Research evaluation

EVALUATION REPORT OF THE UNIT

Institut de psychiatrie et neurosciences de Paris

UNDER THE SUPERVISION OF THE FOLLOWING ESTABLISHMENTS AND ORGANISMS:

Université Paris Cité,
Institut national de la santé et de la recherche médicale – Inserm

EVALUATION CAMPAIGN 2023-2024
GROUP D

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High Council for evaluation of research and highter education

In the name of the expert committee[1] :

Philippe Marin, Chairman of the committee

For the Hcéres[2] :

Stéphane Le Bouler, acting president

Pursuant to Articles R. 114-15 and R. 114-10 of the French Research Code, evaluation reports drawn up by expert committees are signed by the chairmen of these committees and countersigned by the Chairman of Hcéres.

To make the document easier to read, the names used in this report to designate functions, professions or responsibilities (expert, researcher, teacher-researcher, professor, lecturer, engineer, technician, director, doctoral student, etc.) are used in a generic sense and have a neutral value.

This report is the result of the unit's evaluation by the expert committee, the composition of which is specified below. The appreciations it contains are the expression of the independent and collegial deliberation of this committee. The numbers in this report are the certified exact data extracted from the deposited files by the supervising body on behalf of the unit.

MEMBERS OF THE EXPERT COMMITTEE

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Representatives of Université Paris Cité :

Michel VIDAL (Vice-Dean Research) and Christine GUILLARD (Director Research and Innovation)

CHARACTERISATION OF THE UNIT

- Name: Institut de psychiatrie et neurosciences de Paris
- Acronym: IPNP
- Label and number: UMR1266
- Composition of the executive team:

SCIENTIFIC PANELS OF THE UNIT

SVE Sciences du vivant et environnement
SVE5 Neurosciences et troubles du système nerveux

THEMES OF THE UNIT

The Institut de Psychiatrie et Neurosciences de Paris (IPNP) develops a multidisciplinary neuroscience research program aimed at understanding the pathophysiological mechanisms underlying psychiatric and neurological diseases thanks to a multiscale strategy from molecules to cells, neuronal networks and whole organs. Its ultimate goal is to promote the transfer of its discoveries into medical advances for neurological and psychiatric diseases, such as the development of new therapeutics, devices or diagnostic tools. The specific research topics developed cover various fields of basic and translational neuroscience, including brain evolution and development, psychiatric diseases, neurodegenerative diseases, epilepsy, brain tumours and neurovascular system using a large variety of approaches ranging from molecular and cellular biology to multiscale imaging, cognitive and translational neuroscience.
Over the previous contract period, this project has been conducted by ten senior teams (around 10–15 people) and 4 junior teams (around 6–8 people), which independently develop their own program in frame of the general topic of the IPNP. Following the departure of two teams at the end of the contract, the arrival of new teams and internal reorganisation, the IPNP will include thirteen research teams at the beginning of the next term:

- Team 1 investigates neuron-oligodendroglia reciprocal interactions during postnatal cortical development and in pathological conditions.
- Team 2 investigates the dynamics of intracellular membranes in developing and mature neurons, in physiological and pathological conditions, including psychiatric diseases, brain tumours and neurodegenerative diseases (Parkinson, Alzheimer).
- Team 3 explores abnormalities in neuronal, synaptic and network activity in neurological diseases such as epilepsy and glioma, using electrophysiological approaches mostly from human material. The team is also involved in the development of innovative organic electrodes designed to record network activity in human cortex in order to identify epileptic tissue and tumour cell infiltration biomarkers.
- Team 4 investigates the pathological mechanisms of small vessel diseases of the brain, such as CADASIL, and explore their causal link with stroke, with the goal of developing novel biomarkers and therapeutic approaches.
- Team 5 investigates at the molecular and systems levels the mechanisms underlying the onset and outcome of psychotic disorders, with a special attention paid to the developmental and/or genetic background, by using a translational strategy combining studies in rodent models and patient cohorts.
- Team 6 investigates the regulation and function of neurotransmitter receptors, such as the cannabinoid CB1 receptor, the μ-opioid receptor and the serotonin 5HT2A receptor and how they modulate cytoskeleton and neuronal network activity and connectivity.
- Team 7 focuses on the development and clinical validation of quantitative neuroimaging biomarkers to improve the diagnosis, treatment decision, prognosis, and ultimately outcomes of patients with neurovascular or mental disorders or brain tumours.
- Team 8 explores how neurons transiently expressed during brain development shape cortical networks, how their acquisition in mammals has contributed to the evolution of the neocortex and how their dysfunction affects neural circuits and leads to pathological conditions.
- Team 9 investigates predictive or vulnerability factors of addictive behaviours, including eating disorders, substance misuse, or other psychiatric disorders with comorbid drug abuse, such as depression and schizophrenia.
- Team 10 investigates neuronal signalling mechanisms (mostly protein kinases) affected in neurodevelopmental disorders such as autism spectrum disorders.
- Team 11 investigates the determinants of stroke prognosis and subgroups at higher risk of unfavourable outcomes, and assesses in these patients the benefit/risk ratio of novel therapeutic strategies.
- Team 12 (FRM Emergence team) investigates cholinergic modulation of cortical inhibitory circuits in health and disease conditions.
- Team 13 (Atip/Avenir team) investigates how thalamocortical circuits enable the formation and stabilisation of sensory cortex-dependent memories and emotional associative learning.

HISTORIC AND GEOGRAPHICAL LOCATION OF THE UNIT

The IPNP was created in 2019 as a result of the restructuration of the former Centre for Psychiatry and Neuroscience of Paris located in the vicinity of Sainte-Anne Hospital in the south area of Paris. The goal was to create a research institute with strong ties with this hospital and to bridge the gap between basic and clinical research to understand the pathophysiology of psychiatric and neurological disorders. The IPNP is located in a single building of around 4,300 m² dedicated to experimental research, with laboratory and office spaces, technological core facilities, administration and meeting rooms. This building was extensively renovated and opened in the fall of 2017. Over the evaluation period, the institute has been hosting around 200–250 people working in ten senior and four junior teams (many of them joined the institute at the beginning of or during the previous contract), two start-up companies, administrative support services and technological platforms.

RESEARCH ENVIRONMENT OF THE UNIT

The IPNP benefits from of the outstanding technological environment provided by a large variety of highly competitive platforms located in Paris area and equipped with state-of-the-art facilities. In order to complete this technological offer, the IPNP has developed locally a technological core of platforms essential to the realisation of its projects. These include

i) a behavioural phenotyping platform that provides a wide variety of behavioural tasks for studies on rat and mouse models of neurodegenerative and neuropsychiatric disorders, and for testing novel therapeutic agents,

ii) an imaging platform, that is part of the national France Bioimaging infrastructure and combines imaging techniques from whole organism to single molecule level,

iii) a biochemistry and biophysics platform that offers a large portfolio of services in molecular biology, biochemistry and biophysics,

iv) and a bioinformatics platform recently implemented to fulfil the needs of IPNP research teams in image as well as genetic and epigenetic big data analysis.

A hallmark of IPNP is its strong interactions with the neighbouring Sainte-Anne Hospital, which is part of the Groupe Hospitalier Universitaire (GHU) Paris Psychiatrie & Neurosciences, one of the leading centres for the treatment of neuropsychiatric disorders in France. The IPNP hosts around 40 teacher-hospital practitioners/hospital practitioners. Five of them are leading an IPNP team. The IPNP hired one junior PI with the support of GHU that also funded one technician position to support the newly created team. Five IPNP teams are developing collaborative project dedicated to the characterisation of imaging biomarkers in collaboration with the 3T research MRI platform for human brain imaging implemented at the GHU. Furthermore, IPNP organises every two months with the GHU a series of basic-clinical research seminars entitled '12:30 of the research' and made available on Youtube with the goal of strengthening the links between the two communities.

Over the past years, the IPNP has significantly strengthened its participation and visibility in teaching programs of the University Paris-Cité. The IPNP had a key role in the creation of Master Neuro in 2019, a new interdisciplinary master's degree in neuroscience that provides students with a broad knowledge in the field of neuroscience ranging from molecular and cellular to integrative neuroscience. The IPNP director is a co-founder of the Institut Neuroscience et Cognition (and is still a member of its COPIL), a structure federating research and teaching in Neurosciences within the University Paris-Cité. Finally, IPNP scientists are strongly committed in the Cognition and Brain Revolutions Artificial Intelligence, Neurogenomics and Society project (C-Brains), a five-year program selected in frame of the Major Research and Innovation Domains (DIMs) of the Region Île-de-France and aimed at solving the complexity of the brain by bridging technological barriers, in order to make the Île-de-France region a major centre for innovation in neuroscience and cognitive sciences.

UNIT WORKFORCE: in physical persons at 31/12/2022

Catégories de personnel	Effectifs
Professeurs et assimilés	20
Maîtres de conférences et assimilés	12
Directeurs de recherche et assimilés	12
Chargés de recherche et assimilés	13
Personnels d'appui à la recherche	37
Sous-total personnels permanents en activité	**94**
Enseignants-chercheurs et chercheurs non permanents et assimilés	24
Personnels d'appui non permanents	14
Post-doctorants	20
Doctorants	61
Sous-total personnels non permanents en activité	**119**
Total personnels	**213**

DISTRIBUTION OF THE UNIT'S PERMANENTS BY EMPLOYER: in physical persons at 31/12/2022. Non-tutorship employers are grouped under the heading 'autres'.

Nom de l'employeur	EC	C	PAR
INSERM	0	16	37
AUTRES	15	11	18
UNIVERSITÉ PARIS-CITÉ	28	0	8
Total personnels	**43**	**27**	**63**

GLOBAL ASSESSMENT

The IPNP is a young institute that has become within a few years a respected, visible and attractive institute in the field of psychiatry and neuroscience, thanks to the remarkable work carried out by the unit director and all the unit's staff. He has managed to rally them around the IPNP project. A hallmark of the IPNP is its close proximity with the Groupe Hospitalier Universitaire (GHU) Paris Psychiatrie & Neurosciences (Sainte-Anne Hospital) that offers unique opportunities for interactions between basic research and translational/clinical research. To achieve its ambitious objective to perform world class research in neuroscience and psychiatry, the IPNP has successfully brought together fourteen research teams based on a rigorous selection by an international Scientific Advisory Board (iSAB). These teams are generally well-funded and well-resourced and strongly benefit from the remarkable technological environment offered by:

i) the IPNP technological core platforms handled by skilled staff who provide technical, methodological and operational expertise in behavioural phenotyping of rodents, imaging from single molecule to the brain *in vivo*, biochemistry and biophysics,

ii) and the 3T research MRI platform for human brain imaging implemented at Sainte-Anne Hospital.

The IPNP also stands out by its large scientific production, with 1892 publications, including 1474 original articles, over the reporting period, even though this production is imbalanced in favour of clinical teams. Nearly 40% of these publications are signed in position of responsibility (first, last and/or corresponding author), and some of them were published in wide readership generalist journals (Nature Communications, PNAS, Elife, Cell Report, J. Cell Biol, N Engl J Med, etc.) or high-ranked journals in the fields of neuroscience and neuropsychiatric disorders (Nature Genetics, Neuron, Molecular Psychiatry, Brain, Neurology, JAMA Neurology, Cerebral Cortex, etc.). Around 10% the IPNP publications involve several teams of the unit, which is remarkable given the recent creation of the institute and highlights the strong capacity of the IPNP teams to generate synergies and their strong commitment in the scientific policy of the unit. The IPNP has implemented an efficient management structure composed of a steering committee (DirCo), a Team and Platform Leader Committee (TeamCo) and the Laboratory Council (LabCo), that ensures fluidity of the decision-making process, and seems to be generally well accepted by the unit's staff. The IPNP management also ensured a good spirit and strong cohesion within the institute, an active participation of all staff categories in its daily life and activities, and the visibility of all the scientific staff of the unit, who can develop their own line of research, apply to grants and supervise students in an independent manner, thereby favouring the progression of their career. Overall, the IPNP is an excellent research institute which has considerably improved its attractiveness and its scientific production over the past years and should capitalise on its recent successes and the strong complementarities between its basic and translational/clinical research to further enhance its visibility in France and abroad.

DETAILED EVALUATION OF THE UNIT

A – CONSIDERATION OF THE RECOMMENDATIONS IN THE PREVIOUS REPORT

To improve the cohesion and maximise the potential of the new institute, the previous committee recommended the IPNP to favour internal collaborations across the unit's teams in grant applications.
The IPNP followed this recommendation by developing several collaborations across IPNP teams, which led to the obtention of common grants (more than ten listed) and/or common publications (more than 10% of total publications involve at least two IPNP teams).
The committee recommended the IPNP to increase engagement with private companies to enhance activities, particularly of the platforms.
The IPNP followed this recommendation by hosting two start-up companies (PannTherapi in 2022 and AtmosR in 2023) with common interests with IPNP's research topics (innovative treatments for neurological diseases), and using the unit's platforms.
The committee recommended the IPNP to favour the development of self-directed learning and social activities between students.
The IPNP followed this recommendation by helping PhD students to launch several initiatives for self-directed learning and social activities (feedback sessions between M2/Ph.D. or PhD/Post-docs, doctoral school defence training for M2 students, student meetings the 4th Friday of each month, young researcher day once a year, after-works, etc.), by implementing a 'lunch with the speaker' session after external seminars, by implementing doctoral and postdoctoral travel grants for national and international meetings and sponsoring the fees of PhD students and postdocs for attending the FENS Forum 2022 in Paris.
The committee recommended the unit to strengthen its translational activities by adding data management and bioinformatics, statistical, and computing resources, as a core platform.
The IPNP followed this recommendation by creating a bioinformatics platform and recruiting a bioinformatician in charge of its activities.
The committee recommended the unit to implement governance and management structures ensuring transparency of decision-making and a collegial approach, to encourage further interactions between clinical and non-clinical teams and to ensure that the core facilities platforms are adapted to the team's projects and not require input from research teams for normal running.
The IPNP followed this recommendation by implementing a rigorous governance based on the DirCo, TeamCo and LabCo, organising weekly seminars and an IPNP retreat, and improving student mentoring. In spite of the strong efforts of the IPNP director, there is still room for improvement of the IPNP organisation, governance, financial self-sufficiency and opening of the platforms to the community.
The committee recommended that the reflection groups ensure that the IPNP remains focused and avoids dilution of effort across too many areas.
The IPNP develops programs centred around a few well-defined research topics, namely brain evolution and development, psychiatric diseases, neurodegenerative diseases, epilepsy, brain tumours and neurovascular system.
Overall, the IPNP followed the recommendations of the previous committee.

B – EVALUATION AREAS

Considering the references defined in the unit's evaluation guidelines, the committee ensures that a distinction is made on the outstanding elements for strengths or weaknesses. Each point is documented by observable facts including the elements from the portfolio. The committee assesses if the unit's results are consistent with its activity profile.

EVALUATION AREA 1: PROFILE, RESOURCES AND ORGANISATION OF THE UNIT

Assessment on the scientific objectives of the unit

The objective of the IPNP is to perform world-class basic, preclinical, and translational/clinical research in neuroscience by using a multiscale strategy from molecule to cell and organ. This is an ambitious but quite large objective, even though the project is centred on a few more specific domains, such as neurodevelopment, psychiatric disorders, neurodegenerative disorders, epilepsy and neurovascular system, where the visibility of the IPNP in France and abroad is excellent. To achieve its goals, the IPNP gathers teams of researchers and clinicians with internationally recognised and complementary expertise. These teams are rigorously selected by an international Scientific Advisory Board (iSAB). Overall, the scientific objectives of the unit are excellent.

Assessment on the unit's resources

Over the past contract, IPNP has been composed of ten senior research teams and 4 junior teams that independently develop basic and translational research programs in adequation with the institute's objectives and relying on complementary experimental strategies to cover the full spectrum of brain description from molecules to the whole organ. The human resources and expertise present in the different teams are generally well balanced and adapted to their project. The local technological environment is outstanding, with state-of-the art technological facilities handled by skilled staff who provide technical, methodological and operational support in behavioural phenotyping of rodents, imaging from a single molecule to the brain *in vivo*, biochemistry and biophysics. The unit has been successful in securing funding, with a total annual income of about 4–5 M€, including 800 k€ annual recurrent funding from IPNP institutions. Overall, the IPNP resources are excellent to outstanding and strongly benefit from local, well-equipped, technological platforms and its close collaboration with the GHU Paris (Sainte-Anne Hospital) and the Imagine Institute that are highly relevant to preclinical and translational research in neuroscience.

Assessment on the functioning of the unit

The IPNP has implemented an efficient management structure composed of:

i) a Steering Committee (DirCo) that ensures the daily management of the unit and is the central place of decision-making for any issues, being administrative, financial or scientific,

ii) the Committee of Team and Technology Platform Leaders of the Unit (TeamCo)

iii) and the Laboratory Council (LabCo).

These three levels of management ensure fluidity of the decision-making process and are generally well accepted by the staff, even though team leaders might progressively be more implicated in the strategic orientations of the unit. Overall, the functioning and management of the unit are excellent.

1/ The unit has set itself relevant scientific objectives.

Strengths and possibilities linked to the context

The IPNP has set the ambitious objectives to produce high-quality and original research in psychiatry and neuroscience by using an interdisciplinary approach from molecular and cellular mechanisms to clinical research, and to recruit top-level scientists. To achieve that goal, the IPNP has implemented a rigorous selection process by an international Scientific Advisory Board (iSAB) consisting of independent scientists, with expertise in clinical, translational and basic neuroscience fields related to those investigated at the IPNP. The iSAB is also consulted for the promotion of junior team leaders to senior team leaders 3–5 years after their recruitment, the restructuration of the teams, the scientific strategy and future orientations of each team, and the plans for the renewal of the director of the Unit. Among the major scientific achievements of the IPNP, one can quote:

i) the demonstration of reciprocal interactions between oligodendrocytes and neurons that are key for remyelination and maintenance of the excitation/inhibition balance;

ii) the demonstration of the role of VAMP7-dependent secretion of Reticulon 3 in neurite growth;

iii) the characterisation of pathophysiological roles of Cajal-Retzius cells;

iv) the discovery of new synaptic plasticity mechanisms in hippocampal CA2 area;

v) the identification of epigenetic changes during conversion to psychosis in high-risk of transition patients;

vi) the characterisation of key mechanisms of cerebral small vessel diseases;

vii) the identification of genetic susceptibilities to anorexia nervosa;

viii) the discovery of a novel mechanism of spontaneous intracerebral hemorrhage,

ix) and major breakthrough in the prevention of stroke recurrence.

