INTERNATIONAL RESEARCH NETWORK (IRN)

1) *PRESENTATION*

a) **Nom et acronyme du projet**

Developmental and biological basis of psychosis onset in adolescents and young adults (Dev-O-Psy)

b) **Nom, laboratoire, organisme d'appartenance et adresses des coordinateurs**

Coordinateur français : Pr Marie-Odile Krebs

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c) **Noms, laboratoires, organismes d'appartenance et adresses des autres participants (français et étrangers)**

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2) *ABSTRACT IN FRENCH AND IN ENGLISH*

La schizophrénie et les troubles psychotiques sont des troubles neurodéveloppementaux débutant à l'adolescence ou à l'âge jeune adulte et résultant d'interactions entre gènes et environnement durant une période critique de maturation cérébrale. Malgré des résultats prometteurs issus des partenaires, les facteurs influençant l'évolution d'un état mental à risque à un premier épisode psychotique restent largement méconnus. Pourtant, leur découverte pourrait permettre d'identifier de nouvelles cibles thérapeutiques et biomarqueurs prédictifs. Le but de ce projet est de permettre une psychiatrie prédictive dès les premiers stades d'un trouble psychotique, en intégrant les données extensives provenant de champs variés comme le phénotypage intensif (dont les symptômes neurodéveloppementaux, l'imagerie cérébrale) et la biologie moléculaire (génomique et

épigénomique). L'intégration de ces différentes strates de données soulève le problème de leur harmonisation ainsi que celui des ressources et algorithmes nécessaires à leur analyse. L'IRN Dev-O-Psy aidera à atteindre ces objectifs en structurant une communauté autour des mêmes intérêts pour la biologie de la psychose débutante, en particulier centrés sur le neurodéveloppement, et en permettant l'accès à de larges cohortes de réplication, au séquençage de nouvelle génération et à d'importantes ressources de calcul. Pour atteindre ces objectifs, (nous développerons (i) une stratégie commune d'évaluation, d'harmonisation et de collection d'échantillons (ii) un accès aux ressources de séquençage et de bioinformatique; (iii) former des jeunes chercheurs, étudiants et médecins à l'intervention précoce, au phénotypage intensif (imagerie et Clinique) aux analyses génétiques et multiniveaux. Les équipes françaises bénéficieront de l'expertise de l'équipe coordonnatrice canadienne et auront un accès privilégié à l'infrastructure canadienne de séquençage (Génome Québec Innovation Centre) et d'interprétation des données génomiques. Les ressources de calcul pour des analyses multicouches seront disponibles par des infrastructures françaises et canadiennes. Le succès de l'IRN est garanti par l'existence de plusieurs collaborations à long-terme entre les partenaires et par le haut niveau scientifique déjà atteint à travers ces collaborations. L'IRN Dev-O-Psy permettra d'étendre la structuration réalisée au niveau national par GDR3557-Institut de Psychiatrie et renforcera d'autres collaborations développées plus récemment. Il fournira un cadre pour la collecte de fond et le développement des carrières en servant de levier pour des recherches de financements nationaux et internationaux dont certains ont déjà été identifiés (ERANET Neuron, Genome Canada, CHIR, FRQS, ANR…). Les jeunes chercheurs et étudiants seront inclus dans l'organisation de l'IRN et bénéficieront de la mise en place d'une école de formation annuelle, d'un financement pour des échanges entre équipes et d'un mentorat.

Schizophrenia and chronic psychosis are neurodevelopmental disorders emerging during adolescence and early adulthood, and resulting from gene-environment interactions during a critical phase of brain maturation. Despite recent encouraging findings from the partners, the factors influencing the transition from ultra-high-risk mental states to first episode of psychosis remain largely unknow. Their identification could potentially provide new targets for early interventions and new prognostic biomarkers. The aim of the project is to achieve predictive psychiatry in early psychosis based on the integration of deep-phenotyping (e.g. neurodevelopmental features, imaging data) and the molecular biology (genomics and epigenomics). The integration of multilevel data raise the issue of harmonization as well as the resources and algorithms available for their computation. Dev-O-Psy IRN would serve these objectives by structuring the community around the common interests for the biological background of early stages of psychosis, with a specific focus on developmental features, and by providing the access to larger and replication cohorts, to deep sequencing and computational resources. To achieve these goals,we will (i) develop a shared culture: shared methods of recruitment, harmonization of clinical assessment and collection of clinical samples; (ii) develop access to sequencing and bioinformatic resources for large scale computations; (iii) train young researchers and medical students on the topic of early intervention, the deep-phenotyping (imaging and clinical assessments), complex genetic analyses and computation of large-scale data. The French teams would benefit from the expertise of the Canadian collaborator's team as well as a privileged access to the Canadian facilities for sequencing (Genome Quebec Innovation Centre) and interpretation of the genomic data. The computing resources for multi-layers analyses would be provided through access to the bioinformatic facilities of both French and Canadian teams. The success of the IRN is warranted by several long-term collaborations between the different partners and by the high scientific quality of their collaborative work. It would extend the previous CNRS-labelled GDR3557-Institut de Psychiatrie. The IRN will also reinforce recent collaborations and provide a framework for fundraising and career development. Indeed, the IRN would be a lever for joint application to national and international tenders and several have already been identified (ERANET Neuron, Genome Canada, CHIR, FRQS, ANR…). Young researchers and trainees would be involved in the organization of the IRN and would directly benefit from it through yearly training school, exchange fellowships and mentoring.

3) *HISTORICAL CONTEXT OF THE COLLABORATION*

Long lasting collaborations (since 2005) exist between the two coordinators MO Krebs and G Rouleau in the field of schizophrenia and neurodevelopmental disorders. As listed below, this was facilitated by exchanges of students and common projects, including a competitive European project ERANET neuron "AUSZ" studying the continuum between autism and schizophrenia. More recently, and facilitated by the post-doctoral stay in G Rouleau's lab of B Chaumette (PhD student from MO Krebs' group), collaborations have intensively started between both groups and S Jacquemont's lab, in Montreal (Brain Canada project). In parallel, clinical and scientific collaborations have started between the group of R Joober (in Montreal) and the coordinating Parisian group, in the field of early psychosis services for adolescents and young adults. R Joober have been instrumental in the implementation of the first Early Intervention Service in Paris, (C'JAAD), by structuring and sharing assessment tools and visits from both sites (A Malla stay as invited professor in Paris, MO Krebs visited three times the PEPP clinic). This initiative has fostered the French national initiative "Transition Network", a specific network included in the Institut de psychiatrie (GDR3557) for the promotion of early intervention, including training and research programs initiatives. Along the first initiatives, contacts have become closer with the AQPEPP and MO Krebs and Amal Abdel-Baki (Montreal) have initiated the French Speaking Branch of the International Early Psychosis Association (fr-IEPA). Now we seek to extend the perimeter of the teams and expertise included in the collaboration, taking advantage of the structuring effect of the GDR in France, the Brain Canada project and the frame of the fr-IEPA.

