this respect, an additional experimental dimension will be brought to the project by the merging with an other group, still located in Nice, and a well-known specialist of the behavioral neurobiology of fear. The project is very diverse and devided between different team members with little overlap, the link between them seemingly being the team leader.

The team has a record of 69 publications in peer-reviewed international journals, which is quite high for a relatively small team with just a single full-time researcher. There is a good proportion of good to excellent journals (e.g., a Lancet Neurology paper with two team members as first and last authors). There is also a good number of articles of clinical diffusion. However the tracking record is very unequal across team members but consistent with the fact that the youngest members with the heaviest teaching load have clearly less published.

- Appreciation on the impact, the attractiveness of the team and of the quality of its links with international, national and local partners

The team leader has a clear ability to bring people together, including team members around his scientific activity. A large number of PhD (15) and MSc (24) students have been supervised in the past exercice, indicating a strong ability to attract students. There is no evidence of recruitment of high-level scientists from abroad such as postdoctoral students, but the team groups together several senior researchers with relatively different reseacrh topics in a coherent whole.

No postdoctoral fellows are recorded in the document, which is a bit surprising, but probably due to the fact that most investigators in the project are medical doctors with clinical duty.

The team leader has very good success with funding. He is noteably scientific coordinator of an important European project with industrial partners (Pharmacog, 30M euros) but the team has also received consistent funding at the national level from clinical programs (PHRC) or pharmaceutical companies.

No international collaboration is currently listed in the document, but the group leader or other members of the teams have been often invited to international (40 invitations) and national (15 invitations) meetings, a sign of the wide recognition of the group.

- Appreciation on the scientific strategy and the project

This an ambitious and attractive project concentrating on the interactions between medial prefrontal cortex (mPFC) and amygdala/limbic system as a potential defective mechanisms in models of stress such as PTSD. Stress is very loosely defined, however, and several fairly different models of stress (Schizophrenia, sleep-deprived subejcts, depressed elderly patients…) will be examined.

A valuable effort is made to test whether potentially defective mPFC-amygdala connectivity could be a preliminary contributing factor, rather than a consequence of PTSD: longitudinal studies are planed in Firemen as a population likely to develop PTSD allowing within subject coimparison before vs. after the PTSD-inducing traumatic event. The committee noted the excellent access to a huge cohort (~1000 per year) of firemen thanks to privileged research links between the team leader and the French military. The team is thus in a very strong position to comparison of innate vs. acquired potential contributors to PTSD.

A similar longitudinal approach is proposed in PTSD patients before and after treatment with behavioural methods, and in elderly individuals with depression. This has the potential to bring important new results on the indications of these behavioural methods and the cerebral bases of their effect and could lead to changes in treatment practice.

A strong feature of the project is the effort made to bridge the human research (largely fMRI) conducted by the team leader's exisiting team with the animal (rodent) work of one member of the propsoed team currently located in a different University. The effects of mPFC stimulation (electrical in rodents, via rTMS in humans) will be compared in the two species, potentially creating important links and illustrating the integrative approach of the INT. However, this link seems to be still loose at it stands, and the way of making meaningful comparison is lacking.

Many of the human experiments will require access to fMRI scanning, but this does not seem to be a problem given the exisiting links and collaborations of the team leader with several fMRI teams and the very good funding of the team.

- Conclusion

  - Summary

The team has a very good productivity and attractiveness (particularly in terms of funding). The project as it is described, although relatively heterogeneous, includes very strong parts. Linking animal study of emotion and fear processing, models of retraumatization to human pathological situation (PTSD for example) is laudable. The group has been very successful in attracting funds and is in excellent position to undertake ambitious research program.

  - Strengths and opportunities

The team develops potentially interesting research themes, of both neurobiological and clinical interest. This sets the basis for new and fruitful translational researches.

The new group is strong and many members are highly productive especially the team leader.

They have access to exceptional cohort of patients, and this should be used for highly ambitious studies. Such an opportunity is rarely found worldwide.

Putting together animal research and pre-clinical and clinical investigation is potentially very efficient.

Researches in the group are well funded and supported.

- Weaknesses and threats

Younger team members not yet very productive, certainly due to high teaching load.

The proposal is made of fairly different subprojects with little proven interaction between team members apart from team leader.