To favour the development of translational research, the IPNP has established strong interactions with Sainte-Anne Hospital. These interactions are facilitated by the fact that more than 40 teacher-hospital practitioners/hospital practitioners are doing their research in IPNP teams and the organisation of a series of basic research-clinical research seminars entitled '12:30 of the research'. They also led to the recruitment of a young PI and the opening of a technician position thanks to GHU's funding. The development of translational research at the IPNP also benefits from a tripartite UPC/GHU/Inserm agreement formalising cooperation between the site's basic and clinical research teams and the support of mixed research/clinics profiles by GHU Paris and INSERM. Finally, one IPNP team has developed strong partnership with the Imagine Institute (Institut des Maladies Génétiques at Necker Hospital) to foster interactions with human geneticists and clinicians, experts in rare diseases, brain imaging and malformations. The IPNP has also been proactive in defining the

forward-looking aspects of its policy by favouring discussions on its scientific strategy around weekly-organised seminars or during IPNP scientific retreats that are planned every two years after the success of the first edition in 2022.

Weaknesses and risks linked to the context

There is no major weakness or risk identified in the IPNP scientific strategy even though the importance given to the iSAB's recommendations (e.g. for new team recruitment or team reorganisation) seems to be a bit high compared to that of the TeamCo, which has the best knowledge of the possibilities and opportunities offered by the unit's environment. The selection of teams using scientific excellence as the sole criterion could lead to an increase in the number of research topics at the IPNP. Such a dispersion could be detrimental to the institute's visibility on the long term.

2/ The unit has resources that are suited to its activity profile and research environment and mobilises them

Strengths and possibilities linked to the context

The IPNP benefits from substantial funding from its institutions (~800 k€ yearly) that is mostly (~55%) used for common expenses (maintenance contracts, shared software licenses, shared equipment mainly on platforms and common services) and the acquisition of novel common equipment (~170 k€/year). The remaining recurrent funding (~320 k€/year) is allocated to teams whether well or poorly funded so that they are not totally dependent on external funding. In addition, IPNP has been very successful in securing funding with a total annual income of about 4–5 M€ yearly. Its financial resources increased over the past contract, reflecting the arrival of new teams. Regarding technological resources, the IPNP hosts technological platforms with state-of-the-art equipment that are handled by skilled staff and provide technical, methodological and operational support especially adapted to research projects in psychiatry and neuroscience. These include:

i) a behavioural phenotyping platform for the behavioural evaluation of rodents (both mice and rats) in the fields of anxiety, depression, reward, eating behaviours, olfaction, motor behaviours, sensorimotor gating, communication, social behaviours and cognition;

ii) an imaging (NeurImag) platform that is part of the national France BioImaging infrastructure and the national network of platforms IBiSA, ensuring high-quality equipment and services as well as technological developments. This facility is equipped with 7 advanced microscope systems that cover a wide range of spatiotemporal resolution, from videomicroscopy to super-resolution imaging (PALM, STORM, STED 3D and SIM). Notably, the technological offer of the NeurImag platform has recently been implemented with fUS (ultrasounds) imaging and a unique service for the production of ready-to-use primary cultures of different CNS cell populations;

iii) and a biochemistry and biophysics facility that provides a wide range of services including nucleic acid and protein production, protein purification and functionalization, analysis of protein-protein and protein-lipid interactions, etc.).

The IPNP also benefits from the technological resources of Sainte-Anne Hospital, such as a 3T research MR platform for human brain imaging allowing collaborative translational projects dedicated to imaging biomarkers, and a new methylomics platform launched under the supervision of an IPNP scientist. This large technological offer on site provides a strong added value to the research projects of the IPNP and largely contributes to its visibility and success.

Weaknesses and risks linked to the context

Although the human resources and technical skills present in the teams are generally adapted to the teams' projects, four teams do not benefit from the technical support of a tenured technician/engineer to ensure the important function of lab manager. Overall, there is a deficit of tenured technical staff not only inside certain teams, but also in support services and some platforms, such as the animal and behavioural testing facilities, which can be detrimental to the projects of the unit and its teams on the long term. Maintaining the technological offer and the level of expertise of technological core platforms at the highest international standards requires the constant renewal of equipment and the recruitment of highly skilled engineers that is uncertain in the current context, even though the IPNP seems to benefit from a strong support from its supervising bodies.

3/ The unit's practices comply with the rules and directives laid down by its supervisory bodies in terms of human resources management, safety, environment, ethical protocols and protection of data and scientific heritage.

Strengths and possibilities linked to the context

In line with the recommendations of its institutions, the IPNP complies with principles of human resource management that respects professional and gender equality, and lack of discrimination in terms of training, internal mobility and career development for its staff. Women are well represented in all staff categories, including team leaders (7 men and 7 women in the current contract, five men and eight women in the future contract) and IPNP executive bodies are all gender balanced (DirCo: 4 women/4 men; TeamCo: 17 women/15 men; LabCo: 11 women/9 men). Regarding career development, promotions at the IPNP affect all categories of staff (technicians, engineers, administrative staff, researchers) with a success rate of 25% for researchers and 52% for engineers, technicians and administrative staff, between 2017 and 2022. All staff categories had access to training, including doctoral students and staff with fixed-term contracts (20% of trainees). The rate of access to training has significantly improved between 2017 and 2022, reaching 47% of people trained, and 30% of them were trained for animal experimentation. IPNP has also implemented a Mediation Committee in charge of the initial investigation of problems reported by any alerting party (conflict within a team, non-compliance with the Research Ethics Charter, conflict of interest, authorship issues, etc.) and of proposing solutions after the interview of the different protagonists. Regarding data traceability, the IPNP has implemented the laboratory notebook solution proposed by Inserm (LabGuru) to guarantee durable follow-up of experiments, rapid access to data and aid to decision-making. The IPNP is strongly committed to sustainable development and has implemented a number of actions to limit the environmental impact of its activities. These include the setting of freezer temperature to -70 °C instead of -80 °C, improvement of equipment maintenance in order to extend its life, recycling of computers, limiting trips for staff in the same team, encouraging selective waste collection and favouring cycling by planning the acquisition of a bike shelter in 2023, etc. Thanks to the experience acquired and the tools developed during the Covid-19 crisis, the IPNP has all the tools necessary to quickly build a continuity plan or a disaster recovery plan, whenever required. It has also been proactive in the prevention of biological and chemical risks and implemented adequate actions such as specific training, and raised awareness of its staff on these issues according to the recommendations of its supervising bodies.

Weaknesses and risks linked to the context

There is no permanent dedicated staff for the IT service of the unit and all the data storage systems seem to be located within the IPNP building with currently no remote backup in another building. Likewise, there is no staff dedicated to the maintenance of the IPNP building and often the Executive Director needs to find solutions for these kinds of issues, even though it is not the role of staffs with such a position who also ensure the numerous administrative tasks of the unit. The role and the existence of the Mediation Committee are not well known to all the unit's personnel. Even if the promotion rate of engineers/technicians is high, there is a huge lack of a human resources contact person for the staff employed by the University. The technicians/engineers with a fixed term contract do not systematically benefit from a yearly interview with their supervisor.

EVALUATION AREA 2: ATTRACTIVENESS

Assessment on the attractiveness of the unit

The IPNP attractiveness is excellent to outstanding, as shown by:

i) the recruitment of seven new team leaders over the reporting period,

ii) the fundraising capacity of IPNP researchers (~4–5 M€ collected yearly from various national and international agencies),

iii) their participation in ~35 different editorial boards as well as international and national scientific committees,

iv) their responsibilities in international learned societies

v) and their invitations to give conferences at important international meetings (SfN, FENS, NeuroFrance, ASCB CellBio, GRCs etc.) or prestigious universities (UCL, Harvard, Yale, Tokyo University, etc.). IPNP researchers also received more than twenty awards, including prestigious prizes from academic and private institutions.

1/ The unit has an attractive scientific reputation and is part of the European research area.

2/ The unit is attractive because for the quality of its staff support policy.

3/ The unit is attractive through its success in competitive calls for projects.

4/ The unit is attractive for the quality of its major equipment and technical skills.

Strengths and possibilities linked to the context for the four references above

The IPNP has been very successful in attracting new team leaders (7 over the evaluation period), including junior PIs who were all supported by competitive starting grants (ATIP Avenir, FRM Emergence, MSCA-IF (Marie Skłodowska-Curie Actions Individual Fellowships). The IPNP obtained a large number of competitive grants, which reflects the relevance of the research topics covered and its contribution to the global research strategy at the national and international levels. These include international grants (3 ERANET-Neuron, one ERA-FLAG, one MSC ITN program and 2 NIH grants), ANR grants (30 over the evaluation period totalling ~6 M€, 90% of which being coordinated by IPNP members), grants from other French public agencies (IDEX, RHU…), and 42 grants from charities (FRM, FRC, Fondation de France, Fondation Leducq, ARSEP etc.) totalling ~4.3 M€. The IPNP attractiveness also benefits from the outstanding technological environment in the Paris area, and from the platforms hosted at the institute with highly skilled dedicated staff and state-of-the-art instruments acquired thanks to grants obtained in response to calls dedicated to platforms from INSERM, University and Région Île de France among others. The attractiveness of the IPNP also benefits from its interactions with Sainte-Anne Hospital, that hosts a 3T research MRI platform and a methylomics platform, facilitating the development of translational projects. IPNP scientists are strongly involved in editorial activities and fifteen of them hold editor positions in ~35 editorial boards of specialised and general journals such as Cell. Mol. Life Sci., eLife, EMBO Journal, Nucleic Acids Res., Mol. Cell Biol., Physiological Reviews, etc., and regularly review manuscripts submitted to these and other journals. IPNP members also participate in national and international scientific committees, such as Era-Net Neuron and ERC consolidator panels, FRM, Alzheimer Foundation (chair), ANR, FRC (president), French Society of Neurology (president), Idex scientific council, INSERM CSS1 and CSS4, etc. Several IPNP researchers obtained prizes, including prestigious ones such as the Prize of the Fondation Lefoulon-Delalande-Institut de France, the young researcher prize of Fondation Bettencourt-Schueller, and the Camille Wohringer prize (FRM). Notably, several prizes rewarded young scientists, underscoring the quality of the formation through research and mentoring at the IPNP.

Weaknesses and risks linked to the context for the four references above

No IPNP researcher obtained an ERC grant over the past contract, but one PI holder of an ERC consolidator grant will join the institute at the beginning of the forthcoming contract. The number of young scientists recruited at the IPNP on competitive researchers and/or associate professor positions is somewhat limited for such a large institute. Only one of the four researchers who obtained such a position is currently working at IPNP. Although the IPNP provides a 60 k€ package to newly created teams, which a represents a valuable effort with respect of the core funding of the unit, such a package is not competitive, compared to those proposed by other sites in France and abroad.

EVALUATION AREA 3: SCIENTIFIC PRODUCTION

Assessment on the scientific production of the unit

Overall, the IPNP scientific production is excellent in a quantitative and qualitative point of view, with 1892 publications completed over the reporting period, of which 1474 are original articles, and nearly 40% of these are signed in a leading position (first, last, corresponding authors). The original articles of the unit obtained an excellent international visibility as revealed by the standardised citation index almost twice higher than the world average (average ICN = 1.99). These include a number of articles published in internationally reputed journals, but relatively few in top-notch scientific journals, and the contribution to leading scientific journals is unevenly distributed between the teams. Around 10% of publications involved at least two IPNP teams, which is remarkable for such a young institute.

1/ The scientific production of the unit meets quality criteria.

2/ The unit's scientific production is proportionate to its research potential and properly shared out between its personnel.

3/ The scientific production of the unit complies with the principles of research integrity, ethics and open science. It complies with the directives applicable in this field.

Strengths and possibilities linked to the context for the three references above

When it was created, the IPNP has set the ambitious objectives to:

i) produce seminal discoveries with contributions from several teams gathering clinical and basic data answering important fundamental and clinical questions

ii) and contribute to technological developments and their translation into the clinics via a few highly visible publications.

The consolidated collaborations between the IPNP and Hospital Sainte-Anne (GHU Paris Psychiatrie Neurosciences) together with the presence of state-of-the-art technological platforms at the institute and the participation of IPNP teams in international consortia provides a unique environment to carry out highly visible multidisciplinary research in fundamental and applied neuroscience.

In line with these objectives and its original positioning at the interface of basic and translational neuroscience, the IPNP stands out by its large scientific production, with 1892 publications, including 1474 original articles over the reporting period, even though this production is imbalanced in favour of clinical teams. Nearly 40% of IPNP publications are signed in position of responsibility (first, last and/or corresponding author). Some of them were published in wide readership generalist journals (Nature Communications, PNAS, Elife, Cell Report, J. Cell Biol, N Engl J Med, etc.) or high-ranked journals in the fields of neuroscience and neuropsychiatric disorders (Nature Genetics, Neuron, Molecular Psychiatry, Brain, Neurology, JAMA Neurology, Cerebral Cortex, etc.). The visibility of the IPNP production is excellent, as shown by its standardised citation index almost twice higher than the world average (average ICN = 1.99) as well as by the proportion of articles classified in the Top 10% corresponding to more than twice the global share of original articles most cited (21%). Articles signed in position of responsibility by at least one researcher from the unit are also very visible with 14.3% of them ranked in the Top 10%.

Around 10% the IPNP publications involve at least two teams of the unit, or one team and one of its technological platforms, which is remarkable given the recent creation of the institute and highlights the strong capacity of the IPNP teams to generate synergies and their strong commitment in the scientific policy of the unit. The scientific production of the IPNP complies with the EU guidelines (2007/526/EC) for the accommodation and care of laboratory animals. None of its projects is conducted without official approval by ethics committees. The unit is strongly committed in the reduction of animal experiments to the minimum required for achieving statistically significant data and follows the recommendations from the Gircor, the national network for transparency in animal research. The IPNP is also strongly engaged in open science: one IPNP engineer is in charge of depositing IPNP publications to public archives and the institute is open to sharing its data with the community.

Weaknesses and risks linked to the context for the three references above

In quantitative terms, the scientific production of the unit is strongly unbalanced in favour of the clinical research. However, the pandemic emergency might have more affected some of the teams with intense preclinical activities. Activity is now back to normal and contingency plan are in place to improve production in the next years.

Publications in highly visible journals are not equally distributed among the teams.

Only 60% of the IPNP articles are deposited in a public archive in spite of the strong commitment of the unit in open science and the presence of a scientific officer in charge of depositing publications in the Hal public archive.

EVALUATION AREA 4: CONTRIBUTION OF RESEARCH ACTIVITIES TO SOCIETY

Assessment on the inclusion of the unit's research in society

Overall, the inclusion of IPNP research in society is excellent to outstanding. The IPNP is strongly supported by numerous charities (>4 M€ collected during the reporting period) and has developed regular interactions with several patient associations. The IPNP scientific staff are committed in scientific knowledge diffusion to the lay public and various science outreach activities, including conferences, digital workshops, visits of the lab, interventions in various media. The interactions of the IPNP with the economic world are outstanding, with the hosting of two start-up companies, the cofounding of three additional biotechs by IPNP staff and scientific partnerships with several companies (Leica, Bruker, Hybrigenics).

1/ The unit stands out for the quality and the amount of its interactions with the non-academic world.

2/ The unit develops products for the cultural, economic and social world.

3/ The unit shares its knowledge with the general public and takes part in debates in society.

Strengths and possibilities linked to the context for the three references above

The goal of the IPNP is to understand the pathogenesis of psychiatric and neurological diseases in order to propose new biomarkers and curative strategies for these strongly debilitating disorders, which positions the unit at the heart of major societal concerns. In line with this central place, IPNP researchers regularly give conferences to the lay public organised by various charities (Unafam, Generation 22, ARAPI, Unafam, Generation 22, ARAPI) and are present on various media (France Culture, France Inter, France 5…). They developed websites for youths seeking for information on mental health (www.santepsyjeunes.fr) and for health professionals by providing training, documents in relation of youth mental health (www.institutdepsychiatrie.org/reseau-transition/). They are also present on social networks, including Instagram, 'X', Tik Tok, LinkedIn and Youtube. The institute is strongly supported by numerous charities (FRM, FRC, Fondation Bettancourt, Fondation de France, ARSEP, AFM, Fondation Maladies Rares etc.) with a total amount of 4.3 M€ collected over the reporting period, and regularly organises visits of its platforms by patient associations (Alzheimer's Foundation, ARSEP, Rotary Club/FRC, Csnk2a1 Foundation). One IPNP team received the label FRM team and one team leader has been the President of the FRC Scientific Council. With regard to interactions with the economic world, the IPNP hosts two biotechs, namely Panntherapi, which develops inhibitors of pannexin channels as therapies for epilepsy, and AtmosR which develops therapeutic solutions for patients suffering from congenital central hypoventilation syndrome (CCHS, Ondine syndrome) and other severe neurological disorders. IPNP scientists were co-founders of three other companies, Iconeus (provider of fUS imaging), Dextrain (diagnosis and treatment of hand impairment) and AiiNTENSE (AI-based data treatment and integration into eCRFs contained in various clinical sources). The IPNP has partnerships with industry in the CIFRE (Conventions industrielles de formation par la recherche) framework and recruited a postdoc in frame of a partnership with Hibrygenics. It collaborates with two companies specialised in microscopy, and marketed membrane probes and lipid droplet probes to more than 200 companies through the Idylle company.