●*Co-publications with complete citations:* Pr Krebs and Dr Rouleau have co-authored 15 articles in peer-reviewed journal in the last ten years including high-impact journals (New England Journal of Psychiary, Nature Genetics, Molecular Psychiatry). For a list of the 10 most relevant publications see the annexes.

●*Joint participation to scientific animation:* Dr Ridha Joober (CAN) is member of the international committee of the Deniker foundation and Pr Krebs (FR) is member of the national committee. The foundation organizes annual conferences with awards and fellowships for young researchers. https://www.fondationpierredeniker.org/organisation-fr

●*Co-direction of PhD students:*

- Dr Julien Tarabeux has been co-directed by the team of Dr Rouleau and Dr Krebs (years 2009-2011)
- Ms Zoe Schmilovich is co-directed during her master by Dr Rouleau and Dr Chaumette (team of Pr Krebs)

●*Exchanges of researchers, post-docs:*

- Pr Marie-Odile Krebs stayed in Montreal as invited Professor for a sabbatical period in 2009, and several one-week stays from 2007 until now.
- Dr Oussama Kebir had regular exchanges between teams of Pr Krebs and Dr Joober during 2013 and 2018 for a duration of two weeks each.
- Dr Boris Chaumette, after his PhD under the supervision of Pr Krebs (2013-2016) has worked in team of Dr Rouleau during his two years of postdoc (2016-2018). He is clinician researcher from team of Pr Krebs (since 2018).
- Dr Qin He, has been working in close partnership with the team of Dr Rouleau during her PhD (2018-2019) and has been recruited as postdoc in the team of Pr Krebs in may 2019.

4) *DESCRIPTION OF THE SCIENTIFIC PROJECT*

State-of the art

Schizophrenia (SCZ) and chronic psychosis are among the most disabling disorders striking adolescents and young adults involving cognitive impairment and reduced vocational achievement. Over the past 20 years, researchers and psychiatrists in the field of psychosis have moved from a conception of a chronic presentation to a more dynamic paradigm[1]. Accordingly, SCZ is now

conceptualized as a **neurodevelopmental and progressive illness driven by gene-environment interactions during adolescence, a critical phase of brain maturation encompassing transitions across several stages**: early vulnerability with neurodevelopmental features, at-risk mental state (also called ultra-high risk, abbreviated UHR), first episode of psychosis (FEP), and chronic disease. The duration of untreated psychosis has been associated with a poorer symptomatic and functional outcome[2]. Consequently, early intervention of psychosis has been proposed in dedicated services like the C'JAAD[3] in France (directed by Pr Marie-Odile Krebs) or the PEPP in Montreal (directed by Dr Ridha Joober). Pharmacotherapy is only available for full-blown psychosis, in a "one-size fits all" manner with 30% of unsatisfactory results. It has not demonstrated its efficiency to prevent psychosis onset and pharmacological treatment specific to early phases of psychosis remained to be developed. A major issue in clinical practice is the **prediction of the prognosis** when facing attenuated symptoms or a first episode of psychosis. Indeed, only one-third of UHR individuals, defined on clinical symptoms, will convert to a FEP after 3 years of follow-up[4]. Two-third will still present attenuated psychotic symptoms or will be remitters. Among the FEP, it is estimated that around one third will develop SCZ, one third will develop bipolar disorder and one-third will not relapse or have different conditions. Another unresolved issue is the determinants that influence psychosis onset (or resilience) in some patients with autism spectrum disorders during adolescence[5], suggesting that maturation processes may reveal some other psychopathological dimensions. There is currently no biomarker available to predict the clinical outcome in routine care or to predict response to treatment. This plaids for more research to better understand the pathophysiology of the early phases of psychosis, in order to develop prognostic biomarkers and new therapeutic targets, at an individual level[6]. Based on current state-of-art literature and on previous results from the consortium partners, the background hypotheses of this project are (i) that the neurodevelopmental burden impacts on the outcome and ability of recovery and (ii) that disease progression is related to impaired resilience, due to deficit in neuroprotective systems. Both processes could result from the same genetic / epigenetic alterations of from distinct interacting ones.

The understanding of the genetic, epigenetic and environmental causes of SCZ has considerably improved, as well as their link to aberrant patterns of neurodevelopment. Both common alleles with low penetrance and rare variants like Single Nucleotide Variants (SNV) and Copy Number Variations (CNV) play a role in genetic vulnerability to SCZ[7]. Several recurrent CNVs (overall prevalence 3-4%) common to other neurodevelopmental disorders are associated with an increased odd of SCZ, especially those containing synaptic genes[8]. Genome-Wide Association Studies (GWAS) leads to the polygenic risk score (PRS, addition of risks from common variants) that discriminates, at a group level, patients from healthy individuals[9]. Through a long-term collaboration, Pr Krebs, Dr Rouleau, Dr Joober have been instrumental in the identification genetic factors for SCZ. For instance, they have reported the first study about the rare *de novo* variants in SCZ[10]. Dr Rouleau has conducted a large-scale deep resequencing study called Synapse to Disease (or S2D) to identify single nucleotide variants (SNV) in neuropsychiatric disorders including autism and SCZ. Over the past twenty years his team has acquired critical expertise in disease gene identification technologies from candidate gene sequencing projects, to Next-Generation Sequencing technologies. Through funding from Genome Canada, Genome Quebec and the Canadian Institutes of Health Research, the team has developed his capacity to sequence, analyze and store more than 3.500 Whole Exome Sequencing data and 1.500 Whole Genome Sequencing data to date. Dr Krebs and Dr Rouleau have both been involved in an ERANET Neuron grant 'AUSZ' to detect the variants linked to autism and SCZ. Other variants like rare copy-number variants (CNV) have been shown their interest in psychiatric disorders. Dr Sebastien Jacquemont has a large experience of interpretation of CNV and has developed a model to predict their effect on human cognition[11]. Through advanced statistical