The definition of the neurobiological concepts and paradigms used in the different subproject (stress, vulnerability, fear conditioning…etc), or the delineation of the clinical groups under study are often too vague and loose to understand the precise objective of the undertaken investigations.

Human and animal subprojects need to be more accurately defined since they currently do not display clear interaction.

- Recommendations

The team has a great potential to obtain cutting edge data, and to build efficient pathophysiological and translational research. A recommendation from the committee is to work on the synergy between different team members as they are currently working on fairly separate topics; the reunion of these members in a single team in the INT will clearly foster such interactions. It will be also necessary to clarify and expand potentially highly interesting human-animal links.

Team 8: Social cognition across the lifespan and pathologies (SCALP)

Team Leader: Ms. Christine DERUELLE

- Staff members

	Past	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)		4
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)		4
N3: Number of other researchers including postdoctoral fellows (Forms 2.2, 2.4 and 2.7 of the application file)		4
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)		0
N5: Number engineers, technicians and administrative staff without a tenured position (Form 2.6 of the application file)		
N6: Number of Ph.D. students (Form 2.8 of the application file)		2
N7: Number of staff members with a HDR or a similar grade		5

- Appreciation on the result

The team is investigating how social interaction among humans are affecting cognitive abilities from perception/reprsentation to social behaviors. This is a very important research topic with high relevance for basic human research, psychiatric disorders, and modern society in general.

Past research strongly focused on cognitive neuroscience, social psychiatry, epidemiology and clinical drug trials. The latter work was conducted within international (European) consortia. The approaches and methodologies are implicitly complex and show a great level of diversity. Some of the results have a good impact at the international level. Past work, however, does not yet include molecular neurobiological concepts to complement (social) cognitive neuroscience approaches. Some aspect of the past work are only distantly related to the question of social cognition, as it stands from the presented project.

The group has been well productive with 97 original and peer-reviewed publications. Some publications are in high-impact journals (Curr. Biol., Lancet, Brain, PTRS London, Neuroimage, Br. J. Psychiatry, Schizophr. Res….etc); only part of them are directly concerning the core issue of social cognition. Also many do not concerns first and senior authorships, and there are strong descrepancies among the group members. The group leader has a very good track record.

- Appreciation on the impact, the attractiveness of the team

The highly fascinating topics studied in the team should attract scientists at differently level of their training both nationally as well as internationally. This is not yet the case and the current number of postdoctoral fellows (currently one only) and PhD students is rather small for the size of the group (currently only two, and five thesis have been defended during the four past years).

The success in raising funds is a bit disappointing and support currently depends mostly on grants obtained by the current director of the Institut des Neurosciences Cognitives de la Méditerranée, from which the group originates. Notably, the group leader has no major grant on her own name. Other group members participates to funded projects from ANR, European Community or a few other sources. There are some link with the pharmaceutical industry for therapeutic, clinical research.

The number of external collaborations remains rather limited which is also reflected by mutual publications.

- Appreciation on the scientific strategy and the project

Although not very clear from the way how the proposal is written, the project relies on the studies of interaction between subtle developmental disorders and the personal history of individuals all along their lives, and leading to pathologies such as autism and related disorders, William Syndrom or Attention Deficit with Hyperactivity Disorders. While the concept is potentially exciting and quite novel, some of the details still need to be further specified and the work program requires further structuring. Findings in genetics, epigenetics and animal research were not enough discussed in this context. The envisioned project needs to be more deeply rooted to neurobiological hypothesis, and this will require linking some genetics and animal research through highly recommended collaborations. Currently, although potentially excellent, the relevance cannot be overstated. There is no doubt that the successful completion of the project would have a strong impact on the further development of psychiatric neurosciences in France.

Assuming that clinical partners are responsible for the phenotyping of population and clinical cohorts, it remains unclear how the data are organized, stored and transferred. It is recommended to put high priority on the further establishment of strong collaboration specifically in the field of molecular genetics, cell biology, imaging and animal research.The projects are certainly feasible but strongly depend on the involvment and availability of good psychophysiology investigation (fMRI, genetics). The projects could have cutting edge quality if the approach were more integrative, e.g., including genetically modified animal models, genetics and epigenetics …etc.