Weaknesses and risks linked to the context for the three references above

The number of patents filled (5) is quite low with respect to the valorisation potential of IPNP research and the size of the unit.
The participation of the different teams in scientific mediation events is unbalanced and certain teams could be more active in this area, given the potential societal and medical outcomes of the research carried out at the IPNP.

ANALYSIS OF THE UNIT'S TRAJECTORY

Over the past few years, the IPNP has seen a marked increase in its funding capacity and a marked improvement of its publication record, making it a highly visible research centre specialised in Neuroscience at the national and international levels. These past successes put the institute in ideal position to pursue during the forthcoming term the projects implemented since its creation, aimed to:

i) understand how the brain works at different levels, from molecular mechanisms to cells, neuronal networks and whole organ thanks to innovative and interdisciplinary researches,

ii) and bridge the gap between basic and clinical research to understand the pathophysiology of psychiatric and neurological diseases in order to propose new therapies, devices and diagnostic tools.

This multiscale strategy from bench to bed side strongly relies on state-of-the-art facilities supported by skilled staff and the closed interactions with Sainte-Anne Hospital's clinicians established during the current contract. IPNP proposes to further extend these interactions by taking advantage of a tripartite university/hospital/Inserm agreement formalising cooperation between the site's basic and clinical research teams and of the opportunity offered by GHU and Inserm to hospital practitioners holding a PhD awarded less than ten years ago, to spend between four and five half-days per week, for three years, on a collaborative project with an IPNP team. To increase the attractiveness of IPNP towards medical staff, GHU and IPNP are also planning to implement funding for medical students carrying out their master's thesis at IPNP.

The institute's teams will only evolve marginally, with a core of eleven teams remaining at IPNP, while two teams will leave and three will join the institute. The IPNP will remain focused on topics that have made its reputation (genetics and epigenetics of psychiatric diseases, neurodevelopment, brain tumours, aging and neurodegenerative diseases and neurovascular system) while reinforcing basic and translational research related to psychiatric diseases, and the use of iPSCs and organoids. The committee also endorses the decision to prioritise recruitment of a team working on zebrafish following the planned departure of the team using this model.

Regarding technological core development, the IPNP plans to build bioinformatics and electrophysiology platforms. The IPNP also plans to develop bridging technologies, such as combining behaviour and 2-photon microscopy, and to acquire skills in machine learning approaches for image analysis, which is perfectly in line with its objectives. One risk is the difficulty of raising funding for 'basic' equipment renewal and keeping the technological offer of the hosted platforms at the best international standards.

Recommendations

The committee recommends that the IPNP prioritises the strengthening of its current topics for the recruitment of new teams. The committee also recommends that the IPNP pursues its policy of opening up the platforms to outside users, and to this end optimises their management and pricing policy, which will enable them to access regional and national calls specifically dedicated to the platforms. One way for management optimisation is to adopt an ISO9001 and/or NFX 50–900 certification policy for the main facilities. Integration of the main facilities to the GIS IBiSA can strongly help to that direction.

RECOMMENDATIONS TO THE UNIT

Recommendations regarding the Evaluation Area 1: Profile, Resources and Organisation of the Unit

The committee recommends that the IPNP better defines its scientific strategy for recruiting new teams, and considers strengthening of existing topics and the use of models and technologies available at the institute, rather than basing its decisions solely on the scientific excellence of applicants, in order to avoid excessive thematic dispersion that might be detrimental to the institute's visibility. In particular, it recommends that the IPNP prioritises the recruitment of teams performing preclinical research in the fields, making its reputation on the clinical side (psychiatric disorders and stroke) to better match its preclinical and translational research and, ultimately, to further improve its international visibility in these specific fields. The committee acknowledges the key role played by the international SAB during the first years of the institute and especially its role in the selection of talented and promising young team leaders. Nevertheless, it recommends that the team leaders are progressively more involved in the IPNP strategic orientations and, to that aim, that the institute organises annual team leader retreats so that they can discuss in a collegial manner about any strategic issues. The committee recommends that the IPNP finds a solution in concertation with its institutions to hire permanent staff in charge of infrastructure/building maintenance and IT. It also recommends that the IPNP implements a unique strategy for backing up data generated by its teams and platforms and a remote backup in a different building.

Recommendations regarding the Evaluation Area 2: Attractiveness

The committee recommends that IPNP scientists are more proactive in applying to European grants, including ERC grants, Doctoral Networks and Marie Skłodowska-Curie postdoctoral fellowships, in order to attract high-potential research fellows from abroad who might be potential candidates to INSERM/University tenure positions. In this regard, the committee also recommends that IPNP favours the reinforcement of its smallest teams, especially those that comprise only one tenured researchers (the PI), through the recruitment of permanent researchers and/or lecturers.

Recommendations regarding Evaluation Area 3: Scientific Production

The committee recommends that the IPNP pursues its effort to increase the number of publications in top-notch journals and to increase the percentage of publications deposited in open archives in order to achieve a coverage as complete as possible. The committee also recommends that the IPNP increases the proportion of multidisciplinary publications involving several teams of the unit, for instance by encouraging collaborations between IPNP teams through the internal funding of common projects.

Recommendations regarding Evaluation Area 4: Contribution of Research Activities to Society

In view of the valorisation potential of the research made at IPNP, the committee recommends that the unit tries to fill more patents in order to better exploit this potential. Some teams should more actively participate in science outreach events, capitalising on the strong experience of other teams in this field.

TEAM-BY-TEAM OR THEME ASSESSMENT

Team 1: Interactions between neurons and oligodendroglia in myelination and myelin repair

Name of the supervisor: Maria Cécilia ANGULO

THEMES OF THE TEAM

The team focuses on the roles and mechanisms of neuron-oligodendroglia interactions during postnatal cortical development in physiological and pathological conditions. It explores how neuronal activity regulates the function of the oligodendrocyte (OLs) lineage and, how OLs cells and myelin affect neuronal activity by ultimately influencing the behaviour of neuronal networks as well as sensorimotor and cognitive functions. The team uses a multidisciplinary approach, including *ex vivo* and *in vivo* electrophysiology, calcium imaging, optogenetics, advanced optical methods, and behaviour studies in relevant mouse models. Its ultimate goal is to clarify the function of interneuron-oligodendroglia interactions in the cerebral cortex and define new processes supporting myelin repair.

CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT

The previous recommendations were to publish at least one article in 'top' journals. This has been fulfilled since the team published two articles in Nat Comm, which together with other articles have definitely increased its international visibility and allowed it to obtain prestigious grants and fellowships. The committee also suggested the team to aim for a better gender balance, which has improved (9 women and 6 men over the 2017 to present period), to be involved in the supervision of more students and to recruit postdocs. During the 2017–2022, the team has hosted five PhD students and five postdocs. Finally, the committee recommended considering a strategy for translation (still in progress) and seeking both internal and external collaborations (definitely improved). Overall, the team followed the recommendations of the previous report.

WORKFORCE OF THE TEAM: in physical persons at 31/12/2022

Catégories de personnel	Effectifs
Professeurs et assimilés	0
Maîtres de conférences et assimilés	0
Directeurs de recherche et assimilés	1
Chargés de recherche et assimilés	0
Personnels d'appui à la recherche	1
Sous-total personnels permanents en activité	**2**
Enseignants-chercheurs et chercheurs non permanents et assimilés	0
Personnels d'appui non permanents	2
Post-doctorants	3
Doctorants	3
Sous-total personnels non permanents en activité	**8**
Total personnels	**10**

EVALUATION

Overall assessment of the team

The team focuses on the interactions between neurons and oligodendroglia in myelination and myelin repair and is very well recognised at the international level. The committee considers that the team is globally excellent to outstanding. The scientific production is excellent with respect of the size of the team, the attractiveness and link with society are both excellent. Resources and funding are excellent with prestigious fellowships obtained by postdocs. However, the team suffers from a lack of permanent positions even though a permanent technician has been recruited in 2023.

Strengths and possibilities linked to the context

The team hosts ten persons including the PI and one recently recruited technicians as permanent staff and eight as non-permanent (IE, PhD, postdocs) and focusing on the interactions between neurons and oligodendroglia (OLs) in myelination and myelin repair. Its main contributions are the demonstration that:

i) myelination of Parvalbumin interneurons is relevant for both cortical inhibitory circuit function and behavioural performances

ii) and neuronal activity improves remyelination and conduction by increasing the density of OLs and myelin.

The team published nineteen articles and reviews, including ten (52%) signed in first or last position. Some of its papers are in excellent Journals (Nat Comm (2), Glia, JCI Insight, eLife) and have been well cited. During the evaluation period, the team hosted five PhD students and five postdocs. Out of the five postdocs, only two published very well, while only three PhD students published as second or third co-authors. Resources are excellent with several prestigious fellowships obtained by postdocs (for a total of 687 k€) and a remarkable level of funding as PI (1,850 k€ from FRM, ANR, ARSEP, ERA-NET Neuron) or co-PI (4 grants from NMSS, EJP RD and ANR). The team received the prestigious FRM Team label in 2021. The funding obtained was essential to implement new techniques, particularly for the *in vivo* experiments, some of which have already yielded publications and others are still in progress. The team's expertise in neurophysiology and neuron-oligodendroglia interactions has also been reinforced by various collaborations at IPNP (teams 7 and 8, NeurImag) and abroad, bringing different and complementary expertise.

The team leader has assumed collective responsibilities (treasurer of the French Society of Neuroscience) and has contributed to various scientific networks and meetings at national (NeuroFrance 2021 and 2023, French Club of glial cells) and international (FENS 2022, 13th to 15th European meeting on glial cells in health and disease, the largest meeting on glial cells worldwide) levels. She has been invited at ten international and national conferences or seminars, and has been interviewed by national and international media.

Several team members have been involved in outreach activities promoting the research on Multiple Sclerosis and in events organised with patients in collaboration with the ARSEP Foundation. The PI is an associate editor of Cell Mol Life Sci, a Springer Nature Journal. She is also highly involved in teaching at the Master 1 and 2 levels and has taken part in several national and international institutional committees (member of the INSERM CSS4 Neuroscience, member of the scientific committee of the FRC Foundation and ANR CES16, member of the panel of the ERA-Net Neuron program, etc.). One postdoc of the team has been awarded the L'Oréal-UNESCO Young Talent Award France for Woman in Science in 2021.

Weaknesses and risks linked to the context

The reporting period has been marked by a large progress of the team in terms of publications, invitations to give conferences, and overall visibility. However, the team's trainees, and in particular PhD students, have mainly co-first authorships and only some of the postdocs trained in the team have very good publications. The team leader has not published an experimental article coming from her team and as last author since 2020. The team leader is strongly involved in several institutional and organisational committees, which might be detrimental to the lab work and her team. After the leave of an engineer, the team suffers from a lack of technicians and young researchers with permanent positions, but could recently recruit a technician with a permanent position.

Analysis of the team's trajectory

The team aims to understand the role of neuron-oligodendroglia interactions during postnatal cortical development and in pathological conditions. It investigates how neuronal activity regulates the function of oligodendrocyte (OL) lineage cells and, in turn, how these cells and myelin affect neuronal activity, and thus influence sensorimotor and cognitive functions. The team has used acute slices in the past but has recently developed skills for i*n vivo* studies. Accordingly, the team will combine electrophysiology, calcium imaging, optogenetics, chemogenetics on *ex vivo* and *in vivo* preparations with behavioural studies in relevant mouse models.

The team develops two research lines:

i) understanding the function of interneuron-oligodendroglia interactions in cognition

ii) and assessing whether specific behavioural paradigms are an attractive strategy for myelin repair in myelin-related disorders.

The first research line focuses on the study of the close relationship between GABAergic interneurons and oligodendrocyte precursor cells (OPCs) in the developing neocortex. The team hypothesises that early interneuron-oligodendroglia interactions are crucial to establish proper execution of complex brain processes and that cortical impairments in neurodevelopmental and myelin-related disorders are caused by abnormal interneuron myelination. The team will assess the effect of demyelination and remyelination on the conduction of action potentials of parvalbumin (PV) interneurons by using genetically encoded voltage indicators to record membrane potential fluctuations in single axons of acute cortical slices in control conditions, after demyelination and during remyelination. Moreover, it will decipher the role of PV interneuron-OPC synapses in the construction

of cognitive functions by performing behavioural tasks combined with *in vivo* electrophysiology. The second research line seeks to evaluate the role of neuronal activity in promoting myelin regeneration in preclinical models. The team aims to understand which neuronal signalling mechanisms controlling the function of OPCs and OLs and whether stimulating neuron-oligodendroglia interactions improves remyelination. In collaboration with the NeurImag platform at IPNP, it will assess the role of Ca^{2+} signals of oligodendroglia in neuronal activity-dependent myelin repair by characterising Ca^{2+} signals from OL lineage cells *in vivo* by using miniscopes. The team expects that OL Ca^{2+} signals increase during remyelination and that the behavioural intervention will improve myelin regeneration. Furthermore, in collaboration with Team 8, the team will study the contribution of developmental cell death of interneurons and OPCs to the assembly and myelination of cortical networks, and their impact on cognitive processes.
Each research line is well funded and performed by trained postdocs and PhD students.

RECOMMENDATIONS TO THE TEAM

The committee recommends the team leader to continue on this very positive trajectory by focusing on the two major lines of research she has proposed and which are well funded.
The committee also suggests to partially decrease her extra lab activities (institutional and congress organisation) in order to follow the different experiments proposed in the project and make sure that PhD students and postdocs obtain high-level publications.
The team leader should also increase the potential translational impact of her research by interacting with the GHU and start-ups hosted at the IPNP. The time- and effort-consuming set-ups of the different *in vivo* approaches in which the team has invested over the last two years should be maintained in the lab and transferred to long-term team members, such as the permanent technical staff and young researchers.

Team 2: Membrane Traffic in Healthy & Diseased Brain

Name of the supervisor: Thierry GALLI

THEMES OF THE TEAM

The team investigates the dynamics of intracellular membranes in developing, maturing and aging neurons, in physiological and pathological contexts, including psychiatric diseases, brain tumours and neurodegenerative diseases, using cutting-edge techniques of biochemistry, biophysics, genetics, cell biology and live and super-resolution microscopies. The focus is on the proteins that are at the heart of intracellular membrane docking and fusion events.

CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT

The previous committee recommended that the team tries:

i) to increase its international interactions (e.g. by obtaining international funding),

ii) to supervise more PhD students,

iii) and to avoid project diversification or to give responsibilities of some projects to senior members.

Most of these recommendations have been fulfilled: e.g. 4 foreign postdocs and 9 PhD students have been trained, even though international funding remains low (one ERA/FLAG). Specific competences (e.g. in imaging and biophysics) and responsibilities of senior scientists are now well recognised and their visibility increased accordingly.

WORKFORCE OF THE TEAM: in physical persons at 31/12/2022

Catégories de personnel	Effectifs
Professeurs et assimilés	0
Maîtres de conférences et assimilés	0
Directeurs de recherche et assimilés	2
Chargés de recherche et assimilés	2
Personnels d'appui à la recherche	2
Sous-total personnels permanents en activité	**6**
Enseignants-chercheurs et chercheurs non permanents et assimilés	1
Personnels d'appui non permanents	1
Post-doctorants	2
Doctorants	6
Sous-total personnels non permanents en activité	**10**
Total personnels	**16**

EVALUATION

Overall assessment of the team

The committee considers that the team is globally **excellent.** The team is internationally recognised for its expertise and methodological knowhow on proteins that are essential for intracellular membrane docking and fusion events, and its developments in biophysics and photonics imaging. Its **excellent** scientific data have been published in high-profile journals and the best journals of the discipline. The team gathered ~1.5M€ of grant funding from mostly national sources over the evaluated period. Its attractiveness is **outstanding,** as shown by the recruitment of one foreign permanent researcher and five foreign postdocs, the training of 9 PhD students and international collaborations. The link with society is **excellent.** The senior members are invited and/or organised international courses and conferences. They also successfully fulfilled heavy administrative or scientific responsibilities.

Strengths and possibilities linked to the context

This is a large and well-established team with five permanent researchers, including one 'chargé de recherche' (CR) recently recruited who obtained a JCJC 'Jeunes Chercheuses et Jeunes Chercheurs' ANR grant and three permanent technical staff. The team is internationally recognised for its contributions to unravel the functions of proteins that are essential for intracellular membrane docking and fusion events.

(1) Recent data deal with the function of Mitofusin, a protein that mediates the outer mitochondrial membrane fusion, and showed that its HR2 domain mediates membrane docking, while the HR1 domain induces membrane fusion through its amphipathic helix. This mechanism for fusion is distinct from that described for SNARE and viral proteins but is related to that of the Endoplasmic Reticulum (ER) fusion protein Atlastin (Embo Report, 2018).

(2) Capitalising on previous data, the team described a mechanism whereby biomechanical constraints regulate VAMP7-dependent lysosomal secretion via the trafficking adaptor LRRK1 and VARP, a VAMP7- and kinesin 1-protein partner that interacts with VAMP7 in a competitive manner to control the peripheral pool of secretory lysosomes (iScience, 2018; Traffic, 2018). The team also showed that VAMP7-dependent late endosomal/lysosomal secretion mediates secretory reticulophagy (Autophagy, 2018; Front. Cell Dev. Biol, 2022) a pathway allowing for UPS of ER proteins such as reticulons and atlastins, which play a major role in neurons. Importantly, the team bridged two yet unconnected cellular pathways. It showed that in neurons, nutrient restriction and autophagy regulate axonal growth and neuronal polarity and that VAMP7 mediates nutrient restriction/autophagy-dependent neurite growth and the secretion of ER-phagy factor Reticulon (Cell Report, 2020).

(3) The team also contributed to the development of:

a. MemBright: a family of fluorescent molecules that stain in different colors the cell plasma membrane in an efficient manner. These probes are compatible with various microscopy techniques (Cell Chem Biol, 2019);

b. Statistical Object Distance Analysis (SODA) that significantly improves the detection of associated proteins in conventional and super-resolution microscopy.