model, including the probability of being damaging, his team is able to predict the effect of the variants on human cognition. He is extending his results with Dr Joober, Dr Rouleau and Pr Krebs (funded by Brain Canada) to estimate the effects of CNV and SNV on other phenotypic continuous traits. Beside these rare variants, many common variants with small effect sizes have also been associated with psychosis, although they only explained a small fraction of the heritability. They have been used to calculate a polygenic risk score (PRS) and predict various clinical outcomes. In a recent study, researchers from the team of Pr Krebs and Dr Rouleau have jointly computed PRS based on GWAS and tested their predictive value for conversion to psychosis and multiple longitudinal dimensional outcomes (Chaumette et al, manuscript under review). This study indicated a lack of individual prediction based on the PRS. Psychosis is better explained by an interaction between gene and environment rather than genetics only. This interaction could be mediated by epigenetic, that refers to the change in gene expression without change in DNA sequence[12]. Pr Krebs' lab has recently contributed to improve the understanding of the epigenetic changes accompanying conversion from prodromes to full-blown psychosis. For instance, they have been the first to report longitudinal epigenetic changes in DNA methylation during the onset of psychosis onset[13]. Interesting pathways may be involved, including regulation of oxidative stress, axonal guidance, inflammation. Some of these DNA methylation changes correlated with variation in gene expression[14]. A patent derived from these findings is pending (WO2017182529A1 - *Methylomic and transcriptomic changes during conversion to psychosis*). Despite these new findings, the molecular mechanisms that trigger (or prevent) illness progression remain largely unknown and the identification of reliable biomarkers requires replication in larger cohorts.

Seminal studies carried out in birth cohorts have indicated that developmental features reflecting early alteration are associated with higher risk of psychosis and SCZ. Neurological assessment is a neglected dimension in SCZ, although there are compelling evidence showing that it could be reliable markers for early diagnosis or for subgrouping patients with more developmental load, and especially Neurological Soft Signs (NSS) or assessment of complex sensorimotricity[15]. In a preliminary study from the team of Pr Krebs, NSS are associated with the genetic load for SCZ. Brain anatomical biomarkers also could reveal developmental features and predict response to treatment[16] and recent studies have shown the interest of using Machine Learning on structural MRI data to predict the outcome of UHR at the individual-level[17]. Brain imaging has revealed reliable biomarkers but translation to routine care need specific requirement due to variability of the acquisition conditions. Team of R Jardri / P Thomas in Lille has already the expertise of harmonization of MRI acquisition, quality checks and data-transfer with the support of CATI's platform. They have developed advanced machine-learning algorithms[18] that can exploit the known structure of the data (i.e. spatial structure of brain images, gene pathways) in order to force the solution to adhere to biological priors, thereby producing more reproducible and interpretable solutions, even in the case of multicentric recordings. They also generalized the method to the detection of patients at early stage (43 FEP and 90 controls - 72% accuracy)[19] indicating, in preliminary results, 60% of prediction accuracy of the transition to psychosis based on whole brain structural neuroimaging and clinical data acquired in UHR patients. The homogeneous neuroimaging-based subtypes replicated across stages of the disorder from UHR, FEP to chronic SCZ and support the idea that machine-learning algorithms could be reliable in early diagnosis strategies.

Overall, the literature, including that from the partners support the view that predictive psychiatry, at the individual level, may be realistic if we are able to integrate multi-layers extensive data including genetic, epigenetic, imaging and deep-phenotyping data, including developmental features. This raises issues regarding having **access to large samples with harmonized phenotyping**, access to **deep sequencing data and resources,** as well as regarding **specific**

bioinformatic needs in terms of infrastructures and developments of new algorithms for data integration.

Objectives

The overall aim of the project is to achieve predictive psychiatry in early phases of psychosis based on the integration of big data from different fields including the deep-phenotyping (e.g. neurodevelopmental features, imaging data) and the molecular biology.
List of specific objectives for the IRN:
Objective 1: To develop a shared culture: shared methods of recruitment, harmonization of clinical assessment and collection of clinical samples, setting up comparable parameters and pipelines
Objective 2: To develop the access to sequencing and bioinformatic resources for large scale computations
Objective 3: To train young researchers and students on the topic of early intervention, the deep-phenotyping (imaging and clinical assessments), complex genetic analyses and computation of large-scale data

Scientific project and its interest

The IRN would benefit from ongoing projects involving both French and Canadian teams. The Brain Canada project has funded the whole-genome sequencing (WGS) of 400 samples of early psychosis, 128 of them with UHR and 272 with FEP, recruited either by the team of Pr Krebs and Dr Joober. Using machine learning approach implemented through the infrastructure of Dr Rouleau and Pr Jardri / Thomas, the FEP data would serve as a training set and the UHR data as a target set. Dr Jacquemont will be in charge of the analyses for continuous phenotypes and the CNV detection. The IRN would open the recruitment to new centers (Pr Dollfus, Pr Thomas & Pr Jardri, Pr Stip & Pr Abdel-Baki, Pr Bonnet-Brilhaut) and harmonize the recruitment and the clinical and imaging assessment. This would allow replication and complementary analyses in the future. Sequencing more individuals would need additional funding and the partners from the IRN have planned to apply for the next jointed calls: ERANET, ANR, CIHR, FRSQ, Genome Canada… The project would also include an integration of epigenetic data, funded by the ANR Jeunes Chercheurs of Dr Kebir (who belong to the team of Pr Krebs). The DNA methylation data from 100 UHR is ongoing with new bisulfite sequencing methods (Reduced Representation of Bisulfite Sequencing). The analysis will be done with a pipeline developed in the laboratory of Pr Krebs. For replication of the top findings, additional samples would be required from the other teams, or from international consortia in which we are involved (e.g. EU-GEI, Pronia). The clinical assessment between the different partners is similar but can diverge regarding some scales. Training of the psychiatrists and psychologists from the different teams is mandatory to estimate and improve the inter-rater reliability. Standardization of the parameters for the collection of the imaging data, as well as sharing of the bioinformatic pipeline for their analyses would be useful for improving the replicability of the analyses. By joined meetings and discussions, the partners would develop a core minimal dataset which will help each team to increase the quantity of data collected and to develop their own topics with the effort of the whole network. Finally, machine learning methods would be applied to predict the outcome of UHR and FEP by integrating all the layers: deep clinical phenotyping, neurodevelopmental assessment, imaging data, genetic and epigenetic data. Complementary expertise in imaging (Jardri, Dollfus) and in genetic / epigenetic will ensure to optimize the chance of success of the complex integration.