- Conclusion

  - Summary

The team's project that focuses on social interactions as a mean to explore the pathophysiology of diseases such as autism and William Syndrome is original and of high potential interest. The group has good – although heterogeneous- productivity. Based on clinical, neuropsychological approaches and imaging studies, the project can produce important output, especially if other aspects (genetic, neurobiological data) could be added to the proposed investigation.

  - Strengths and opportunities

Social cognition and its related upstream and downstream event his is an exciting and highly relevant research topic to be analysed in human subjects, but also in animal models.

The idea of using this common theme to focus on phenotypically contrasting pathologies could be fruitful, although the theoretical bases of such assumption are still weak and/or naive and should be specified.

The group has the skills, the technical means and the forces to carry out the project, with a very large clinical components, and access to relevant cohort of subjects. In this respect, looking for early markers of psychiatric disorders is welcome.

  - Weaknesses and threats

Theoretical and neurobiological basis, as well as specific aims, should be more clearly defined and focused.

The technical approaches needs to be more integrative, and integrate genetics and neuropsychological investigation to brain imaging.

The current interest of some members of the group seems to be distant from the mainstream project.

  - Recommendations

The team could certainly do well and obtain highly meaningful data. It is also in good position to develop efficient pathophysiological research in psychiatry. A recommendation from the committee is to establish links to other fields of psychiatric neurosciences by further establishing strong working collaborations. It should also be wise to focus on fewer human pathologies: ASD/WS, bipolar disorder for example, as well as to concentrate on neurodevelopmental trajectories in the above mentioned disorders, particularly when focussing on early markers. Then, as far as it is possible, it will be necessary to hire more post-docs and PhD students and to attract more specific grant money in the future.

Intitulé UR / équipe	C1	C2	C3	C4	Note globale
INT - INSTITUT DES NEUROSCIENCES DE LA TIMONE	A	A	A+	A+	A+
BASAL GANGLIA, MOTIVATION AND REWARD [MASSON-BAUNEZ]	A+	A+	Non noté	A+	A+
STRESS AND VULNERABILITY [MASSON-BLIN]	A	A	Non noté	A	A
SOCIAL COGNITION ACROSS LIFESPAN AND PATHOLOGIES [MASSON-DERUELLE]	A	A	Non noté	B	A
PHYSIO-PATHOLOGY OF MOTONEURONS IN MICE AND HUMANS [MASSON-DURAND]	A	B	Non noté	B	B
MOTOR NEURON DISEASE MODELLING AND THERAPY [MASSON-HAASE]	A+	A	Non noté	A	A
INFERENCE AND VISUAL BEHAVIOR [MASSON-MASSON]	A	A+	Non noté	A+	A+
COGNITIVE MOTOR CONTROL [MASSON-RIEHLE]	A	A+	Non noté	A+	A+
PLASTICITY AND PHYSIO-PATHOLOGY OF RHYTHMIC MOTOR NETWORKS [MASSON-VINAY]	A+	A+	Non noté	A+	A+

C1 Qualité scientifique et production

C2 Rayonnement et attractivité, intégration dans l'environnement

C3 Gouvernance et vie du laboratoire

C4 Stratégie et projet scientifique

Statistiques de notes globales par domaines scientifiques

(État au 06/05/2011)

Sciences du Vivant et Environnement

Note globale	SVE1_LS1_LS2	SVE1_LS3	SVE1_LS4	SVE1_LS5	SVE1_LS6	SVE1_LS7	SVE2 _LS3 *	SVE2_LS8 *	SVE2_LS9 *	Total
A+	7	3	1	4	7	6		2		30
A	27	1	13	20	21	26	2	12	23	145
B	6	1	6	2	8	23	3	3	6	58
C	1					4				5
Non noté	1									1
Total	**42**	**5**	**20**	**26**	**36**	**59**	**5**	**17**	**29**	**239**
A+	16,7%	60,0%	5,0%	15,4%	19,4%	10,2%		11,8%		12,6%
A	64,3%	20,0%	65,0%	76,9%	58,3%	44,1%	40,0%	70,6%	79,3%	60,7%
B	14,3%	20,0%	30,0%	7,7%	22,2%	39,0%	60,0%	17,6%	20,7%	24,3%
C	2,4%					6,8%				2,1%
Non noté	2,4%									0,4%
Total	100,0%	100,0%	100,0%	100,0%	100,0%	100,0%	100,0%	100,0%	100,0%	100,0%