The team validated this technic on several models (e.g. with three-color SIM images of hippocampal neurons, or by applying it to ER-plasma membrane contact sites). Altogether the four senior members raised ~1.5 M€ funding from mostly national sources (ANR, EC/ERA-FLAG, INCa, Fondation de France, Fondation pour la Recherche Médicale, IDEX Université Paris Cité, France-Relance 2030, and AFM) which provided security for the continuation of all the research lines. During the reporting period, the team attracted one foreign permanent researcher as CR Inserm, 4 foreign postdocs and 9 PhD students. The team actively collaborates with French and international scientists resulting in approximately twenty co-publications. The team leader and the senior members organised conferences and symposia (e.g. Mechanisms of Autophagic and Endolysosomal Trafficking in Neuronal Function and Neurodegeneration, ASCB CellBio 2022, Washington DC, USA, 2022; Functional Microscopy of the Living (MiFoBio) –2018, 2021, 2023). They are regularly invited to give conferences at international meetings (ASCB-EMBO 2019, Frontiers in Neurophotonics (Quebec) 2022). They are involved in editorial activities (associate editor of Traffic since 2021, member of the Editorial Board of the Journal of Biological Chemistry (2012–2022), member of the Editorial Board of Contact since 20,218) and were awarded prizes (excellence INSERM premium reward PEDR). The senior members of the team are also highly committed in teaching (founding of Master Neuro, co-direction of Graduate interdisciplinary School EURIP), and have institutional (director of ITMO at INSERM) or scientific responsibilities (direction of the institute, direction of national platform and set up of internal facilities).

Weaknesses and risks linked to the context

The team is strong in terms of international collaborations, but this is not yet represented in the acquisition of funding at international level. However, the team has successfully secured grants at the international level to maintain these collaborations.

The commitment of the team members in many different activities could represent a risk to carry on maintaining international recognition due to the strong competition in the team's research field dedicated to intracellular membrane docking and fusion events.

The team pursues several themes, the publication record during the period is unevenly spread between the permanent researchers and several of these publications are quite distant from the main theme of the team. The senior researchers build their independent profiles, and a possible risk could be a divergence between the team's major line of research and the scientific goals of its senior scientists that are often based on external collaborations.

So far, publications on dysfunctions of sorting/trafficking mechanisms in pathologies have been scarce. Collaborations with other IPNP teams working on pathologies could be intensified.

Analysis of the team's trajectory

Projects for the next term are organised around four research lines that can be conducted in parallel. Most of them capitalise on assays and tools developed or mastered by the team and the recent data obtained by the team. The first line is dedicated to biophysical studies of fusion proteins and their regulators and aims at generating new data on the structure/function of VAMP-7 and its interactions as well as the role of the lipidic environment. Line 2 widens the investigations on the function of v-SNAREs and their identified regulators at the cellular level using cultured cells. An innovative approach will be to explore the effects of blocking nanobodies used as intrabodies and to use them to collect vesicles at the cell surface. Complementary experiments will be done on wild-type and VAMP7-null neurons expressing mutant alpha-synuclein to unravel how VAMP7 could regulate aggregate formation. Line 3 addresses late endosomal autophagic secretion in glioblastoma and Parkinson's disease. This question is supported by solid observations indicating that VAMP7 knockout affects the distribution of late endosomal and mitochondria markers in extracellular vesicles. The team will explore the growth and dissemination of VAMP7-KO and ATG5-KO rat glioblastoma cells grafted into WT and VAMP7-KO rat brains and characterise their secretome in order to identify potentially active molecules relevant to tumour progression and decipher the role of late endosomal autophagic secretion in glioblastoma. With regard to Parkinson's disease, the team observed that the related kinase LRRK2 interacts with the post-Golgi v-SNAREs and that LRRK2 might regulate the unconventional VGF (a potential Parkinson marker) secretion via interaction with VAMP4 and VAMP7. The team plans to confirm the importance of this mechanism *in vivo* by expressing mutant LRRK2 or alpha-synuclein in WT and VAMP7-KO rat. Line 4 investigates membrane dynamics in an Alzheimer mouse model and the impact of antipsychotics. The team will pursue two objectives:

i) characterising the composition of immuno-isolated VAMP7 vesicles by lipidomics and their mobility by FCS

ii) and characterising the effects of antipsychotics on the fusion activity and biophysical properties of synaptic membranes *in situ* and in model membranes of various lipid compositions mimicking healthy or psychiatric conditions *in vitro*.

Overall, the team's project is innovative and ambitious and the team is technically well equipped and has all the necessary expertise to successfully complete it. Some difficulties might arise to demonstrate in more complex environments the validity of the data obtained in biophysical experiments. A major risk is to ensure in the middle term the financial support to carry on all the projects. Conversely, their diversity might help to diversify the grant applications.

Recommendations for the trajectory/project

The committee recommends the team to pursue its research plan along these four research lines and to capitalise on its previous expertise. The research plan clearly illustrates that the subsequent directions are well defined and that critical scientific questions will be addressed.

RECOMMENDATIONS TO THE TEAM

The committee acknowledged that beside the team leader, senior members successfully insured a hard load of responsibilities in the scientific management of platform and facilities. These responsibilities and the development of collaborations should remain reasonable to keep the team's identity and increase its productivity on its major research lines. The committee encourages the team to pursue its lines of research based on its strengths and achievements in the current evaluation period. At the same time, the novel research direction of the team emphasising on the cellular and pathological significance of its previous observations is particularly promising. New biophysical and imaging methods and tools established by the team during the evaluated period for studying interactions, lipid composition, trafficking and neuronal activity, should be applied in more integrative and physiological models. Given the potentially novel challenges posed by this research direction, the team should consider collaborations with experts in pathologies within the IPNP to benefit from their complementary expertise which might also further increase the team's visibility and funding opportunities.

Team 3: Neuronal Signaling in Epilepsy and Glioma

Name of the supervisor: Gilles HUBERFELD

THEMES OF THE TEAM

The team joined the IPNP in 2023 where it will explore abnormalities in neuronal, synaptic and network activity in neurological diseases such as epilepsy and glioma, using electrophysiological approaches mostly from human brain tissue. The team is also involved in the development of innovative organic electrodes designed to record network activity in human cortex in order to identify epileptic tissue and tumour cell infiltration biomarkers and decipher synaptic alterations in epilepsy and glioma. Finally, it will develop focused, ultrasound stimulation techniques to drive neuronal plasticity.

CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT

This team's past is being evaluated at the Collège de France because it joined the IPNP in 2023.

WORKFORCE OF THE TEAM: in physical persons at 31/12/2022

Catégories de personnel	Effectifs
Professeurs et assimilés	1
Maîtres de conférences et assimilés	0
Directeurs de recherche et assimilés	0
Chargés de recherche et assimilés	0
Personnels d'appui à la recherche	0
Sous-total personnels permanents en activité	**1**
Enseignants-chercheurs et chercheurs non permanents et assimilés	0
Personnels d'appui non permanents	0
Post-doctorants	2
Doctorants	2
Sous-total personnels non permanents en activité	**4**
Total personnels	**5**

EVALUATION

Overall assessment of the team

This team's past is being evaluated at the Collège de France because it joined the IPNP in 2023.

Strengths and possibilities linked to the context

This team's past is being evaluated at the Collège de France because it joined the IPNP in 2023.

Weaknesses and risks linked to the context

This team's past is being evaluated at the Collège de France because it joined the IPNP in 2023.

Analysis of the team's trajectory

The team aims at better understanding pathophysiological mechanisms that regulate epileptic seizures and brain/glioma interactions using mostly surgically resected human brain tissue. The team has developed an extensive and valuable expertise in harvesting, maintaining and analysing human pathological brain tissues. This

is a privileged standpoint which enables the team to investigate pathological processed directly in human brain tissues. The team will continue to carry out hypothesis-driven studies mainly focused on understanding the role of NKCC1/2 transporters in epilepsy, the effects of the D2HG metabolite in epilepsy and tumour growth, and the combined analysis of brain cancer cell excitability and transcriptome in different *ex-vivo* microenvironment by patch-seq. The proposed work is very well conceptualised and can be fully addressed with the models and technologies available in the team and the unit. The personnel and financial resources are in line with the proposed project. Altogether the trajectory of the team is excellent.

RECOMMENDATIONS TO THE TEAM

The team will continue to exploit new technical developments and address specific biological questions using human pathological brain samples. The team might consider expanding the use of genetic reporters to extract more information from these biological specimens. For instance, the use of calcium indicators can facilitate the simultaneous recording of neuronal activity from large neuronal/cancer cell ensembles at single cell resolution. Moreover, spatial transcriptomics would be an excellent addition to follow the dynamics and fate of cancer cells in the different experimental conditions.
Given the value of this *ex-vivo* system and its solid expertise accumulated over the past years, the team is involved in multiple and diverse scientific collaborations. Although this is of great value and maximises the use of the tissues, it might also substantially dilute the efforts of the team into many directions. The team leader should carefully balance the involvement in external collaborations and the focus on his own research.

Team 4: Pathogenesis of small vessel diseases of the brain

Name of the supervisor: Anne JOUTEL

THEMES OF THE TEAM

The overarching goal of this team is to decipher the pathophysiological mechanisms of cerebral small vessel diseases (cSVDs) by investigating two monogenic forms caused by mutations in the Notch3 (CADASIL) and collagen IV genes. The group has pioneered the generation of the CADASIL mouse model, elucidated disease mechanisms and identified new molecular targets and pathological molecular interactions by advanced technical assessments of vascular structures and functions.

CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT

The previous report recommended that:

i) the team maintains its very high quality of scientific outputs and grant funding,

ii) it recruits more PhD students, participate in the activities and life of the unit and develops active internal collaborations,

iii) and it increases its interactions with the clinics to ensure that animal model observations are replicated in the human disease states.

The team raised more than 2.6 M€ funding over the reporting period and published 6 original papers in the Top10% citations. It was also engaged in collaborations with at least two other IPNP teams as well as international collaborations in the frame of two NIH grants, two Leducq networks and one H2020 network that led to fifteen publications. Several observations made on preclinical models have been validated on clinical samples. Although the team trained three students (5 Master-2, 3 Master-1, 3 engineers and 2 other students) over the reporting, the team did not train any PhD student.

Overall, the team fulfilled most of the recommendations of the previous report.

WORKFORCE OF THE TEAM: in physical persons at 31/12/2022

Catégories de personnel	Effectifs
Professeurs et assimilés	0
Maîtres de conférences et assimilés	0
Directeurs de recherche et assimilés	1
Chargés de recherche et assimilés	0
Personnels d'appui à la recherche	2
Sous-total personnels permanents en activité	**3**
Enseignants-chercheurs et chercheurs non permanents et assimilés	0
Personnels d'appui non permanents	0
Post-doctorants	3
Doctorants	0
Sous-total personnels non permanents en activité	**3**
Total personnels	**6**

EVALUATION

Overall assessment of the team

This is an **outstanding** team with a strong international leadership in the studies focused on monogenetic forms of cerebral small vessel diseases. The team has been carrying out high-quality research, obtaining groundbreaking insights on the fundamental pathological mechanisms of these diseases. These results have been published in highly visible journals. The team leader has a high international visibility and received the prestigious Brain prize in 2019 in recognition of her influential work in the field. She has established a large network of consolidated collaborations worldwide that recognises her leadership in the field. The team is relatively small with only one engineer with a permanent position beyond the team leader. Scientific staff is composed of postdoctoral fellows and five out of eight obtained a first authorship publication. The team trained 7 Master students but did not recruit PhD students. Outreaching activities of the team are mainly limited to annual meetings with the French CADASIL's patient organisation.

Strengths and possibilities linked to the context

The team has a worldwide leadership position on the studies related to the pathophysiological mechanisms of monogenic forms of cerebral small vessel diseases. Since the original discovery of Notch3 as the causative gene of CADASIL, the team has contributed to numerous findings on the pathological mechanisms, exploiting a home-made mouse model and patients' tissues. Overall, the team has published 29 articles during the contract period of which about a fourth with the corresponding authorship. Major findings of the team are: the identification of excessive muscularization of mural cells as a key pathological cause of intracerebral hemorrhage in Col4a1 mutant mice (Circulation, 2020; 2.52 field-weighted citation impact); beneficial effects of a new passive immunisation approach in CADASIL (TgNotch3R169C) mice (Annals of Neurology, 108; 1.56 field-weighted citation impact); pericyte coverage loss and BBB leakage are not primary drivers of brain lesions in CADASIL patients and mice (*Acta Neuropathologica Communications*, 2019; 2.38 field-weighted citation impact). The team leader has created an outstanding collaborative network with experts in the most promising technologies and developments in the field, including advanced 2-photon and MRI imaging, human genetics of the sporadic small vessel diseases and neuropathological assessment of autoptic patient brain tissues. The team has been highly successful in obtaining prestigious and wealthy local (3 ANR, RHU, FRM), European (H2020, EraNet-Neuron) and International (2 NIH-USA and 2 from the Leducq Foundation) grants, raising about 4.5 M€ in the last 6 years. Notably, more than half of these grants (2.5 million euros) were awarded in 2022, with funding starting in 2023, providing a great opportunity to recruit more personnel, expand the current research of the team and further consolidate her leadership in the field.

Weaknesses and risks linked to the context

The team is relatively small and includes only one engineer with a permanent position in addition to the PI. Most postdoc researchers had a junior profile and remained in the team for a few years. The lack of permanent researchers is an important challenge for the long-term stability of the team and the implementation of a successful next-generation turnover.

Analysis of the team's trajectory

The team's trajectory appears to be extremely positive, with an impressive list of cutting-edge projects that look likely to continue the remarkable research that the team has maintained over the past evaluation period. The topics under consideration are fascinating, and look set to reinforce the team's international standing as a major centre for research on small vessel diseases worldwide. Funding and staff to be recruited are perfectly in line with the proposed projects.
One particularly interesting new hypothesis of the team is that brain arterial smooth muscle cells do undergo a cell fate switching which leads to their subsequent degeneration during the pathological progression in small vessel diseases. The team has conceived a coherent and articulated experimental plan to specifically investigate this hypothesis and obtain likely new and valuable insights.

RECOMMENDATIONS TO THE TEAM

This is an outstanding team with a research program mostly based on the strong expertise, reputation and visibility of the team leader.
The first recommendation is to identify and recruit experienced researchers who could step in to support the research program of the team and help the team leader to mentor students and oversight scientific projects and administrative workload.
The team should also explore novel collaborations within the institute either to exploit/establish novel methodological approaches and/or create scientific collaborations with the other teams. Although the team has already a large wealth of external collaborations, it is of fundamental importance to develop internal synergies that can promote the development of cutting-edge technologies and/or scientific interests that can enrich the institute and can be helpful to the local community.
Finally, given the high scientific reputation of the team leader, science communication to the general public could be reinforced with the participation to more general science outreach events and not only restricted to the specific disease investigated by the team.

Team 5: Pathophysiology of psychiatric diseases

Name of the supervisor: Marie-Odile KREBS

THEMES OF THE TEAM

Team 5 is dedicated to advancing the understanding of the pathophysiology of psychiatric disorders, with a primary focus on schizophrenia, various forms of psychosis, bipolar disorder, and autism. The team is made of a dynamic and multidisciplinary group of investigators that synergistically applies diverse methodological approaches to unravel the complexity of these disorders. The team uses a translational strategy integrating omics data (especially genetics), neuroimaging, neuropsychology, and clinical research with a focus on prevention.

CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT

The previous report put forth recommendations that emphasise the importance of sustaining scientific output and securing external funding. Furthermore, it suggested the formulation of a well-defined strategy for team organisation and dynamics, aiming to maintain gender balance. Additionally, the report advised enhancing translational aspects by actively recruiting preclinical researchers. Following this recommendation, the team has developed collaborations within the IPNP with teams 2, 7, 8, 9, and 11 leading to several publications (>10) and grants (Fondation de France, RHU, starting grant) in preclinical areas. Space has been allocated to the RHU PsyCARE project and support from stakeholders has been obtained to improve staffing: one assistant professor, one clinician assistant professor and one technician. Both the scientific output and external funding have shown a consistent upward trend.

WORKFORCE OF THE TEAM: in physical persons at 31/12/2022

Catégories de personnel	Effectifs
Professeurs et assimilés	4
Maîtres de conférences et assimilés	2
Directeurs de recherche et assimilés	0
Chargés de recherche et assimilés	1
Personnels d'appui à la recherche	6
Sous-total personnels permanents en activité	**13**
Enseignants-chercheurs et chercheurs non permanents et assimilés	6
Personnels d'appui non permanents	5
Post-doctorants	2
Doctorants	3
Sous-total personnels non permanents en activité	**16**
Total personnels	**29**

EVALUATION

Overall assessment of the team

This is an **excellent** team that conducts pioneering research at the national level and boasts a robust international presence. The team has an **excellent** scientific production in a quantitative and qualitative point of view, with over 140 papers since 2017, many in high-impact psychiatric journals and half of them with leading authorship roles. Its attractiveness and capacity to raise funding is excellent to outstanding: the team has trained eleven PhD students, received three postdocs, and obtained over 500 k€ on average per year. Beyond research, the team is actively engaged in numerous outreach activities. The link with society is outstanding.

Strengths and possibilities linked to the context

This research team stands out as a robust and prolific entity, engaged in numerous productive projects and international collaborations. Its financial support primarily stems from successful applications in national calls, indicating a solid funding base. Over the assessment period, the team's publication output has not only

increased but also demonstrated diversity in authorship, with several team members assuming primary author roles. Remarkably, the team has exhibited exceptional fundraising capabilities, securing an impressive funding level (3 M€) from various local, national (ANR, RHU), and international institutions (ERA-NET) or charities (FRC, Fondation de France). The team's commitment to public outreach is noteworthy through various channels, including public events and lectures. The team's scientific appeal is underscored by the supervision of a large number of PhD students (11) and the recruitment of several postdoctoral researchers (3) during the evaluation period. The team's research methodology is characterised by comprehensive assessments of large clinical cohorts, incorporating both cognitive and biological data. Their focus on translational approaches is evident, with the team showcasing an adept ability to conduct integrative studies linking animal models to clinical research. Significant contributions during the assessment period include various papers exploring alterations associated with the conversion to full-blown psychosis, published in reputed journals such as Schizophrenia Bulletin (Chaumete et al., 2019; Tognin et al., 2020; Iftimovici et al., 2022). These contributions provide a comprehensive profile of changes spanning epigenetics, transcriptomics, and cognitive alterations, offering practical applications in the detection and prevention of such conversions. The selected highlights, reflecting international collaborations not led by the team's researchers, may not accurately represent the team's research orientation.