Quality and originality of the project

Several projects are ongoing to predict the outcome in early phases of psychosis. Pr Krebs is involved in the consortium EU-GEI[20] and in the pending program EUNIA. However, these programs often neglect the biology and focus on clinical and imaging data. We are aware of only one program (NAPLS) developed in the US with biological data but no longitudinal samples have been reported so far. With the pioneer articles from her lab, Pr Krebs has been the first to report longitudinal epigenetic changes associated with the onset of psychosis[13]. Replicating this approach in another cohorts is promising. The WGS approach remains poorly developed in psychiatry. Several groups have

indicated their wish of developing WGS in the next years and a consortium (WGSPD)[21] has been constituted but few data have been generated yet. By sequencing 400 samples from the team of Pr Krebs and Dr Joober, the Brain Canada project conducted by Dr Jacquemont and Dr Rouleau will represent one of the largest studies in the field. With the sequencing of additional samples harmonized across several sites, we have the ambition to become a major leader in WGS in psychiatry in the next years. Finally, we will improve the assessment of patients with early psychosis. Until now, the phenotyping is based on functioning or symptomatic scales but rarely explores the neurodevelopmental features. For instance, Pr Krebs has developed a specific scale to assess the neurological soft signs[22] which can be detected years before the first episode of psychosis. In addition, harmonized anatomical brain imaging have be developed thanks to the expertise of Pr Jardri / P Thomas. Involvement of other clinicians and researchers from the field of autism (Pr Bonnet-Brilhaut, Dr Jacquemont) will emphasize this innovative approach of studying the influence of neurodevelopmental features in the risk of conversion to psychosis in adolescence and young adulthood.

Futures perspectives

The international research network (IRN) will immediately help to these objectives by structuring the community around the same interests for the biology of early phases of psychosis and by providing the access to large computational resources. In a second time, the IRN will constitute a structure able to submit grant applications to several organisms. At a national level, researchers would receive the support to apply for ANR in France and for Genome Canada, CIHR and FRQS grant in Canada. At an international level, the network would be helpful to prepare jointed application to ERANET grants. In a longer-term perspective, we aim to identify biomarkers or to promote medical devices able to predict the outcome in early phases of psychosis. We also hope to better understand the mechanisms of the onset of psychosis. This could potentially open the way to the identification of new therapeutic targets to attenuate the negative impact of early developmental anomalies and promote resilience during the critical phase of adolescence.

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5) *DESCRIBE THE INTEREST OF STRUCTURING THE SCIENTIFIC COMMUNITY AROUND THE CHOSEN THEME AND THE PERTINENCE OF THE CONSORTIUM*

A major innovation in this project is to bring together complementary expertise in the field of neurodevelopmental disorders and early psychosis, while the influence of neurodevelopment and brain maturation on the emergence of psychosis during adolescence has been overlooked and still require further understanding. We will also bring complimentary expertise in genetics and brain imaging. The previous collaborations are the best context to propose the current project. The IRN will enable to develop further a timely and innovative field of research in psychiatry i.e. early detection and intervention in emerging disorders in young adults and adolescents by extending previous collaborations to new partners in the frame of the Transition network and the Institut de psychiatrie, as well as the “Federation Recherche Autisme” and Centre d’excellence Autisme (F Bonnet Brilhaut), the AQPPEP (Association Québécoise des Programmes pour Premiers Épisodes Psychotiques, E Stip / A Abdel Baki) and Brain Canada project partner (S Jacquemont). Deep phenotyping in large multicentric samples raise the issues of harmonization and being able to recruit or have access to large reliable data set. The IRN will enable to perform comparable recruitment, a better harmonization of the assessment and of the clinical scales. Changing the clinical assessment supposes a shared training for young psychiatrists and psychologists, as well as a discussion about the protocols for collecting the biological data. The IRN would help to structure the community with regular meeting and training schools. Second, the IRN would allow access to shared expertise and resources in bioinformatic, as needed for large-scale analyses. Dr Rouleau and Dr Jacquemont have access to large computational resources thanks to Compute Canada (server Beluga). Jacquemont’s team has an important expertise in annotation of Copy Number Variants (CNV) and prediction of their deleterious effects. Rouleau’s team has high expertise in rare single nucleotide variants (SNV) analyses. Krebs’ team has proven its efficacy in DNA methylation and gene expression analyses. The structuration will help to Increase training of students and attract new talents, in order to provide sustainable development of the research programs. To identify anatomical or functional variations, a large sample size is needed. This number can only be reached by merging smaller dataset from several platforms. This supposes a comparability across sites which need a detailed adjustment of the parameters. Guy Rouleau is director of the Montreal Neurological Institute (MNI) which has established the international coordinates for brain imaging. This issue of harmonization is since a long time the field of expertise of the MNI. On the other hand, Pr Jardri/ PrThomas have developed standardized procedure allowing harmonized anatomical brain imaging in multicentric MRI machine with the support of CATI ‘s platforms. convergent strategies could optimize future studies especially including first line clinical settings.