*** les résultats SVE2 ne sont pas définitifs au 06/05/2011.**

Intitulés des domaines scientifiques

Sciences du Vivant et Environnement

• SVE1 Biologie, santé
- **SVE1_LS1 Biologie moléculaire, Biologie structurale, Biochimie**
- **SVE1_LS2 Génétique, Génomique, Bioinformatique, Biologie des systèmes**
- **SVE1_LS3 Biologie cellulaire, Biologie du développement animal**
- **SVE1_LS4 Physiologie, Physiopathologie, Endocrinologie**
- **SVE1_LS5 Neurosciences**
- **SVE1_LS6 Immunologie, Infectiologie**
- **SVE1_LS7 Recherche clinique, Santé publique**

• SVE2 Ecologie, environnement
- **SVE2_LS8 Evolution, Ecologie, Biologie de l'environnement**
- **SVE2_LS9 Sciences et technologies du vivant, Biotechnologie**
- **SVE2_LS3 Biologie cellulaire, Biologie du développement végétal**

UNIVERSITÉ DE LA MÉDITERRANÉE
AIX-MARSEILLE II

Objet : Réponse au rapport d'évaluation - **S2UR120001644 - INT - Institut des Neurosciences de la Timone - 0131843H** - de l'unité INT - Institut des Neurosciences de la Timone

Observations d'Aix-Marseille Université

The efforts will in particular focus onto building strong scientific interactions between teams as well as the recruitment of new team leaders in order to strengthen the scientific continuity across the different teams. Such policy will be launched already in 2012, in particular regarding functional neuro-imaging.. Lastly, the Ph program will start as early as January 2012, as soon as all the teams are installed in the new Building.

The Committee has pointed out two potential threats for both the Institute and several of its teams. Despite the fact that Institute will regroup most of the ITAs from the founding laboratories (INCM, P3M) and the former IFR131, the technical support to our teams remains largely insufficient. The AERES Committee acknowledges the efforts done to structure both shared facilities and technical teams, as a way to better cope with this shortage. It also clearly mentions the urgent need to increase the number of engineers and technicians in order to fully benefit from the scientific tools and competences that are already available. The other threat is the fact that several teams have a rather small amount of PhD and post-doctoral students, respective to the number of scientists and academics. As explained during the visit, the unit has diversified its recruitment scheme, looking for students from Physics, Computer Sciences or Psychology and is also doing his best to attract students from outside the Marseille area.. Solving these two threats will require a strong support from CNRS and Aix-Marseille University. Aix-Marseille University will help the unit.

Lastly, the Committee highlights the urge to upgrade the 3T MRI scanner. The Institute will host the fMRI Center as a consequence of the end of the IFR131. Since the AERES visit, the unit action has been devoted to change the management of the Center, to redefine the scientific strategy and to insert its future into the evolution of the imaging network on the Timone site. Such strategy is based on strengthening the links of the Center with the in vivo photonic imaging platform to be started at the INT as well as building new partnerships with molecular and multi-model imaging center (CERIMED) and physics laboratories (Fresnel, CPPM).

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Equipe 1. Motor Neuron Diseases Modeling and Therapy (MoMoThe) – Group leader : G. Haase

The team is considered by several review boards as one of the very best in the field of ALS pathology, as attested for instance by the coordination of an ERANET consortium. One of the main critics raised by the Committee was about the Golgi hypothesis as being too narrowly focused. This hypothesis pursued by the team perfectly illustrates the multifactorial nature of ALS. The Golgi apparatus is morphologically altered in all forms of ALS and Golgi-localized proteins such as Optineurin, TBCE and VPS54 have recently been found mutated in genetic forms of ALS. Based on the important roles of the organelle in protein secretion and cell death signaling, the interplay of degenerating motor neurons and neighboring glial cells is now being addressed mechanistically. The experts state that studying only the motor neurons in isolation may hardly end up with effective therapies and recommend that more emphasis should be given in validating the results in a more complex in vitro paradigm and in animal models Precisely, the team extensively uses complex systems such as iPSC, SOD and pmn mice as stated in the written project. However, the project will be better integrated with the other teams, heading for more integrative approaches. This was one main reason for joining the Institute.