Weaknesses and risks linked to the context

The team's research predominantly relies on clinical cohorts, with translational approaches appearing to take on a more central role over the assessment period, particularly through collaborations within IPNP. Although the majority of the team's research effort is centred on psychotic disorders, it applies a diverse range of methodological approaches and investigates other mental illnesses. This poses the risk of losing focus and scattering the research interests. While there is a significant emphasis on dissemination activities, fuelled by substantial public funding, there is a concern that such efforts might divert attention from constructing a robust research strategy rooted in well-defined scientific hypotheses. Balancing dissemination with the development of a solid research framework is essential for ensuring sustained scientific excellence.
Additionally, coordinating efforts with other teams in IPNP or elsewhere to obtain European and international calls could enhance the impact of the scientific output. Recruitment capacities might pose a threat to the team's projects by limiting the number of available technicians and young researchers in the team.

Analysis of the team's trajectory

A major challenge for the team lies in predicting which individuals at ultra-high risk for psychosis (UHR) or experimenting a first psychotic episode will evolve into a full-blown psychosis. During the evaluation period, the team has shown through epigenetic investigations that the conversion to psychosis involves dynamic changes in oxidative stress regulation, axon guidance, and inflammatory pathways. It also identified rectifiable deficits in folate/hyperhomocysteinemia, redox imbalances, and polyunsaturated fatty acids, with a potential but yet unproven utility for preventative interventions. Genetic analyses identified associations between variants, such as the glutamate metabotropic receptor 7 polymorphism, and cognitive deficits in UHR and FEP individuals. Polygenic risk scores for schizophrenia and resilience were found to influence cognition in UHR individuals. The team has also created Monocyte-Derived-Neuronal-like Cells (MDNCs) models to investigate the genetic influence on neurite formation and the impact of pharmacological treatments. The team's research extends to stress and its effects on neuroplasticity, particularly in the prefrontal cortex. Since 2020, the team was awarded with a large grant that will run until 2026 (RHU PsyCARE). Subsequently, regular resources have been obtained from national public or associative funding.
The team will pursue three main axes of research: genomic and epigenomic (integration of omics data), phenotypic (transdiagnostic approach exploring phenotyping markers), and translational approaches (animal models). Within each of these axes, the team considers the use of innovative diagnostic methods and high-throughput bioinformatics data analysis. Clinical trials to test personalised strategies in UHR patients and first-episode psychosis are also planned.
The team's research is supported by grants from RHU PSYCARE, ANR Schizophrenics, FRC, National consortia (Réseau Transition, GDR), and international collaborations (IRN, PGC).

RECOMMENDATIONS TO THE TEAM

The committee recommends that the team enhances its international visibility by actively responding to international calls with innovative translational projects. To achieve this, the more senior members of the team can play a supporting role, leveraging the wealth of existing collaborations.
Additionally, the committee advocates for the collaborative construction of a global long-term research strategy (based on integrative hypotheses) within the team to improve the exploitation of the rich existing databases and encourages proactive initiatives with international consortia. This proactive engagement will not only elevate the team's global presence but also contribute to advancing impactful research in the field.
Given the complexity of longitudinal databases with comprehensive multidimensional assessments, the pursuit of development of machine learning capacities to integrate data vertically is also encouraged.
High-impact generalist journals should be targeted.

Team 6: Dynamics of Neuronal Structure in Health and Disease

Name of the supervisor: Zsolt LENKEI

THEMES OF THE TEAM

Team 6 is a small research team focused on mechanisms of cerebral plasticity, neuronal cell biology and neuropharmacology, by means of techniques ranging from quantitative imaging of GPCR activation in cell cultures to animal models of brain plasticity. Recent projects led to the development and implementation of new techniques to evaluate the role of the actomyosin cytoskeleton in neuronal function and neuropsychiatric pathogenesis. In frame of a collaboration, the team developed and employed an innovative functional ultrasound (fUS) brain imaging method in awake behaving mice, to assess functional connectivity and task – or pharmacologically induced modulation of global network activities.

CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT

The team was encouraged to publish in first tier journals.
The team published a total of 34 articles over the 2017–2022 period, fourteen of these with a team member as first, last, or corresponding author (41%). These include publications in high-ranked journals (PNAS, Annu Rev Cell Dev Biol, Mol Psy, Small, etc.).
It was recommended to prioritise publications led by the team over collaborations.
Less than 60% of publications were generated through collaborations, in which the team published in good to excellent *(Nat* Comm, Mol Psy, Biol Psy, Nat Biotech) journals.
The advice for recruiting PhD students was followed: 4 PhD students have been working in the team. However, the publication level of PhD students was low, as only 3 out of 34 publications included a doctoral student.
Finally, the committee recommended keeping the scientific project of the team focused on biological questions rather than technological development.
Many publications of the team dealt with technological development during this period (8 out of 34 articles, 24%). However, the significant technological investment starts to bear fruits for the team (Ferrier et al. *PNAS* 2020, Rabut et al. *Neuroimage* 2020), and several studies applying technology to some core biological questions of the team are under way.

WORKFORCE OF THE TEAM: in physical persons at 31/12/2022

Catégories de personnel	Effectifs
Professeurs et assimilés	0
Maîtres de conférences et assimilés	0
Directeurs de recherche et assimilés	1
Chargés de recherche et assimilés	3
Personnels d'appui à la recherche	0
Sous-total personnels permanents en activité	**4**
Enseignants-chercheurs et chercheurs non permanents et assimilés	0
Personnels d'appui non permanents	2
Post-doctorants	1
Doctorants	6
Sous-total personnels non permanents en activité	**7**
Total personnels	**12**

EVALUATION

Overall assessment of the team

This is **very good to excellent** team which had a core scientific contribution in the application of the Ultrafast Functional Ultrasound or fUS technique in awake rodents as alternative to fMRI-based imaging. Overall, the team's productivity **is excellent**, with publications in reputed specialised and generalist journals. Team members have regularly obtained grants and the team has an excellent level of funding. The team's attractiveness is **excellent** being highly connected at national and international levels. Research valorisation (fUS technology) is **excellent to outstanding**.

Strengths and possibilities linked to the context

The scientific projects of the team are highly interdisciplinary, making available exceptional opportunities for technological development and valorisation. The major contribution of the team during the 2017–2022 period was the evidence of a default mode network in mice and its deactivation and disconnection during high demanding cognitive or sensory tasks, using functional ultrasound (fUS) imaging (*PNAS*, 2020). This publication opens unforeseen perspectives for translational research in the field of neuropsychiatry and neuropharmacology. The team globally presents a very good to excellent publication record over the evaluated period with 34 publications in peer-reviewed journals, thirteen of these with a member of the team as first, last or corresponding author (38%). All permanent researchers of the team regularly publish as last authors, sometimes in high-ranked journals such as PNAS, Annu Rev Cell Dev Biol or Small. The local (IPNP), national and international (Germany, Portugal, Austria, Hungary) collaboration network of the team is excellent and highly supportive. Notably, a highly productive collaboration allowed the development of the fUS technology (6 co-authored papers during the period). The team trained several PhD students (3 completed, 2 ongoing) and 9 master students who published or will soon publish with the researchers of the team. The team has demonstrated a very good capacity to raise funding to sustain its activity. A total of eight grants (one grant with the team leader as coordinator) were obtained for a total of 1 M€ during the reporting period. A tight collaboration of the team with the start-up Iconeus, co-founded by the team leader in 2016 (now about 30 employees), offers a great opportunity for technological development and illustrates its commitment to the research valorisation process. One of the PhD projects in the team was financed through a 4-year collaborative fUS project with Boehringer-Ingelheim (Germany). The members of the team have been invited to give conferences at international (Gordon Conference, Canadian Association for Neurosciences) and national (French Society of Cell Biology) scientific meetings and seminars in prestigious universities and research institutes (Harvard University, Yale University, Tokyo University, University of Buenos Aires). The team leader was co-chair of the Gordon Research Conference on Cannabinoid Function in the CNS in Spain (2019).

Weaknesses and risks linked to the context

Regarding human resources, there is no permanent technical staff in the team, to ensure the important function of lab manager and provide the team some stability. The number of PhD students remains somewhat low when compared to the number of permanent senior researchers in the team. A senior scientist left the team at the end of the evaluation period, but another senior researcher joined it in 2023. There is still a significant risk of thematic dispersion in the team, leading to a split between research on GPCR-related processes (actomyosin, GPCR-dependent plasticity mechanisms, receptor trafficking and posttranslational modifications) on one hand, and technical developments of the fUS imaging technique, on the other hand.

Analysis of the team's trajectory

The perspectives for the team's trajectory are excellent. Very interesting new data showing how modulation of the actomyosin cytoskeleton can modulate presynaptic structural organisation and neuronal transmission during cannabinoid-induced long-term synaptic plasticity will be published soon. This will reinforce the internationally recognised expertise of the group in studying the role of actomyosin and CB1 receptor in neuronal plasticity. The recent arrival of a senior scientist with complementary expertise in trafficking and post-transcriptional modifications of neurotransmitter receptors offers a unique opportunity to further explore mechanisms of synaptic receptor trafficking and glycosylation, notably for the CB1 receptor. Further development and application of fUS imaging for the assessment of pharmacologically induced modulation of global brain function, through the fine monitoring of neurovascular coupling, will allow the team to collect the benefits of considerable technological investment over the last years and has started to bear fruits through an invitation to submit recent results of one of the projects to a top-ranked scientific journal. More applications of this technique include clinical translation for assessing vascular and connectivity changes in cerebral ischemia, providing opportunities to develop new collaborations.
Regarding funding of future projects, 0.6 M€ is already secured for the next contract period, and three ANR grant applications by the senior scientists of the team are currently under assessment that should permit to fund the research in the next years. The team also works in tight collaboration with the start-up Iconeus, co-founded by the team leader, for technological development of fUS. Non-permanent technical staff has been recruited to support the team's research activity.

RECOMMENDATIONS TO THE TEAM

The committee recommends that the team maintains its thematic cohesion, by limiting dispersion between numerous fundamental topics in the field of GPCR pharmacology (actomyosin, GPCR-dependent plasticity mechanisms, receptor trafficking and posttranslational modifications) on one side, and technological development of fUS imaging on the other side. Exploiting fUS imaging will likely open new research perspectives in multiple fields, from neurovascular physiology and pathology, to pharmacology and neurodevelopment. However, the committee encourages the researchers of the team to focus on cell biology around common central questions in neural plasticity and to bring their use of the fUS imaging technique to converge towards pharmacological investigations. A wider exploration of the impressive potential of this technique may be undertaken through collaborations.
The committee encourages the team to pursue its efforts to publish its work in high-ranked specialised or generalist journals, and the team's members to increase their contribution as first or senior authors. The committee also recommends the recruitment of Master and PhD students, and a more active role of the trainees (particularly PhD students and postdocs) in the process of scientific production and output (i.e. first authorship in publications). Finally, the committee encourages the team to increase scientific outreach activities (participation in outreach events, intervention in media, etc.).

Team 7: Imaging biomarkers of brain development and disorders

Name of the supervisor: Catherine OPPENHEIM

THEMES OF THE TEAM

Team 7 leads research on imaging biomarkers of brain disorders, with a specific emphasis on cerebrovascular, neuro-oncology and neurodevelopmental imaging. Its work includes the development of techniques for imaging-based diagnosis and prognosis of strokes, modelling the impact of brain tumours and conducting comprehensive follow-ups on individuals with neurodevelopmental disorders. This corresponds to three main axes: Neuro-Vascular imaging, Brain Tumours/Epilepsy, and of Neurodevelopment/Mental disorders.

CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT

The team was created after the 2018 HCÉRES evaluation.

WORKFORCE OF THE TEAM: in physical persons at 31/12/2022

Catégories de personnel	Effectifs
Professeurs et assimilés	6
Maîtres de conférences et assimilés	0
Directeurs de recherche et assimilés	0
Chargés de recherche et assimilés	0
Personnels d'appui à la recherche	8
Sous-total personnels permanents en activité	**14**
Enseignants-chercheurs et chercheurs non permanents et assimilés	0
Personnels d'appui non permanents	9
Post-doctorants	0
Doctorants	10
Sous-total personnels non permanents en activité	**14**
Total personnels	**33**

EVALUATION

Overall assessment of the team

This is an **outstanding** team with a remarkable scientific output of over 500 papers, nearly 40% in high-profile journals like Radiology, JAMA Neurology, or Brain. Over half of the publications are signed in positions of responsibility. Capitalising on its strong international recognition, the team is actively engaged in large multicenter trials, industrial collaborations, and maintains a robust scientific network. The team's attractiveness is also **outstanding.** It participates in 23 research projects totalling 18 M€ (400 k€ for the team). It consistently attracts talented early career scientists, with sixteen PhDs and one postdoc. Many of them subsequently secured tenure positions. The team's link with society is **excellent**, reflecting a commitment to impactful research.

Strengths and possibilities linked to the context

This is a large and multidisciplinary team gathering many different medical specialists (17) and two research engineers (technical platform) as permanent staff. The team benefits from a strong recognition in its field worldwide. One of its major contributions during the reporting period is the identification of prognostic biomarkers using magnetic resonance imaging in acute ischemic strokes. This is a remarkable contribution that has very important implications since this knowledge can inform clinical decisions (performing or not mechanical thrombectomy). The team has also made an important contribution in the field of acute ischemic stroke by developing a method to reduce MRI length through machine learning methods. Among their recent impactful

research, one can also quote the development of probabilistic atlases of brain gliomas and the improvement of neurodevelopmental imaging. Collectively, these advances illustrate the high potential for clinical transferability of the team's research outcomes. Between 2017 and 2022, the team published>500 publications (75% of them corresponding to original research). Sixty-five original articles were authored by a PhD student as first author. The publication rate of doctoral students is thus outstanding (>4 publications/student). All the permanent members of the team, including the clinicians, participate in the publication effort. The attractiveness of the team is also excellent, as shown by its participation in numerous collaborative projects and its ability to raise funding (23 funded research projects for a total amount of 18 M€, of which>2 M€ are dedicated to imaging). One third of these projects (n=8) are conducted in collaboration with another IPNP team and a team's member is the leader of the imaging work package in four projects (MYELEX, ULTRASTIM, EMOKET, SUMMIT). Over the reporting period, the team has trained one postdoc fellow and sixteen students. Of the thirteen who defended their PhD, most have obtained tenure track hospital/academic positions either at the GHU (6), including one with university position, or in other institutions. The team members have organised ~15 scientific events including national and international meetings, workshops or European courses (e.g. Workshop on Artificial Intelligence applied to stroke imaging, FLUX Congress, 2022; International Society of Forensic Radiology and Imaging meeting, Galen Foundation Course in Neuroradiology, 2018 etc.). The team members regularly participate in outreach activities, including fifteen interviews on TV programs and other public events. Among the strengths of the team, it should be noted the participation in national and international imaging networks.

Weaknesses and risks linked to the context

One notable weakness identified by the team is the insufficient time dedicated to research of physicians. Additionally, recognising the evolving landscape of machine learning studies and their escalating complexity, it is essential that the team adapts its capacity for such research in the future. Considering the computational demands associated with these studies, the strategic move towards cloud solutions seems sensible. Embracing cloud technology can facilitate the scalability and flexibility required for collaborative projects and optimise resource utilisation. In the rapidly evolving area of machine learning and artificial intelligence, there is a risk of losing access to significant developments if the technological capacities of the team are not supported.

Analysis of the team's trajectory

Over the next five years, the team plans to keep the current axes but developing the third one, neurodevelopmental imaging, to include mental disorders under the direction of a psychiatrist member of the team with experience in brain imaging and brain stimulation techniques. This shift is in accordance with the clinical priorities of GHU Paris, searching imaging biomarkers in pharmaco-resistant mental disorders and would allow increasing the collaboration with other IPNP teams.
The team aims at establishing a synergistic approach across clinical axes to facilitate interdisciplinary collaborations, sharing methods and theoretical approaches, namely multiscale analysis and machine learning. The integration of multiscale imaging would benefit from on-site platforms for Digital Pathology (established in 2021) and epigenetics (methylomics – from 2022). The generation of big data from these platforms will necessitate machine learning methods for integrative analysis with clinical and MR biomarkers.
Focus will be on machine learning approaches, a shared need across the three clinical research axes. Part of the team has received training to implement these techniques. The lab currently possesses three GPUs, with the consideration of a cloud solution under study, along with technical support from the GHU IT team. The team's current funding and staffing levels are consistent with the undertaken projects, indicating a feasible and well-matched resource allocation.

RECOMMENDATIONS TO THE TEAM

Since its establishment, the team has consistently showcased an exceptional capacity for scientific production and seamless collaboration with other groups. It has become a benchmark in the realm of medical imaging, and has been able to foster synergies among diverse researchers and disciplines. Moreover, the team holds significant allure for emerging talents in the research community.
The main recommendation is to persist in its current trajectory and maintain the coherence of the different lines of research. To further enhance the impact of the team's discoveries, a strategic focus on industrial collaborations and technological transfers is recommended. This approach should aim to augment the practical applicability of the team's research outputs, contributing to a broader and more influential reach in the field.