6) *DESCRIPTION OF THE ADDED VALUE OF THE INTERNATIONAL COOPERATION*

The national research network Institut de psychiatrie (IdP,CNRS 3557 www.institutdepsychiatrie.org) that hosts the Transition Network initiative comprised 30 research teams, 15 Centers of Excellence (clinical teams), biotech SME, involved in psychiatry, cognition, genetics, brain imaging and data analysis. We have also already sharing collections and are associated to international consortia such as IMAGEN; EU-GEI; EU-FEST; Intal consortium on Hallucination Research (ICHR) that will facilitate access to the related databases. The partners are linked to research infrastructures and especially to CATI national platform's support for multicenter neuroimaging studies (i.e. harmonization of MRI data acquisition and centralization, monitoring and quality control,). MRI protocols have already been harmonized on more than 30 MRI systems in France, according to a systematic qualification procedure, ensuring parameter uniformity and image quality. The IRN will extend the GDR3557 toward data sharing and ongoing collaborations (on data integration, brain imaging, sensori-motor phenotypes, psychosocial therapy, modeling etc) by bringing complementary expertise and addressing the needs in insufficient resources (e.g. genetic sequencing and analysis). The required population for robust results has grown to several hundred of individuals at least. This supposes to develop international collaborations especially when the phenotyping presentation are uncommon. Research in UHR is not easy and necessitate a joint effort for the recruitment to be able to reach a reasonable number of participants. The expertise of E Stip – A Abdel Baki with the AQPEPP in the implementation of early intervention services will foster the structuration of the centers and help to identify the best assessments and variables for early psychosis. New technologies, like Whole-Genome Sequencing explores millions of common and rare variants at a genome-wide level. Team of Dr Rouleau has a privileged access to large resources for sequencing. New omics have emerged to better explain the complexity of psychiatric diseases. The pathophysiology involves interaction between gene and environment that can be estimated by epigenomics. Several mechanisms are related to epigenomics including DNA methylation, histone modifications, miRNA regulation, chromatin regulation... End products of the epigenetic regulation are expression of mRNA and proteins. All of these regulators and products can be assessed by genome-wide technologies generating multi-layers omic data. Analysis of these different omics and their integration require **advanced bioinformatic** tools that can only be supported by large computing infrastructure. This kind of infrastructure as well as their maintenance necessitate an expertise, which is provided by the team of Dr Rouleau involving 3 bioinformatician and benefiting from a privileged access to Compute Canada/Calcul Quebec. In conclusion, all the aspects of the project would be covered in a comprehensive interaction and each team will benefit from the expertise and facilities of the others.

7) *DESCRIPTION OF THE ACTIVITIES IN THE FRAMEWORK OF THE PROJECT*

We plan to organize a yearly meeting alternatively in France and Canada. Each meeting would be organized in two sessions:

- a training session: to train the young researchers and students to the tasks needed to achieve the studies (similar to a training session). For instance: training around coding for machine learning, training to the clinical assessment by the different scales…
- a workshop session: to define the protocols and long-term strategy of the network. For instance, the first workshop may be dedicated to harmonization of the data collection. In a second time, the workshops would serve to interpret the results of the analyses and to discuss the strategy of valorization.

A yearly exchange program would invite one motivated student or young researcher from one of the groups to spend three weeks in another lab to learn a new technic or to speed up a project.
Each master and PhD student of the IRN would be mentored by a senior researcher/clinician.

8) *INVOLVEMENT OF STUDENTS AND/OR YOUNG RESEARCHERS IN THE PROJECT*

Young researchers and students would benefit from the workshops and training session. They would acquire knowledge and participate to the debates around the perspectives and valorization of the IRN. A mentoring by trained senior researchers and clinicians would be provided to each trainee. One

student or young researcher per year would be invited to participate to the exchange program for learning a new technic or developing a specific project. The IRN would serve as a lever for career development by promoting international networking and perspective of co-direction of PhD or postdoctoral exchange inside the IRN. The IRN would provide a unique opportunity for young researchers to enhance their clinical skills and scientific profiles to become future leaders in these emerging disciplines. Young researcher would be encouraged to take leading positions in the IRN and one would be invited to participate to the organization committee of the IRN.

9) *SCIENTIFIC QUALITY OF THE TEAMS*

SEE ANNEX FOR LIST OF PUBLICATIONS

10) PLANNED ANNUAL BUDGET AND FUNDING SOURCES

The funding will be used to allow the exchange of one student per year (3.000€) and to fund the travels of participants to the annual meeting (10.000 €). The remaining funding (2.000€) will cover the consumables and the communication to promote the IRN or the results of the scientific activities (e.g. leaflets, publication fees).

11) ETHICS

Recruitment of participants will follow the French and Canadian legal framework. In particular, the respective ethic committees of the groups have already validated the recruitment. Written consents are systematically obtained from every participant in the study before inclusion. For the minor patients, a written consent is also obtained from the parents or holders of parental authority before inclusion. The information relative to the rights of persons participating in this research (right of access and of rectification, right of opposition to any transmission of data covered by professional secrecy that are likely to be used as part of this research) is included in the information letter. The patient's personal data, which are included in the Sponsor's database are treated in compliance with all applicable laws and regulations. When archiving or processing personal data pertaining to the Investigator and/or to the patients, the Sponsor take all appropriate measures to safeguard and prevent access to this data by any unauthorized third party. Storage of personal data in France follows the regulation of respective data authority (CNIL). Biological samples are collected in accordance with sampling and ethical guidelines. According to ethical and legal recommendations, samples are accepted for analysis and banking only if an informed consent signed by the patient or his/her legal representative can be provided. For the data that will be shared between multiple organizations, transformed and integrated with other data sources, a special attention will be given to avoid potential privacy risks. Only anonymous data will be shared between the groups to assure the impossibility to identify a participant from another group. Monitoring process and evaluation of re-identification risk will then ensure the best standard of data governance. A consortium agreement will be defined before sharing the data, ensuring that the regulations of countries where the data were collected are correctly addressed and an executive committee will ensure the control of access to data.

ANNEXES

Any project must be accompanied by:

- *a support letter signed by the Unit director of the French coordinator*
- *a support letter signed by the foreign coordinator indicating the resources that may be committed to the project (including travel funds, human resources, use of infrastructures and/or plans to solicit local funding for the project).*
- *the CV of the foreign coordinator.*

List of 10 publications co-authored by members of the team of Dr Rouleau and Pr Krebs

1) Mutations in SYNGAP1 in autosomal nonsyndromic mental retardation. N Engl J Med. 2009 Feb 5

Hamdan FF, Gauthier J, Spiegelman D (CAN), Noreau A, Yang Y, Pellerin S, Dobrzeniecka S, Côté M, Perreau-Linck E, Carmant L, D'Anjou G, Fombonne E, Addington AM, Rapoport JL, Delisi LE, Krebs MO (FR), Mouaffak F, Joober R (CAN), Mottron L, Drapeau P, Marineau C, Lafrenière RG, Lacaille JC, Rouleau GA (CAN), Michaud JL; Synapse to Disease Group.