Equipe 2. Physiopathology of Motoneurons in Human and Mice (PPM) – Group leader: J. Durand

Concerning the need to improve team production, clinicians from the team published in the best journal of their discipline on a regular basis.Among the weaknesses, the lack of studies on ALS patients is pointed out. The originality of our project on ALS relies on the identification of differences during the presymptomatic phase. Such investigation can be performed only on animal models and is impossible in ALS patients who, by definition, enter the symptomatic phase as soon as they are diagnosed.

Equipe 5 : Inference in Visual Behavior (IViBe) – Group leader: G. Masson

The comments and recommendations will be extremely useful to better link up the different sub-projects. The start of European (IST-FET / BrainScales) and national (ANR – Visafix) projects has allowed the team to work to better link up the different sub-projects and this will be reflected into the hiring of 5 open positions that need to be filled before the end of 2011. Second, concerning the absence of publications in the top interdisciplinary journals L. Goffarthas recently published his research in *Science* (2009, ACL-27). Indeed, the *Science* paper already reports that superior colliculus is involved in controlling microsaccades. The team will focus downstream this structure and start investigating the role of brainstem oculomotor structures

Equipe 7 : Stress and Vulnerability (Steve) – Group leader: O. Blin

One key aspect mentioned is the need to better define interactions between human and animal sub-projects as well as better defining some of the neurobiological concepts and paradigms used in the different subproject.Since the team associates researchers that until now belong to different teams and sites (Marseille/Nice), focus is already given on better converging towards well-defined, common research objectives. Despite the difficulties inherent in modeling human psychiatric phenotypes in animals, because of intrinsic limitations, animal models are thought to be useful tools in the study of PTSD mechanisms and development of novel treatment approaches. However, to better understand

mechanisms of PTSD relapse, we need to examine changes related to retraumatisation (inducing relapse) and determine functional interactions between the prefrontal cortex and the amygdala. The team is well equipped to do such experiments with its electrophysiological expertise in behaving rats and its neuroimaging approach in humans. One of key points of the project is to develop a new approach of prevention of PTSD relapse. With human studies,the team will identify the more frequent factors causing PTSD relapse. In animals, it will develop similar models of PTSD relapse. The team will also study mechanisms of prevention of PTSD relapse. Parameters that will be defined in rats will next be adapted to human studies with rTMS to explore similar prevention results. In addition, mechanism involved in EMDR therapy, the main therapeutic approach used, remains unknown. With rat studies, we plan to develop such approach in animals to allow the use of research methods , which cannot be used in humans for ethical reasons, to reach such aim (our understanding of EMDR mechanisms).

Equipe 8 : Social Cognition across the Lifespan and Pathologies (Scalp) – Group leader: C. Deruelle

The Scalp team is the product of a large reorganization that has led to the unification of scientists and clinicians working in the field of cognitive and affective neurosciences as well as psychiatry. Coming from different teams, it is therefore logical that both past research interests and publication records are diverse. Although the high quality of the individual publication records has been acknowledged, the remarks concerning the fact that some publications are out of the scope of the future project shall be considered in this context, as it was for the other teams. As for others, such recent evolution can explain the fact that some sub-projects have to be better defined, in particular regarding neuro-imaging and early markers sub-projects. The Committee highlights the strong interest for social cognition and neuroscience. Still, for the first time, all University psychiatry Units (from children to adult) will be unified. In terms of funding and support, another PHRC grant has been awarded since the Committee visit. The fact that the ANR funding scheme has been recently changed to better support Mental Health and Cognition is important for the future. First, a clinician specialized in molecular imaging will join the team to develop a research program on neurobiological markers of psychiatric diseases.. Lastly, team will create common research projects with other INT teams (Haase, Baunez, Blin) working at these levels. The main strength, as mentioned by the report, is on the detailed behavioral and imaging analysis of cognitive functions and dysfunctions. In the future, we will bring this expertise both to clinics (remediation, training of clinical staff) and to neurobiologists.

En accord avec les deux autres établissements d'Aix-Marseille

Le Président
de l'Université de la Méditerranée

Yvon BERLAND

Le Vice-président du Conseil Scientifique
de l'Université de la Méditerranée

Pierre CHIAPPETTA