Team 8: Genetics and Development of the Cerebral Cortex

Name of the supervisor: Alessandra PIERANI

THEMES OF THE TEAM

The team studies the relevance of transient neurons normally present during development in the etiology of neurological and psychiatric diseases. The PI runs two independent labs, one at IPNP and one at Imagine. At IPNP, the team focuses on psychiatric diseases and collaborates with internal teams on schizophrenia, activity-dependent regulation and behavioural studies. The other lab at Imagine gives the team access to complementary platforms and allows strengthening translational projects on neurodevelopmental diseases. The team uses a multidisciplinary approach including mouse genetics and in utero electroporation, transcriptome profiling, histology, single-cell resolution and time-lapse microscopy. In frame of collaborations, the team uses axonal tracing, electrophysiology and optogenetics.

CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT

The previous committee recommended that the team increases the organisation of academic activities, such as international congresses, or workshops. The team members participated in over twenty international and national meetings/workshops with poster or oral presentations, and the team leader was invited as a speaker for 7 institutional seminars and 22 international meetings.
The committee also recommended that the team avoids loss of focus due to multiple collaborations, and/or an excessive number of sub-projects. It also recommended that the team focuses on fewer projects by securing the funding only for ambitious ones or reducing their numbers. The team has nevertheless been able to fund all projects and to efficiently manage its double affiliation while increasing its publication rate, particularly in 2023. Although the team leader seems to focus on three major topics, she nevertheless proposes subprojects to the major topics, ending with a total of 6 projects. Nevertheless, all of them seem to be led by a permanent researcher together with technical help, students, and eventually a postdoctoral fellow. Funding has been secured until 2027.

WORKFORCE OF THE TEAM: in physical persons at 31/12/2022

Catégories de personnel	Effectifs
Professeurs et assimilés	1
Maîtres de conférences et assimilés	0
Directeurs de recherche et assimilés	2
Chargés de recherche et assimilés	2
Personnels d'appui à la recherche	3
Sous-total personnels permanents en activité	**8**
Enseignants-chercheurs et chercheurs non permanents et assimilés	0
Personnels d'appui non permanents	0
Post-doctorants	1
Doctorants	3
Sous-total personnels non permanents en activité	**4**
Total personnels	**12**

EVALUATION

Overall assessment of the team

The team is internationally well recognised for its excellent to outstanding work. The scientific production of the team is **overall excellent** (12 publications) over the 2017–2022 reporting period. The team leader has been invited to prestigious conferences and obtained excellent level of funding. The attractiveness of the team is **outstanding** with an excellent balance between permanent staff, the number of recruited PhD students and postdocs, and the recruitment of two early-career researchers with permanent positions. Link to society is very good but needs to be improved.

Strengths and possibilities linked to the context

The PI leads a team at IPNP and installed a branch lab at the Imagine Institute at the Necker Hospital with the aim of interacting with clinicians and developing basic and clinical neuroscience projects. The two labs are under the supervision of senior scientists and each has 5–6 people with 1–2 dedicated engineers (IE). There are weekly lab meetings between the two labs and the staff can use the facilities of both institutes. The team has built on earlier discoveries about the importance of transient neurons during cortical development. The team explores the mechanisms by which these neurons die at the end of development and investigates whether aberrant survival would lead to pathological conditions. It also explores whether these transient neurons contribute to the evolution of the neocortex in mammals. Each research topic yielded major publications and was supported by several grants. The team shows an excellent publication record from 2017 to 2022 with twelve original and review articles published in medium to high impact journals. Among the 2017 to 2022 publications, 45% are signed by team members in leading positions (first, last, corresponding), 50% were co-signed by postdoc or PhD students, and 50% were published in renowned journals (e.g. Cell Rep, Cerebral Cortex, Development, Dev Biol). The whole team has an outstanding capacity for training and attracting young people, including foreign students (11 PhD students, 6 postdoctoral fellows). One engineer and one researcher got permanent positions and another engineer and researcher got promotions. The team leader and the senior scientists have an outstanding ability in obtaining funding: eleven grants from various sources (ANR (4), Fondation de France, AFSR, RHU, Idex, ERANET) with a total amount of 1,288 k€ in five years. The team also received the prestigious label FRM Team. These funding has supported salaries for 6 postdoctoral fellows, two PhD students, and three engineers. Most PhD students obtained competitive fellowships from the Ministry of Research or International PhD Programs. Several members of the team have responsibilities in Imagine and IPNP life and participate in evaluation committees and vulgarisation of science. Engineers are also responsible for specific research projects, training of students, and ethical committee approvals. The team leader is highly involved in teaching and was invited at over twenty national and international conferences (e.g. FENS meeting, Gordon Research Conference, Jacques Monod Conference, etc.). She is a reviewer for more than twenty scientific journals and over fifteen national and international granting agencies. Several members of the team are members of evaluation committees of both research institutions and funding agencies or associations (CSS Inserm, ERC, FRC). They also took part in the functioning of these institutions by being representatives in internal committees.

Weaknesses and risks linked to the context

Despite the high number of people and funding, the team has not published accordingly during the evaluation period (2017–2022). Citation indexes have also dropped from 2017 to 2022. This has definitely improved in 2023 and will most probably progress in the next few years. The team leader has to put more effort into the students' publication rate. The outreach activities link with society and institutional investment of the team and the team leader have been considered limited by the committee.

Analysis of the team's trajectory

The team is quite large, hosting twelve persons, including five permanent scientific staff (1 Prof, 2 DRs 2CRCN), three permanent technical staff, one postdoc and three PhD students located in two institutes in Paris, the IPNP, and Imagine. The team still focuses on three major scientific projects (cell death and survival, development, and pathology), each headed by one or two permanent researchers, one or two engineers, one PhD, and eventually one postdoc. In 2023, the team has shown an outstanding track record by demonstrating that:

i) abnormal persistence of Cajal Retzius (CR) cells in the hippocampus leads to several neurological disorders (cognitive deficits, epilepsy) – Nat Comm 2023;
ii) the PI3K/AKT/mTOR pathway is involved in CR cell survival – Int. J. Mol. Sci. 2023;
iii) mouse hem-derived CRs unveil an unexpected multi-ciliated molecular profile – Dev Cell 2023.

This shows that the past investment in the organisation and management of the two labs has been very successful.
The team will continue on the same topics by investigating the molecular mechanisms of CR subtype death and the consequences of their alterations on mouse cortical development and pathology. In particular, the team will focus on:

i) the evolution of CRs in human embryonic life and the impact of their altered programmed cell death and persistence on human neurodevelopmental disorders associated with hippocampal rhythmopathies and epilepsy;
ii) the molecular mechanisms and signalling pathways, such as AKT and mTOR pathways, implicated in the programmed cell death of transient neurons;
iii) the mechanisms involved in CR cell specification and their contribution to brain complexification during evolution;
iv) the molecular and functional characterisation of human Reelin mutations in cortical malformations;
v) and the role of transient neurons in cortical wiring and psychiatric disorders.

To achieve those goals, the team will use mouse genetics, single-cell transcriptomics, pharmacological manipulation in mouse embryos, cell cultures, *in vitro* electrophysiology, *in vivo* functional assays, and

behavioural phenotyping, in addition to studies on human tissues and molecular genetics. Overall, the team leader has organised the team to allow senior members as well as engineers to be fully in charge of their projects, directing subgroups with publication recognition and be in the position to develop their own projects to possibly independent paths in the next five years.
The projects are all feasible because of the excellent investments and results obtained during the last five years. The new projects represent a logical continuation of the previous ones. There is an appropriate expertise and number of people involved in each topic proposed as well as appropriate funding until 2027 (and more pending).

RECOMMENDATIONS TO THE TEAM

The committee encourages the team to pursue publishing in high-ranked specialised or generalist journals, and the team's young staff, PhD students, and postdocs, to increase their scientific production as first or last authors.
The team is still working on several sub-projects from mice to humans. This is also noticed by the huge amount of money (70–100 k€) spent on mouse costs. A reduction in animal models and a gradual shift to human-related projects with IPSCs would also help reducing the pressure the EU puts on the labs working with animals. The committee therefore recommends that the team focuses on fewer projects by securing funding and staff only for the more ambitious and clinically oriented ones.
Leading two labs in different institutes can increase the administrative load, even though this seems to be efficiently managed by the team leader. She has to evaluate in the long run whether keeping two labs has an added value and really favours the cohesion of the different lab members (compared to keeping only one major lab and collaborating with clinicians and platforms on the other site).
The committee also encourages the senior scientists and postdocs to increase their involvement in scientific outreach activities, and the team leader to participate in institutional and national evaluation activities.

Team 9: Genetics of addictive disorders

Name of the supervisor: Nicolas RAMOZ/Philip GORWOOD

THEMES OF THE TEAM

The team aims at better understanding the genetic and molecular basis of addictive behaviours, and especially eating disorders such as anorexia nervosa (AN). The team searches to identify genetic, epigenetic and metabolic biomarkers to improve the diagnosis and prognosis of patients with AN. The research projects are based on patient cohorts and biobanks, established by the team leader and other team members having dual research and clinical activities, as well as on the use of genetic and environmental mouse models of AN.

CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT

The previous recommendations were to focus more on the specific aims of the team (anorexia nervosa) for publication. Indeed, the previous committee thought that the heterogeneity in terms of topics, journal quality, as well as the ratio between reviews and original articles might be an issue and they recommended that the team members publish more focused results related to the specific aims of the team.
The team, that consists of several groups with different topics, has consistently demonstrated its capacity to publish in reputable journals, with a total of 459 original articles, including 174 (37%) signed in position of responsibility and 76 (17%) in were in top 10% journals. However, the team should pursue its efforts to publish its results obtained in the mouse model of AN used in the lab to convince the scientific community of the relevance of this model.
The committee also recommended that the team pays attention to the ability of students to publish during their thesis.
The majority of the team's PhD students have authored more than two papers. These publications extend to diverse areas, including animal models, recruitment of large patient cohorts and biomarkers endeavours, that demand substantial time to be completed since the initial results.
The committee underlined that the scientific life of the team may be challenging and needs to be clearly planned, and that the involvement of the team in international genetic consortia needs to be maintained and improved if possible.
There is no response to the recommendation on the scientific life of the team. Regarding the involvement of the team in consortia, networks and collaborations have been maintained and new collaborations have been developed locally at the IPNP (with Teams 8 and 10) and at the national level (U1215 Bordeaux Neurocampus, UMR8251 Paris).
Overall, the team partially fulfilled the recommendations of the previous committee.

WORKFORCE OF THE TEAM: in physical persons at 31/12/2022

Catégories de personnel	Effectifs
Professeurs et assimilés	6
Maîtres de conférences et assimilés	3
Directeurs de recherche et assimilés	0
Chargés de recherche et assimilés	2
Personnels d'appui à la recherche	2
Sous-total personnels permanents en activité	**13**
Enseignants-chercheurs et chercheurs non permanents et assimilés	7
Personnels d'appui non permanents	0
Post-doctorants	2
Doctorants	7
Sous-total personnels non permanents en activité	**16**
Total personnels	**29**

EVALUATION

Overall assessment of the team

This is an **excellent to outstanding** team that is internationally recognised for its expertise in molecular basis of addictive disorders. The team shows an impressive number of publications and funding. The complementarities between clinicians and fundamental researchers make the team in the best position to address the questions they want to resolve about the molecular characterisation of anorexia nevrosa and its remission. The team's attractiveness and link to society are outstanding.

Strengths and possibilities linked to the context

The team has a very strong link with clinics, as it hosts ten professors or assistant professors having dual clinical/research activities and two clinicians, who are leading important clinical research projects in the field of addiction and psychiatric disorders. In parallel, the presence of two full time INSERM researchers, one assistant professor and one research engineer is a major asset for the development of more fundamental research projects, making this team very complete. Most of the team members have an important teaching activity in medicine and science faculties. The team is also strongly involved in scientific outreach activities (hosting college and high school students as apprentice researcher, week of the brain, quiz Brain and Addiction, National symposium of UNAFAM, etc.). The clinical and fundamental research projects led to an impressive number of publications (459 original articles, mostly in journals specialised in psychiatry – Psychiatry Res, J. Affect Disord, J Clin Psychiatry, Addict Behav etc – , including 225 signed by team members in positions of responsibility, and among them 53 with PhD students) as well as several reviews and book chapters. The team members obtained eighteen grants, mainly from national agencies (ANR, INCA, IREsP etc.) or foundations (Fondation de France, FRM, FRC etc.), to fund their research projects, totalling ~1.5 M€ and several clinicians coming for a PhD obtained FRM fellowships. Moreover, several team members obtained hospital grants to lead their translational and clinical projects, and this benefited to the team even if these grants were not hosted by IPNP. This team is not a PI-based team but is instead a very solid team with several senior researchers and clinicians researchers having complementary expertise and leading their own projects. The research activities, funding, publications and presentations at conferences are well distributed between the different team members. They seem to be all very complementary and work together, as it is illustrated by the presence of different project leaders in the list of authors for numerous publications. The team is also involved in international collaborations (F Fernández-Aranda, Spain, G Maussion, Canada, C Bulik, USA) aimed at identifying genetic factors involved in psychiatric disorders that all yielded several publications.

Weaknesses and risks linked to the context

The amount of scientific publications is impressive, but the number of studies led by the team members as principal investigators in the field of AN published in high-ranked journal is limited.
Some of the PhD students trained in the team, including some PhD students supervised by the team leader, have not yet first author publications while they have defended their thesis a few years ago.

Analysis of the team's trajectory

This is a large team composed of both clinicians and full-time researchers, who leads fundamental, translational and clinical projects to better understand and care additive disorders such as AN. The team was able to attract a senior researcher in 2018 as well as an engineer. Their arrival strengthens the expertise in human genetics present in the team and will help to develop and interpret pangenomic sequencing approaches.
More than twenty papers and reviews have been published by the team on the characterisation of mouse models of AN. According to the last committee's recommendations, the team presented a project centred on AN and aimed at dissecting the molecular mechanisms involved in AN, and at identifying biomarkers for the disease and its remission. Given the number and the expertise of people involved, the different collaborations already established (S. Luquet, S. El Mestikawy, etc.), the funding already been obtained (ANR, FRC, IRES) to start the different tasks, the committee is confident that the team will be able to successfully conduct these projects.

RECOMMENDATIONS TO THE TEAM

The committee encourages the team to publish its research work in high-ranked journals, and must ensure that doctoral students have at least one first-author publication during their thesis.
It also suggests that the team tries to recruit more postdocs or PhD students with a scientific background to participate in the development of the fundamental research topics of the team. The recruitment of a bioinformatician with biological expertise would also be important for the integration and interpretation of the multi-omic approaches used to identify biomarkers.
One of the team's strengths is its complementary clinical and research expertise in the field of addictive disorders, which could enable in the future the development of integrated projects ranging from the identification of genetic factors to the study of pathophysiological mechanisms in mice and preclinical studies in these models, that may hopefully lead to clinical trials in humans.

Team 10: Signalling mechanisms in neurological disorders

Name of the supervisor: Heike REBHOLZ

THEMES OF THE TEAM

Team 10 is a small team whose scientific aim is to characterise mechanisms underlying the Okur-Chung (OCNDS) and Poirier Bienvenu (POBINDS) neurodevelopmental disorders, two recently described ASD syndromes associated with genetic modifications in the Casein kinase 2 (CK2) pathway, using cellular and mouse models. This project relies on techniques from differentiation of patient-derived iPS cells to behavioural evaluation in genetically modified mice. The team showed behavioural alterations and modified inflammatory response in their mouse models, and altered mitochondrial function in cell lines. The PI has initiated a number of local, national, and international collaborations to extend investigations to electrophysiology, gut microbiome sequencing, and cell-specific transcriptomics.

CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT

The team is evaluated for the first time. The team leader started her position as junior team leader at IPNP in 2019.

WORKFORCE OF THE TEAM: in physical persons at 31/12/2022

Catégories de personnel	Effectifs
Professeurs et assimilés	0
Maîtres de conférences et assimilés	0
Directeurs de recherche et assimilés	0
Chargés de recherche et assimilés	1
Personnels d'appui à la recherche	1
Sous-total personnels permanents en activité	**2**
Enseignants-chercheurs et chercheurs non permanents et assimilés	0
Personnels d'appui non permanents	2
Post-doctorants	1
Doctorants	3
Sous-total personnels non permanents en activité	**6**
Total personnels	**8**

EVALUATION

Overall assessment of the team

This small team created in autumn 2019 focuses on cellular and preclinical studies of two recently discovered ASD-related neurodevelopmental disorders, OCNDS and POBINDS. Overall, this is a very good to excellent team with an original, well-focused and well-funded project. Relative to its size, the team's production since its creation is very good**.** The funding allowed the team to recruit two PhD students and one technical staff. A senior scientist with expertise in iPS cells just joined the team, a postdoc is being recruited, and projects are supported by a highly collaborative network, indicating that the attractiveness of the team is already excellent. The links of the team with society are also excellent, as shown by its interactions with patient associations that have partnerships with start-ups.

Strengths and possibilities linked to the context

Prior to arriving at IPNP, in her previous position, the team leader investigated novel roles of CK2 in modulating the activity of Gas-coupled receptors, such as the dopamine D1, adenosine A2a and serotonin 5-HT4 receptors in mediating neural disease-like symptoms in mice. In the meantime, the newly discovered OCNDS and POBINDS

were found to be linked to CK2 function. Based on this, the team opened up a new line of research that focuses on understanding the cellular and molecular mechanisms of OCNDS and POBINDS, and especially the contribution of modified signalling mechanisms and phosphoproteome. Relative to its size, the productivity of the team has been very good with twelve peer-reviewed publications (4 reviews, 8 original articles) of which 50% were signed by the team leader as last author, 17% in collaboration, and 33% as first author, three of the 4 publications not related to the project). These include three publications in good to excellent journals specialised in neuroscience or generalist journals (J Neurosci, Mol Psy, Sci Rep). The team's research program is supported grants from the CSNK2A1 Foundation (USD 377,000), and other foundations (150 k€), and an Inserm junior professor chair grant (200 k€) that provides funding for a postdoctoral researcher. The two PhD students who joined the lab received competitive fellowships. The team leader is also active in teaching locally (Uni Paris Cité) and abroad (Danube Private University, Austria) and has been able to attract several medical and visiting students from abroad for shorter stays in the lab. The team's links with society are excellent, as through the CSNK2A1 Foundation there is a direct involvement with patient associations and participation in patient-scientist conferences. The partnership with two start-ups offers an excellent opportunity for valorisation and clinical translation of research results. The collaboration with Dr T. Bienvenu, who first discovered POBINDS, is an excellent opportunity for access to patient material to investigate mechanisms in iPSC models. This strategy will be strengthened by the recent arrival of a senior researcher in the team who brings a strong expertise in iPSC research. The team started at IPNP in 2019 as a junior team, and has in 2022 been promoted to senior team following a recommendation of the iSAB.