2) De novo mutations in the gene encoding the synaptic scaffolding protein SHANK3 in patients ascertained for schizophrenia. Proc Natl Acad Sci U S A. 2010 Apr 27

Gauthier J, Champagne N, Lafrenière RG, Xiong L, Spiegelman D (CAN), Brustein E, Lapointe M, Peng H, Côté M, Noreau A, Hamdan FF, Addington AM, Rapoport JL, Delisi LE, Krebs MO (FR), Joober R (CAN), Fathalli F, Mouaffak F, Haghighi AP, Néri C, Dubé MP, Samuels ME, Marineau C, Stone EA, Awadalla P, Barker PA, Carbonetto S, Drapeau P, Rouleau GA (CAN); S2D Team.

3) Increased exonic de novo mutation rate in individuals with schizophrenia. Nat Genet. 2011 Jul

Girard SL (CAN), Gauthier J, Noreau A, Xiong L, Zhou S (CAN), Jouan L, Dionne-Laporte A (CAN), Spiegelman D (CAN), Henrion E (CAN), Diallo O (CAN), Thibodeau P, Bachand I, Bao JY, Tong AH, Lin CH, Millet B, Jaafari N, Joober R (CAN), Dion PA (CAN), Lok S, Krebs MO (FR), Rouleau GA (CAN)

4) Systematic resequencing of X-chromosome synaptic genes in autism spectrum disorder and schizophrenia. Mol Psychiatry. 2011 Aug

Piton A, Gauthier J, Hamdan FF, Lafrenière RG, Yang Y, Henrion E (CAN), Laurent S, Noreau A, Thibodeau P, Karemera L, Spiegelman D (CAN), Kuku F, Duguay J, Destroismaisons L, Jolivet P, Côté M, Lachapelle K, Diallo O (CAN), Raymond A, Marineau C, Champagne N, Xiong L, Gaspar C, Rivière JB, Tarabeux J (CAN), Cossette P, Krebs MO (FR), Rapoport JL, Addington A, Delisi LE, Mottron L, Joober R (CAN), Fombonne E, Drapeau P, Rouleau GA (CAN)

5) Rare mutations in N-methyl-D-aspartate glutamate receptors in autism spectrum disorders and schizophrenia. Transl Psychiatry. 2011 Nov

Tarabeux J (CAN), Kebir O (FR), Gauthier J, Hamdan FF, Xiong L, Piton A, Spiegelman D (CAN), Henrion É (CAN), Millet B; S2D team, Fathalli F, Joober R (CAN), Rapoport JL, DeLisi LE, Fombonne É, Mottron L, Forget-Dubois N, Boivin M, Michaud JL, Drapeau P, Lafrenière RG, Rouleau GA (CAN), Krebs MO (FR)

6) Investigation of rare variants in LRP1, KPNA1, ALS2CL and ZNF480 genes in schizophrenia patients reflects genetic heterogeneity of the disease. Behav Brain Funct. 2013 Feb

Jouan L, Girard SL (CAN), Dobrzeniecka S, Ambalavanan A (CAN), Krebs MO (FR), Joober R (CAN), Gauthier J, Dion PA (CAN), Rouleau GA (CAN)

7) Family-based association study of common variants, rare mutation study and epistatic interaction detection in HDAC genes in schizophrenia. Schizophr Res. 2014 Dec

Kebir O (FR), Chaumette B (FR), Fatjó-Vilas M, Ambalavanan A (CAN), Ramoz N, Xiong L, Mouaffak F, Millet B, Jaafari N, DeLisi LE, Levinson D, Joober R (CAN), Fañanás L, Rouleau G (CAN), Dubertret C, Krebs MO (FR).

8) Genetic variability in scaffolding proteins and risk for schizophrenia and autism-spectrum disorders: a systematic review. J Psychiatry Neurosci. 2018 Ma

Soler J, Fañanás L, Parellada M, Krebs MO (FR), Rouleau GA (CAN), Fatjó-Vilas M.

9) Missense variants in ATP1A3 and FXYD gene family are associated with childhood-onset schizophrenia. Mol Psychiatry. 2018 Jun 12

Chaumette B (FR), Ferrafiat V, Ambalavanan A (CAN), Goldenberg A, Dionne-Laporte A, Spiegelman D (CAN), Dion PA (CAN), Gerardin P, Laurent C, Cohen D, Rapoport J, Rouleau GA (CAN).

10) Exome sequencing of sporadic childhood-onset schizophrenia suggests the contribution of X-linked genes in males. Am J Med Genet B Neuropsychiatr Genet. 2018 Oct 30

Ambalavanan A (CAN), Chaumette B (FR), Zhou S (CAN), Xie P, He Q (CAN), Spiegelman D (CAN), Dionne-Laporte A (CAN), Bourassa CV (CAN), Therrien M, Rochefort D (CAN), Xiong L, Dion PA (CAN), Joober R (CAN), Rapoport JL, Girard SL (CAN), Rouleau GA (CAN)

Thierry GALLI, Directeur
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Paris, le 20 juin 2019

Objet : ***Soutien au projet*** **International Research Network (IRN)** ***du Pr MO KREBS***

A qui de droit,

Je soussigné, Dr Thierry GALLI, directeur de l'unité de recherche INSERM U1266, déclare apporter mon soutien enthousiaste au projet International Research Network (IRN) présenté par le Pr Marie-Odile KREBS, chef d'équipe dans l'unité INSERM U1266 « Institut de Psychiatrie et Neurosciences de Paris ».

Cet IRN impliquant des partenaires québécois d'excellence permettra d'identifier les facteurs neurobiologiques associés à l'émergence des troubles psychotiques. Le projet d'IRN s'inscrit dans un partenariat ancien et durable entre l'équipe du Pr Krebs et celle du Dr Rouleau à l'Université McGill ayant conduit à la publication d'articles de haut niveau scientifique mais également à l'obtention de financements européens. La mise en place de cet IRN permettra également une extension internationale du groupe de recherche CNRS GDR3557-Institut de Psychiatrie fondé en 2012 sous l'impulsion du Pr Krebs et regroupant une trentaine d'équipes françaises.

La mise en place d'un IRN serait utile pour structurer la communauté scientifique autour des recherches en génétique et épigénétique psychiatrique dans la perspective de l'identification de biomarqueurs pronostiques. Il donnera à l'équipe française du Pr Krebs l'accès à d'importants moyens bioinformatiques qui sont nécessaires pour le traitement de données massives générées par ces nouvelles approches. Il associera également des jeunes chercheurs et des étudiants qui pourront bénéficier d'une formation de qualité et d'un réseau de collaborateurs internationaux.