Weaknesses and risks linked to the context

The team is rather small at this stage, and the resources to acquire for example scientific equipment, but also to drive the work program and the multiple local and international collaborations forward are currently limited. Also, the team has invested significant time and resources in developing multiple mouse models of OCNDS, including potentially inducible/reversible models. This is a costly and risky approach, as there is no guarantee that all these models will provide exploitable data. The two studied syndromes are rare diseases, which may limit the audience of the research work. Duke University has started a concurrent program on Okur-Chung Neurodevelopmental Syndrome, which could generate a high level of competition at the international level.

Analysis of the team's trajectory

The team is a rising research team, that has developed original and innovative projects related to POBINS and OCDNS. The team leader has built a robust network of collaborations that will allow her to complement the expertise of her group, and has the potential to implement multidisciplinary cutting-edge approaches to address its biological questions. The recent arrival in the team of a senior CRCN with expertise in human iPSC methodology will strengthen the team's efforts in working with patient material in addition to the mouse models. The support of CSNK2A1 Foundation and a number of other grants obtained in 2023 (total of 500 k€ from foundations, including CSHK2A1, 500 k€ from ANR) and several grant applications under way should allow the team to secure sufficient funding for the projects. The partnership with two start-ups collaborating with the CSNK2A1 Foundation is an excellent opportunity for the valorisation of the team's research for therapeutic applications. Planned recruitment of a postdoctoral researcher and two technical staff comes at the right time to drive further the efforts in ongoing research projects.

RECOMMENDATIONS TO THE TEAM

Despite engagement of the team in a large network of collaborations, the committee recommends that the team focuses on building up its core expertise in cellular models and phosphorylation processes/interaction with G protein-coupled receptors, before expanding to highly challenging and risky models and techniques (multiple mouse models, multiple techniques from sequencing to *in vivo* imaging), to avoid dispersion. The committee encourages the team to publish its work in highly ranked journals in the neuroscience field and to continue to favour the involvement of trainees as first authors in original publications. Finally, the committee encourages the team to strengthen and maintain its links with international patient associations and to increase local outreach activities dedicated to the general public.

Team 11: Stroke: from mechanisms and determinants of outcome to randomised clinical trials

Name of the supervisor: Guillaume TURC

THEMES OF THE TEAM

Team 11 investigate different aspects of stroke including:

i) the identification of determinants of stroke prognosis and the definition of subgroups at higher risk of unfavourable outcomes,

ii) and the benefit-risk ratio of novel therapeutic strategies to prevent some specific causes of strokes as well as the long-term outcomes of strokes.

Four main themes are developed by the team:

- Theme 1 aims to improve the efficiency of early reperfusing strategies for a better management and outcome of the patients.
- Theme 2 is dedicated to the prevention of ischemic and hemorrhagic stroke in patients with specific causes of strokes such as carotid atherosclerosis, interatrial septal abnormalities and small vessel disease.
- Theme 3 aims to develop and improve strategies for post-stroke functional recovery, particularly of manual dexterity.
- Finally, Theme 4, which was initiated recently (2022), is a translational research program focusing mainly on the identification of new neurophysiological predictors applied to the neuroprognostication of comatose brain injured patients.

CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT

As recommended in the previous evaluation report, interactions with other IPNP teams (Teams 5, 7 & 9) have been developed and led to a large set of publications co-signed by members of both groups. Innovative technologies and tools have been developed, in particular in the field of the recently initiated Theme 4. Two start-ups have been created by members of the team, that will strengthen the links between the research developed by the team and its applications, provide funding for research activities and contribute to the already excellent reputation and attractiveness of the team.

WORKFORCE OF THE TEAM: in physical persons at 31/12/2022

Catégories de personnel	Effectifs
Professeurs et assimilés	4
Maîtres de conférences et assimilés	3
Directeurs de recherche et assimilés	0
Chargés de recherche et assimilés	1
Personnels d'appui à la recherche	0
Sous-total personnels permanents en activité	**8**
Enseignants-chercheurs et chercheurs non permanents et assimilés	2
Personnels d'appui non permanents	0
Post-doctorants	0
Doctorants	6
Sous-total personnels non permanents en activité	**8**
Total personnels	**16**

EVALUATION

Overall assessment of the team

This is an **outstanding team** that comprises sixteen permanents or contractual researchers, most of them being clinical academics involved in major fields of clinical neuroscience. The scientific production is **outstanding** in quantitative (302 peer-reviewed publications over the reporting period) and qualitative points of view (half of published articles are in high journals – e.g. New England Journal of Medicine, the Lancet, JAMA – with a team member, including students, as first, last or corresponding author). The team attractiveness is also **outstanding** with 4.5 M€ raised from public agencies, medical funding charities and industrial partners, the training of four postdocs and nine PhD students, a large set of national and international collaborations, the organisation of several meetings, conferences and symposia, the implication of several members of the team in editorial activities and institutional responsibilities. Finally, the links with society are **outstanding** with an active participation in scientific outreach events, interviews in various medias and lay press articles, and the creation of two start-up companies.

Strengths and possibilities linked to the context

The team's research activity is of very high quality and well recognised relative to stroke prognosis and outcome assessment of patients at higher risk of deleterious outcomes. The team hosts fifteen permanent scientists, including thirteen clinical academics, one full-time researcher (a second one is a DR emeritus INSERM), and ten non-permanent persons (PhD, postdoc, master degree). The team shows a remarkable productivity with respect of the number of researchers and their limited availability due their clinical activities (302 publications over the 2017–2022 period). A significant number of them were published in high-profile journals (NEJM, The Lancet, JAMA, Annals of Neurology, Stroke). All team members co-signed the papers with 51% of the publications signed by a team member as first, last or corresponding author. Over the period of evaluation, the team welcomed nine PhD students, four of them starting recently their thesis (2021 or 2022), four postdocs and thirteen master degree students. All the PhD students and postdocs are cited as co-authors of publications, often as first authors. The team is very well funded, with 4.5 M€ obtained over the period of evaluation. A substantial part of these funding is dedicated to the set-up of the first Mobile Stroke Unit program in France. The sources of funding are numerous and diversified, the most numerous being public funding agencies (PHRC, ANR), the others being medical funding charities (Fondation pour la Recherche sur les AVC) or industrial partners (Erganeo and Global Blood Therapeutics). Two start-ups that have been created by team members on the basis of existing collaborations with industry will constitute a new opportunity to generate novel scientific findings and new sources of funding. The team has multiple collaborations: within the IPNP with the teams 5, 7 and 9, with other French research units involved in various clinical and basic aspects of stroke research, and numerous international units in the field of stroke recovery (Karolinska Institute), acute ischemic stroke (Stanford University, …), mobile stroke units (Berlin & Houston, Texas), cerebral amyloid angiopathy (Harvard University, …), imaging of the carotid plaque (Dublin University). The team has also contributed to the design and management for France of the H2020-funded PROOF program testing normobaric oxygen therapy in patients with acute ischemic stroke. The team has been involved in the organisation of several scientific events including international congress (French Society of Neurology, Paris, 2021), international symposia (Neurosciences in Critical Care symposium, International Society CBF Metabolism, 2017 & 2021; World Congress on Physical Therapy, 2017; European Neurorehabilitation and Neural Repair Conference, 2019). Several members of the team have an editorial activity and have given a significant number of invited conferences (Brain 2019 Conference, European Stroke Organisation conference, World Stroke Congress etc.). Seven team members have been awarded over the last five years (Prix « Excellence en Neurologie, Société Française de Neurologie ; Prix de la FRM ; SOFMER Innovation prize; ESO Scientific Excellence award ; Fondation Lefoulon-Delalande-Institut de France etc.). Three are involved in teaching, most of them in master courses or inter-university programs. Two members of the team have institutional responsibilities (co-direction of the Département Hospitalo-Universitaire Neuro-Vasc, co-direction of the Fédération Hospitalo-Universitaire Neuro-Vasc, Chairman of a Work Package of the National StrokeLink F-CRIN Network).

Weaknesses and risks linked to the context

The team comprises mostly clinical academics and only one full-time permanent scientist, that may limit the opportunities for interactions although this is a strength in that it enables the cross-fertilisation between clinical care and research. The unbalanced ratio of clinicians to researchers may be a weakness at a time when a new translational research theme has just been launched. The attractiveness of the team, which is otherwise remarkable, should be enhanced by the arrival/recruitment of new researchers.

Analysis of the team's trajectory

The perspectives for the team's trajectory are highly relevant and in line with the work undertaken to date. The team's expertise in the field of stroke and clinical research is widely recognised, and the outlook is particularly promising. A large part of research trajectory is dedicated to the determination and efficiency of predictors for a better early management of acute ischemic stroke (theme 1), a more efficient prognosis and prevention of ischemic and hemorrhagic stroke (theme 2), and the improvement of prognostication in stroke-induced coma (theme 4). This last axis that aims to develop an expertise in neuroprognostication of comatose brain injured patients using a standardised combination of electrophysiological and brain imaging approaches, and machine learning analysis of both signals, is really innovative and promising.
The third research theme is aimed at studying the conditions for improving post-stroke functional recovery, more specifically manual dexterity. The research carried out in this area has led to the creation of two start-ups managed by researchers of for one on Axis 3 and the other on Axis 4 and should enable the developed strategies to be applied to routine practices. The forthcoming funding level is excellent with two ANR grants already funded in 2022 that warrant an amount of 0.36 M€ for the next contract period. The collaboration with the two start-ups recently created is an opportunity for having new funding and allowing the recruitment of young researchers and technicians.

RECOMMENDATIONS TO THE TEAM

The committee recommends that the team increases the level of interactivity between team members beyond the monthly staff meetings, perhaps by organising an annual outside seminar.
The development of translational research projects needs to be strengthened by recruiting new researchers in the areas of expertise associated with this new project. The recruitment of a junior excellence chair may be an opportunity for that and would contribute to the attractiveness of the team.

Team 12: Cholinergic modulation of cortical inhibitory circuits in health and disease

Name of the supervisor: Fani KOUKOULI

THEMES OF THE TEAM

This new junior team aims at investigating cholinergic modulation of cortical inhibitory circuits in health and disease. To achieve that goal, the team uses mouse models and will focus on modulation of layer 1 interneurons by extrinsic and intrinsic sources of acetylcholine and on the specific role of receptor subtypes in prefrontal cortex. The team will use an integrative approach spanning multiple scales from genetic alterations to cellular and network physiology *in vivo* and *ex vivo*, and behaviour.

CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT

New team

WORKFORCE OF THE TEAM: in physical persons at 31/12/2022

New team

EVALUATION

Overall assessment of the team

New team

Strengths and possibilities linked to the context

New team

Weaknesses and risks linked to the context

New team

Analysis of the team's trajectory

This team started its activities with the arrival of the team leader in 2023. The team leader demonstrated excellent success in securing funding, receiving an Atip-AVENIR grant (300 k€ for 5 years + 5 years of PI salary + 2 years postdoc) and FRM funding (500 k€). Prospectively, within the next five years, she plans to apply for a permanent Inserm position. There are several grants pending (Fondation Fyssen, 100 k€) or planned for submission in 2024 (ERC starting grant – EU, BBRF NARSAD grant – USA). The prospects for further funding should be excellent, given the innovative research program and the solid track record of the team leader. The team has attracted three Masters students in 2023, one of which is expected to continue a PhD in the team. In 2024, a research engineer will join the team and recruitment of two post-docs is currently ongoing.

The research of the team focuses on physiological functions of cholinergic modulation of different layer 1 interneurons in mPFC and their alterations in disease states. Several major aims include

i) the cell-type and receptor-dependent processes involved in cholinergic recruitment of interneurons during learning,

ii) the functional architecture and role of the involved circuitry,

iii) the impact of schizophrenia-related genetic variants of acetylcholine receptors to these processes,

iv) and the identification of cholinergic targets that can alleviate neural and behavioural dysfunctions related to schizophrenia and Alzheimer's disease.

The committee found the translational aspects of the work program ranging from molecular mechanisms to circuits and disease symptoms very innovative and promising. The committee also found the feasibility of the aims to be excellent, particularly given the excellent financial resources of the team, the staff situation (provided recruitment of postdocs will be successful), and the fact that several methodologies have already been set up (electrophysiology, opto- and chemogenetics) in the lab. The team has also established a number of collaborations within the IPNP (with 3 teams) and with other national and international partners. As several aspects of the work program heavily depend on *in vivo* 2-photon microscopy, the planned arrival (early 2024) of the new 2-photon microscope at the unit is essential for driving these investigations forward. Notably, the team leader is also active in teaching at both local (University Paris Cité) and international Masters programs (Greece), which offers an excellent opportunity to attract M1/M2 students and PhD candidates to the lab.

RECOMMENDATIONS TO THE TEAM

Team 13: Neuronal Circuits for Memory and Perceptions

Name of the supervisor: Belen PARDI

THEMES OF THE TEAM

This new junior team aims at investigating neuronal circuits for memory and perception. Its main goal is to understand how top-down information from internal representations is processed to affect perception of external stimuli in healthy and diseased brain. Using mouse models, the team focuses on the auditory stimulus processing in auditory cortex. It employs diverse experimental approaches *in vivo* and *ex vivo*, ranging from calcium imaging, primarily of presynaptic terminals, as well as cellular and unit activity to behavioural and optogenetic manipulation.

CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT

New team

WORKFORCE OF THE TEAM: in physical persons at 31/12/2022

New team

EVALUATION

Overall assessment of the team

New team

Strengths and possibilities linked to the context

New team

Weaknesses and risks linked to the context

New team

Analysis of the team's trajectory

The team started its activities with the arrival of the team leader in October 2022, who obtained an Inserm CRCN position. A PhD student and a postdoc were successfully recruited in 2023 and the lab attracted three Masters students. Another MS/PhD student will join the team in 2024. The team leader was very successful in obtaining funding, receiving an Atip-AVENIR grant and several smaller grants (BBRF, Emergence, ED3C PhD fellowship). A number of applications are pending or planned (Fondation Fyssen 100 k€, ANR, ERC consolidator), in addition to several fellowship applications of postdoctoral candidates (Marie Curie, EMBO, HFSP). The prospects for further funding should be excellent, although the committee noted that ERC funding at the consolidator level will be extremely competitive.

The team's research is on neural circuits and mechanisms of memory and perception in health and disease, with a focus on auditory perception, that is commonly affected in a number of neuropsychiatric disorders. Several major aims are outlined including:

i) assessing the critical role of different types of top-down sensory signals in auditory cortex in perceptual decision-making,

ii) understanding how top-down signals affect sensory processing in auditory cortex,

iii) and unravelling the circuit mechanisms that underlie perceptual disturbances in models of psychiatric disorders.

The team employs chiefly circuit and systems neuroscience approaches and initially plans to focus on a schizophrenia model. The committee noted that it would be interesting to extend this to neurodevelopmental disorder models with affected perception (i.e. ASD).

The team has also established a number of national (1 with IPNP) and international partners to complement its core expertise. Overall, the committee found the feasibility of the aims excellent, given the current funding and staff situation. This will be further strengthened if postdocs can be attracted that bring their own fellowships (applications pending).

The team has set up several techniques pertinent to the research program (electrophysiology, optogenetics, behaviour), but particularly the innovative axonal button imaging depends on availability of *in vivo* 2-photon microscopy. The planned arrival (early 2024) of the new 2-photon microscope at the unit is essential for enabling these investigations. Notably, the team leader is also active in teaching locally (M2, University Paris Cité) and by being appointed to the faculty of the prestigious international MBL Summer Course in Woods Hole (USA), which is an excellent opportunity to attract M1/M2 students and international postgraduates to the lab.

RECOMMENDATIONS TO THE TEAM

Team 14: Synaptic Plasticity and Neural Networks

Name of the supervisor: Vivien CHEVALEYRE and Rebecca PISKOROWSKI

THEMES OF THE TEAM

The primary scientific focus of this team is to investigate the role of neural networks and plasticity mechanisms within the hippocampal CA2 region in health and disease in mouse models. In that respect, the team has made several seminal discoveries regarding the network connectivity of CA2 within hippocampus to CA1 and CA3 regions, opioids and cannabinoid-driven synaptic plasticity, ion channel mechanisms mediating intrinsic plasticity of CA2 neurons, CA2 developmental maturation, and the involvement of CA2-related larger brain networks in social behaviours and social memory formation.

CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT

The team was encouraged to continue working at the same level, which was achieved very well.
The PIs were encouraged to organise national and international meetings. Although formally no meeting was organised, the PI showed a strong presence through invited presentations in 6 different countries and at prestigious international conferences (*GRC, SFN, FENS*).
The recommendation to obtain extra funding to secure lab topics, to increase the critical working mass, and to avoid resource dispersion, was met excellently. In the evaluated time period, grants totalling>1 M€, several from ANR and national (FRM) and international foundations (NARSAD) were obtained, that allowed the team to hire PhD students and postdocs and an engineer (temporary contract 3.5 years) to drive projects forward. Four PhDs successfully graduated, published first and co-author papers, and two of them secured prestigious awards (Bettencourt Foundation for postdoc training, FRM for best doctoral thesis).
The team was advised to formally appoint a unique leader, but did remain under a co-directorship, which bore fruits in terms of grant acquisition, growing the team and its scientific output, and being successful in training next generation scientists.
Lastly, the suggestion to initiate collaborations with other IPNP teams was met. There are ongoing collaborations with three other teams, some of which are starting to bear fruits in terms of planned publications and one joint acquisition of an ANR grant.