L'obtention d'un IRN serait une réelle chance pour le rayonnement international des recherches sur les troubles psychotiques débutants et leurs facteurs biologiques qui constituent un enjeu de recherche innovant et prometteur.

Avec mes cordiales salutations,

Thierry GALLI

Guy Rouleau, M.D., Ph.D., F.R.C.P.(C)., O.Q.

Chaire de neurosciences Wilder-Penfield
Directeur
Institut et hôpital neurologiques de Montréal
Wilder Penfield Chair in Neuroscience
Director
Montreal Neurological Institute and Hospital

June 19th, 2019

Letter of support for the constitution of an International Research Network

Dear Members of the Evaluation Committee,

My interest in in psychiatric diseases goes back several years and my team was one of the first to suggest and establish the contribution of *de novo* mutations to the genetic architecture of schizophrenia and autism, an effort which involved a collaboration with Pr Marie-Odile Krebs (École des Neurosciences Paris Île de France). Over the years, I had the opportunity to work with a number of Pr Krebs students and fellows. For instance Dr. Chaumette was until recently a visiting fellow at McGill University (2016-2018), Dr Julien Tarabeux worked on his Ph.D. thesis while I was at the Université de Montréal (2009-2011). More recently (May 2019) a student from my own research team, Dr Qin He, joined Pr Krebs in Paris. Another student from my team, Ms Zoe Schmilovich, recently received funding from McGill University (Don Baxter Collaborative Fund) to visit the team of Pr Krebs and attend specialized courses in psychiatric genetics. In addition to those collaborations, Pr Krebs and myself networked with a number of additional teams from Spain and Germany) to launch an innovative project (ERANET) and characterize rare genetic variants in schizophrenia cases with an ultra-complete diagnosis. In 2018, we have obtained a second ERANET grant with Pr Krebs for the development of genomic based personalized medicine in psychiatry.

In Montreal, I have a long-term collaboration with Dr Joober (Douglas Hospital, McGill University), who is a former fellow researcher from my lab before he launched and developped his own independent research. I am also working with Dr. Sebastien Jacquemont (CHU Ste-Justine, Université de Montréal) in the TACC initiative (Transforming Autism Care Consortium) and on a funded Brain Canada project aiming disentangle the genetic architecture of autism and schizophrenia. This Brain Canada project is ongoing and 400 early-psychosis cases collected by Pr Krebs and Dr Joober will be whole-genome sequenced here at McGill for the data to be jointly analyzed.

Receiving support for the IRN would help to reinforce our collaborative links and provide a structure for training of young researchers and students, an opportunity which would speed up our joint research efforts. I strongly believe that the connection of our efforts which range from the recruitment of deep-phenotyped individuals to cutting-edge bioinformatic analyses of large-scale genomic and phenotyping data will lead to findings that will advance our understanding of the genetic risk factors at play in schizophrenia . As the Director of the Montreal Neurological Institute and Hospital, I certify that additional resources may be committed to the project in term of human resources (with the help of my lab manager) and access to bioinformatic infrastructures (by providing access to Compute Canada core facilities and the Genome Quebec Innovation center). I have recently received a donation from a benefactor of 600,000 $CAN for research in schizophrenia and part of this funding may be used for travel fund. We also plan to solicit financial support from local agencies and Foundation (e.g. The Graham Boeckh Foundation and the CIHR/FRQS funding opportunities) as well international agencies (e.g. ERANET) to help and make the project competitive with the best initiatives currently underway for the study of complex psychiatric conditions.

Sincerely,

Guy A. Rouleau M.D., Ph.D., F.R.C.P.C.

NAME: Rouleau, Guy A.
POSITION TITLE: Montreal Neurological Institute and Hospital Director
AFFILIATION: McGill University, Department of Neurology and Neurosurgery

Education:

Institution and location	Degree	Year(s)	Field of study
University of Ottawa, Canada	M.D.	1980	Medicine
McGill University, Canada	------	1982	Internal Medicine
McGill University, Canada	Residency	1985	Neurology
Harvard University, USA	Ph.D.	1989	Genetics

Positions and Employment:

2013 - present Director, Montreal Neurological Institute and Hospital, McGill University, Canada
2013 - present Professor and Director, Department of Neurology and Neurosurgery, McGill University, Canada
2013 - present Associate Professor, Department of Human Genetics, McGill University, Canada
2013 - present Adjunct Professor, Department of Medicine, University of Montreal, Canada

Selected honours

- Henry Friesen Prize, Royal College of Physicians & Surgeons Canada, 2007
- Officer of the National Order of Quebec, 2007
- NARSAD Distinguished Investigator Award, 2010
- Margolese National Brain Disorders Prize, UBC, 2012
- Prix du Quebec-Wilder Penfield, Government of Quebec, 2012
- Prix d'Excellence du Collège des Médecins du Québec, 2014
- Heinz Lehmann Award from the Canadian College of Neuropsychopharmacology, 2019

Ongoing research projects

- CIHR Foundation Scheme; 07/2015 to 06/2022; 708,381$/year. Genetic & Biological Studies of Brain Disorders. Role: Principal Applicant.
- Brain Canada; 11/2016 to 10/2019; 59,250$/year. Montreal Integrated Neuropsychiatric Cohort: Identifying subtypes of Autism and Schizophrenia integrating genomics, endophenotypes, and cohorts of high-risk genetic variants. Role: Co-applicant.
- ERAPerMed: 06/2019 to 06/2022 100,000$. Personalization of Long term Treatment in Bipolar Disorder. Rôle: Principal Applicant.