WORKFORCE OF THE TEAM: in physical persons at 31/12/2022

Catégories de personnel	Effectifs
Professeurs et assimilés	0
Maîtres de conférences et assimilés	0
Directeurs de recherche et assimilés	2
Chargés de recherche et assimilés	1
Personnels d'appui à la recherche	0
Sous-total personnels permanents en activité	**3**
Enseignants-chercheurs et chercheurs non permanents et assimilés	0
Personnels d'appui non permanents	0
Post-doctorants	3
Doctorants	3
Sous-total personnels non permanents en activité	**6**
Total personnels	**9**

EVALUATION

Overall assessment of the team

This **excellent to outstanding** team is co-directed by two internationally recognised leaders in the field of unravelling the function of the hippocampal CA2 region from cell physiology to behaviour. It has productive national and international collaborations, including three with other teams at IPNP. The team's scientific production is **outstanding** (27 publications including 4 reviews and 2 commentaries), with the majority of articles (14 or 52%) published as senior authors in reputed neuroscience and generalist journals (Neuron, Cell Rep, eLife, etc.). The attractiveness of the team (>1 M€ funding raised, 3 PhD students and 7 postdoctoral fellows trained) and its links with society (scientific outreach activities) are both **excellent.**

Strengths and possibilities linked to the context

The team uses state-of-the-art methodologies (mouse genetics, electrophysiology, behaviour and optogenetics) and has made seminal contributions in the field of hippocampal CA2 region physiology, organisation, and function. These include:

i) the discovery of two synaptic plasticities of inhibitory transmission. One of them has been shown to be a key component of social recognition memory,

ii) the demonstration that delta-opioid mediated-plasticity strongly regulates the output of CA2 pyramidal neurons and how these neurons project to areas CA1 and CA3,

iii) the discovery of how hypothalamic inputs that convey social novelty information act on the inhibitory circuit in hippocampal area CA2,

iv) and the description of an endocannabinoid receptor mediated plasticity distinct to area CA2 that is essential for social memory formation.

Over the reporting period, the team showed a high productivity (27 publications, including 4 reviews and 2 commentaries), with the majority (14 or 52%) signed as senior authors in leading neuroscience journals (Neuron, Cell Rep, eLife), and thirteen (48%) from collaborations including top neuroscience (Neuron, Nature Comm) and top tier scientific journals (Nature), a total of eleven (41%) publications were co-signed by trainees. The team showed strong capacities to raise fundings, with>1 M€ over the 2017–2022 period (3 ANR, 1 FRM, 1 NARSAD Young Investigator Award) and>0.7 M€ secured for the 2023-24 period. This enabled the team to successfully recruit three PhD students and 7 postdoctoral fellows over the past five years through their grant support, with three PhDs and three postdocs currently in the team. This testifies the attractiveness of the team and shows its strong commitment in training through research. Notably, both co-directors give lectures at universities (M1/2). One of the co-directors has for the last five years taught and since 2023 directs the prestigious MBL Neurobiology course in Woods Hole, MA, USA. The team leaders have a high level of internationally recognition as shown by seventeen invited conferences in 6 countries. Some of them were at prestigious meetings (SFN, FENS, GRC). They deliver service to the neuroscience community by peer review for>13 journals (including top-tier Neuroscience and scientific journals: Science, Neuron, Nat Neurosci, Cell Rep, Mol Psy) and national (ANR) and international funding agencies (German, Austria, USA, Israel). In terms of outreach activities, the team actively participates in 'la Semaine de Cerveau' and the 'Apprentis Chercheurs' program. One of the team leaders is appointed for five years in the SFN program committee.

Weaknesses and risks linked to the context

The team conducts primarily basic research with to date little immediate used for translation or valorisation. There were also no interactions with industry.

The team has to reorganise its composition/staff when moving. One senior scientist left the team and an MC took longer leave of absence. It seems that a technician will be required to continue managing the lab and animal resources.

It is unclear how the IPNP internal collaborations will be managed when the team moves.

Analysis of the team's trajectory

No trajectory was provided, as the team has left the IPNP in 2023 and joined the Neuroscience unit at the Institute for Biology Paris Seine (IBPS) after the favourable review by their SAB. In 2022, the team had secured>0.7 M€ for the 2023-24 period to continue its research line. In 2023, two ANR grants were funded (about 475k €, one as partner, one as coordinator) and two ANR applications are currently pending.

RECOMMENDATIONS TO THE TEAM

The committee encourages the team to strive to continue its scientific trajectory and publication strategy in top scientific and neuroscience journals at the same level. It also encourages aiming at successfully recruiting trainees such as PhD students and postdocs to the team and to keep up the PIs engagement in international conferences, invited talks for semination of their research result and service to the scientific community through peer reviewing. Although one PI is involved in the SFN program committee and one team member has been active in 'la Semaine de Cerveau', there is still a room for increasing the team's efforts in interactions with the non-academic world through education/local outreach activities for the general public. After the favourable review by the SAB of the Institute for Biology Paris Seine, the team moved to IBPS in 2023 for the next contract. It is hoped that the team is able to pick up its scientific productivity quickly in the new location.

Team 15: Endosomal dynamics in neuropathies

Name of the supervisor: Guillaume van NIEL

THEMES OF THE TEAM

This junior team explores the endosomal pathway, its molecular mechanisms of regulation and its integration at the macroscopic scale, with a focus on the relevance of the endosomal dynamics in neuropathies. The team used the zebrafish as a model organism and devised advanced *in vitro* and *in vivo* imaging approaches.

CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT

This junior team that joined the institute during the term. No previous recommendation is available.

WORKFORCE OF THE TEAM: in physical persons at 31/12/2022

Catégories de personnel	Effectifs
Professeurs et assimilés	0
Maîtres de conférences et assimilés	0
Directeurs de recherche et assimilés	1
Chargés de recherche et assimilés	0
Personnels d'appui à la recherche	1
Sous-total personnels permanents en activité	**2**
Enseignants-chercheurs et chercheurs non permanents et assimilés	0
Personnels d'appui non permanents	2
Post-doctorants	3
Doctorants	2
Sous-total personnels non permanents en activité	**7**
Total personnels	**9**

EVALUATION

Overall assessment of the team

This is overall an outstanding young team headed by a dynamic leader (starting FRM) who has been successful in defining a set of timely and innovative scientific objectives in the competitive field of cell biology of extracellular vesicles in which he is now considered as an international leader. The team's scientific production is **excellent to outstanding.** Most of his last co-authored publications are in high impact journals and he wrote seminal reviews in prestigious journals. The team's ability to secure grants (more than 3 M€ over the evaluated period) and attractiveness (assessed by the attraction and training of students and postdocs, the involvement in fruitful collaborations and the invitations to and/or organisation of international conferences) are outstanding.

Strengths and possibilities linked to the context

Thanks to the development of new tools, the team has imaged life cycle extracellular vesicles that are small and heterogeneous, in their biological context using the zebrafish as a model and, for example, revealed new regulatory mechanisms of their secretion. In a second line of research, the team studied the dynamics of lysosome compartments, focusing on the PIKfyve complex and showing its role in the process of lysosomal reformation and its relevance to the generation of physiological amyloids. Finally, the team exploited a novel quantitative single cell live imaging approach to identify the compartment of origin of CD63-positive exosomes as a subclass of non-proteolytic endosomes. The team uncovered that exosome secretion is a multi-step process regulated by GTPase switching and dynamic membrane contact sites between Endoplasmic Reticulum and

Rab7-positive endosomes, thus highlighting the ER as a new player in exosome-mediated intercellular communication. The seminal work of the team on the cell biology of extracellular vesicles described above has been published by the team leader as last author in high-profile journals (e.g., Dev Cell, 2019; , J. Cell Biol 2022), together with his innovative imaging approaches (Nature Methods, 2021; Nat. Protoc., 2019). The PI wrote several important reviews on this new and dynamic field (Nat. Rev. Mol. Cell Biol. 2018, Nat. Protoc. 2019, NRMCB 2018, 2022, Nature Methods 2021). Overall, his work is highly cited (> 20,000 citations). The team leader has a high capacity in obtaining funding. He secured about 3 M€. His FRM 'young teams' grant allowed with the support of the IPNP to equip the lab and to set up the zebrafish facility. He then obtained several national and international grants (e.g. MSC ITN program H2020, NIH subcontract) as PI (9>100k€). These grants allowed him to recruit 7 postdocs, two PhD students and two engineers. The remarkable visibility of the team is also testified by the ability to attract students and postdocs and to carry on multiple collaborations with experts of different fields at the national and international levels. The team leader is Guest Editor for Advanced Drug Delivery Review and for FASEB Bioadvance, and the co-founder and President of the French society of Extracellular Vesicles. He organised 6 international meetings since 2017, chaired the yearly EMBO advanced course, was invited to international meetings, and received awards (e.g. 2022 Achievement award from the International Society of Extracellular vesicles).

Weaknesses and risks linked to the context

Although the team leader has incorporated new members, has graduated PhD students and has advanced postdocs to higher career stages, a potential risk is the lack of permanent researcher in the team. The most noticeable weakness is a lack of efforts to better integrate the neuroscience field and to initiate collaborations within the IPNP, which could have been fruitful.

Analysis of the team's trajectory

The team obtained a CRCI2NA grant and has chosen to leave the institute to pursue its project in Nantes.

RECOMMENDATIONS TO THE TEAM

The remarkable scientific performance of the team during the evaluation period has further consolidated the position of the team leader as an international leader in the field of the endosomal pathway. The committee has no specific recommendation beside an encouragement to carry on the same path, hoping that the team relocation in Nantes will not slow down its productivity.

CONDUCT OF THE INTERVIEWS

Dates

Start: 13 décembre 2023 à 8 h 30

End : 14 décembre 2023 à 18 h

Interview conducted: on-site or online

INTERVIEW SCHEDULE

December 12th, 2023
Arrival of the committee and evening dinner (only committee members and Hcéres Scientific advisor)
December 13th, 2023
8:30 a.m.-8:50 a.m. Closed-door meeting of the committee
8:50 a.m.-9 a.m. Presentation of the committee
9 a.m.-10:00 Presentation of the unit with major achievements and Project/trajectory by the director. Thierry GALLI (40 ′ presentation + 20 ′ discussion with the committee)
10:00-10:35 Presentation of Team1: Interactions between neurons and oligodendroglia in myelination and myelin repair. PI: Maria Cécilia ANGULO (15 ′ presentation (ex-post & Project/trajectory) + 15 ′ questions + 5 ′ in private PI-committee)

10:35-11:00 coffee break
11:00-11:35 Presentation of Team 2: Membrane Traffic in Healthy & Diseased Brain. PI: Thierry GALLI (15 ′ presentation (ex-post & Project/trajectory) + 15 ′ questions + 5 ′ in private PI-committee)
11:35-12:10 Presentation of Team 3:Neuronal Signalling in Epilepsy and Glioma. PI: Gilles HUBERFELD (15 ′ presentation (ex-post & Project/trajectory) + 15 ′ questions + 5 ′ in private PI-committee)
12:10-1 p.m. Closed-door meeting of the committee (Rapid debriefing)
1 p.m.-2 p.m. Lunch only the committee
2 p.m.-2:35 p.m. Presentation of Team 4: Pathogenesis of small vessel diseases of the brain. PI: Anne JOUTEL (15 ′ presentation (ex-post & Project/trajectory) + 15 ′ questions + 5 ′ in private PI-committee)
2:35 p.m.-3:10 p.m. Presentation of Team 5: Pathophysiology of psychiatric diseases. PI: Marie-Odile KREBS (15 ′ presentation (ex-post & Project/trajectory) + 15 ′ questions + 5 ′ in private PI-committee)
3:10 p.m.-3:45 p.m. Presentation of Team 6: Dynamics of Neuronal Structure in Health and Disease. PI: Zsolt LENKEI (15 ′ presentation (ex-post & Project/trajectory) + 15 ′ questions + 5 ′ in private PI-committee)
3:45 p.m.-4:05 p.m. Presentation of the Team 14: Vivien CHEVALEYRE and Rebecca PISKOROWSKI: Synaptic Plasticity and Neural Networks (10 ′ presentation (Ex-post) + 10 ′ questions)
4:10 p.m.-4:40 p.m. Visite des plateformes (B&B, NeurImag, PhenoBrain)
4:40 p.m.-5 p.m. Coffee break
17:00-17h35 Presentation of Team 7: Imaging biomarkers of brain development and disorders. PI: Catherine OPPENHEIM (15 ′ presentation (ex-post & Project/trajectory) + 15 ′ questions + 5 ′ in private PI-committee)
5:35 p.m.-6:10 p.m. Presentation of Team 8: Genetics and Development of the Cerebral Cortex. PI: Alessandra PIERANI (15 ′ presentation (ex-post & Project/trajectory) + 15 ′ questions + 5 ′ in private PI-committee)
6:10 p.m.-6:45 p.m. Closed-door meeting of the committee
8 p.m. Dinner in town for the committee
December 14th, 2023
9 a.m.-9:35 a.m. Presentation of Team 9: Genetics of addictive disorders. PI: Nicolas RAMOZ & Philip GORWOOD (15 ′ presentation (ex-post & Project/trajectory) + 15 ′ questions + 5 ′ in private PI-committee)

9:35 a.m.-10:10 Presentation of Team 10: Signalling mechanisms in neurological disorders). PI: Heike REBHOLZ. (15 ′ presentation (ex-post & Project/trajectory) + 15 ′ questions + 5 ′ in private PI-committee)

10:10 – 10:30 Presentation of the Team 15: Guillaume Van Niel : Endosomal dynamics in neuropathies. (10 ′ presentation (Ex-post) + 10 ′ questions)
10:30-11:00 coffee break
11:00-11:35 Presentation of Team 11: Stroke: from mechanisms and determinants of outcomes to randomised clinical trials. PI: Guillaume TURC (15 ′ presentation (ex-post & Project/trajectory) + 15 ′ questions + 5 ′ in private PI-committee)
11:35-12h00 Presentation of Team 12 (New team): Cholinergic modulation of cortical inhibitory circuits in health and disease. PI: Fani KOUKOULI (10 ′ presentation (Project/trajectory) + 10 ′ questions + 5 ′ in private PI-committee)
12 p.m.-12:25 p.m. Presentation of Team 13 (New team): Neuronal Circuits for Memory and Perceptions. PI: Belen PARDI (10 ′ presentation (Project/trajectory) + 10 ′ questions + 5 ′ in private PI-committee)

12:25-1:30 p.m. Lunch only the committee
1:30 p.m.-2 p.m. Meeting with engineers, technicians and administrative personnel in French
2 p.m.-2:30 p.m. Meeting with students and postdocs

2:30 p.m.-3 p.m. Meeting with scientists (Researchers and teacher-researchers), no team leaders, no lab director
3 p.m.-3:30 p.m. Meeting with team leaders
15:30-16h00 Closed-door meeting of the committee
16:00-16h30 Discussion with the unit director
4:30 p.m.-5 p.m. Discussion with the representative of the funding bodies
5 p.m.-6 p.m. Closed-door meeting of the committee (Last Debriefing)

PARTICULAR POINT TO BE MENTIONED

The technicians/engineers who depend on the University Paris-Cité struggle to find their human resource interlocutor. This may be detrimental for the quality of their annual activity reports, their promotions and career development. Even if the University Paris-Cité administration is under reconstruction after the fusion of the previous universities, the information should circulate more smoothly towards the IPNP staffs and their questions should systematically receive a response.
There is a general feeling from all staff categories (from the PIs to support staffs) that administrative issues have markedly increased over the past years. IPNP staffs need better support, reactivity and communication from the Inserm Délégation. Solutions should be found so that *i)* IPNP scientists do not spend a huge time on administrative tasks and can focus on their research, and *ii)* the support services of IPNP can work efficiently by receiving adapted responses to their queries from their Inserm interlocutors.

GENERAL OBSERVATIONS OF THE SUPERVISORS

Université Paris Cité

Le Président

Paris, le 25 Mars 2024

HCERES
2 rue Albert Einstein
75013 Paris

Objet : Rapport d'évaluation de l'unité **DER-PUR250024176** - **Institut de psychiatrie et neurosciences de Paris.**

Madame, Monsieur,

L'université Paris Cité (UPCité) a pris connaissance du rapport d'évaluation de l'Institut de psychiatrie et neurosciences de Paris.

Ce rapport a été lu avec attention par la direction de l'unité (cf courrier joint), par le vice-doyen Recherche et le doyen de la Faculté de Santé d'UPCité, par la vice-présidente Recherche d'UPCité, et par moi-même. L'ensemble des acteurs UPCité remercie le comité pour son travail d'évaluation.

Le Doyen de la Faculté de Santé et moi-même souhaitons insister sur le fait que l'Institut de Psychiatrie et Neurosciences de Paris (IPNP) est une UMR reconnue par l'Inserm et l'université Paris Cité notamment pour la recherche totalement translationnelle qu'elle développe, allant de la compréhension moléculaire de mécanismes physiopathologiques à la psychiatrie et la neurologie clinique et incluant des modèles précliniques. Cette approche est favorisée par les très forts liens tissés entre l'unité et le GHU Paris psychiatrie & neurosciences sur le site Sainte Anne. Un important travail de restructuration interne a été réalisé ces dernières années. Ce travail a été mené, avec le soutien des tutelles, en s'appuyant sur un appel d'offres et sur l'avis d'un scientific advisory board international, ce qui a débouché sur l'accueil de nouvelles équipes pour renforcer le centre au prochain quinquennat. Il est également à noter que l'unité est active en termes de valorisation et est à l'origine de 3 start-up.

Je vous prie d'agréer, Madame, Monsieur, l'expression de ma considération distinguée.

Édouard Kaminski

Présidence

Référence
Pr/DGDRIVE/2023

Affaire suivie par
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