Publications: co-author of 814 publications; a complete list can be found here https://www.ncbi.nlm.nih.gov/myncbi/1-53VHqKjFjQj/bibliography/public/

5 recent selected publications

- Chaumette B, Ferrafiat V, Ambalavanan A, Goldenberg A, Dionne-Laporte A, Spiegelman D, Dion PA, Gerardin P, Laurent C, Cohen D, Rapoport J, Rouleau GA. Missense variants in ATP1A3 and FXYD gene family are associated with childhood-onset schizophrenia. Mol Psychiatry. 2018
- Ambalavanan A, Chaumette B, Zhou S, Xie P, He Q, Spiegelman D, Dionne-Laporte A, Bourassa CV, Therrien M, Rochefort D, Xiong L, Dion PA, Joober R, Rapoport JL, Girard SL, Rouleau GA. Exome sequencing of sporadic childhood-onset schizophrenia suggests the contribution of X-linked genes in males. Am J Med Genet B Neuropsychiatr Genet. 2018
- Cruceanu C, Schmouth JF, Torres-Platas SG, Lopez JP, Ambalavanan A, Darcq E, Gross F, Breton B, Spiegelman D, Rochefort D, Hince P, Petite JM, Gauthier J, Lafrenière RG, Dion PA, Greenwood CM, Kieffer BL, Alda M, Turecki G, Rouleau GA. Rare susceptibility variants for bipolar disorder suggest a role for G protein-coupled receptors. Mol Psychiatry. 2018
- Callaghan DB, Rogic S, Tan PPC, Calli K, Qiao Y, Baldwin R, Jacobson M, Belmadani M, Holmes N, Yu C, Li Y, Li Y, Kurtzke FE, Kuzeljevic B, Yu A, Hudson M, McNaughton AJM, Xu Y, Dionne-Laporte A, Girard S, Liang P, Separovic ER, Liu X, Rouleau GA, Pavlidis P, Lewis MES. Whole genome sequencing and variant discovery in the ASPIRE autism spectrum disorder cohort. Clin Genet. 2019
- Soler J, Fañanás L, Parellada M, Krebs MO, Rouleau GA, Fatjó-Vilas M. Genetic variability in scaffolding proteins and risk for schizophrenia and autism-spectrum disorders: a systematic review. J Psychiatry Neurosci. 2018

BIOGRAPHICAL SKETCH

NAME	CURRENT POSITION TITLE
Marie-Odile Last names KREBS Date of Birth: 08/02/1962	First class Professor in Psychiatry, University Paris Descartes, Paris Staff psychiatrist –Sainte-Anne Hospital, Paris Head of clinical department Service Hospitalo-Universitaire – S14 Team Leader 'Pathophysiology of psychiatric disorders' in CPN Coordination of Research Group in Psychiatry GDR 3557 – Institut de Psychiatrie (www.institutdepsychiatrie.org) Prix Philippe & Maria Halfen, Grand prix de l'Académie des Sciences, 2014; Prix Camille Woringer, FRM, 2018

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	MM/YY	FIELD OF STUDY
UPMC, Univ Paris 6	Master	1987	Biology
UPMC, Univ Paris 6, College de France	DEA (Master 2)	1988	Cellular and Molecular Neuropharmacology, option Neurobiology
University Paris XI	Master 2	1990	Informatics, Statistics and Epidemiology
University Paris 6	MD	1990	Glutamatergic systems and neuropsychiatric diseases
APHP, CHSA Paris	Residency	1985-91	Internat de Paris, psychiatry
College de France	Doctoral internship	1987-89	Full time research, Psychopharmacology
University Paris 6	Qualification in Psychiatry	1991	Phencyclidine induced Psychosis
University Paris 6	PhD	1992	Molecular and cellular pharmacology, Neurobiology, Glutamatergic regulation of DA release
University Paris 5	Director of Research HDR	1994	New pathophysiological models for schizophrenia

A. Personal Statement and keywords (present subject of interest)

Since 2006, I have been the pioneer of **early intervention** in France with the support of international mentors (P Mc Gorry, P McGuire, A Malla, P Conus) through **translational research** programs in **early psychosis** and have initiated the dissemination of knowledge (35 publications directly in relation, many lay conferences, symposium, book). We have contributed to the identification of **developmental markers** as prognostic factors (**neurological dysfunction**, rare **mutations**) and recently found peripheral **biomarkers** for more personalized interventions (including neuronal-like cells EP 13 306 428.7 17.10.2013) and **epigenetic** changes during **psychosis onset** in **at-risk mental state** (methylomic and transcriptiomic changes during conversion, EP17305038.6). I coordinate the 'Institut de Psychiatrie', (GDR 3557 – CNRS), a federation of 30 research teams in Psychiatry, Integrative Neurosciences and bioinformatics of which 10 members are partners of PsyCARE (and most if the associated clinical centers) and the **Transition Network** a national network that promote early intervention and encompasses all clinical centers. In 2018, we organize a task force to adapt and diffuse consensual guidelines for Early intervention in France. With A Abdel-Baki (Ca) and P Conus (CH), we launch in 2018 the Francophone Branch of IEPA.

B. Positions

1985-1987 and 1989-1991 Residency in Psychiatry and Psychopharmacology– Paris
1987-1989 Full-time PhD student at College de France (fellowship from Fondation pour la Recherche Médicale)
1991-1994 Head Residency – Associate professor (Chef de Clinique - Assistant) Paris
1995-2005 Permanent Position as reseacher (CR1 Inserm) Director of research DR2 in 2005
2005 Second class professor in Psychiatry Univ Paris Descartes, SHU CH Sainte-Anne (PUPH2C)
2012 First class full professor at Univ Paris Descartes SHU CH Sainte-Anne (PUPH1C)
2018-2022 substitute Management Committee member of the COST Action CA17130

D. Current Research Support

As Coordinator:

ICAAR : PHRC National project Factors influencing at risk mental state (470 €, 2008->2015)

ERANET – Neuron - project + Fondation de France AUSZ: A continuum from autism to schizophrenia (250€ + 80€ 2011-2017)
PHRC START: Stress in at risk mental state : a controlled randomized study of efficacy of CBT (500k€) (2013-2017)
FRM grant Personalized approach of biological basis of schizophrenia using neuron-like cells derived from genetically defined patient's blood monocytes (299 900€, 2016-2019)

As a participant:

Investissement D'avenir-Brainomics (2011-2015)– Methodological and software solutions for the integration of neuroimaging and genomic data (Coordinator CEA-V Frouin)
FRM grant (2015-2018) Inhibition and motor noise: neural correlates of deficient manual control in schizophrenia. (PI P Lindberg).
Fondation Deniker (2018-2020) Cortico-cerebellar mechanisms in motor adaptation and motor learning in schizophrenia - a combined behavioural and TMS study (PI P Lindberg)
Fondation de France (2018-2020) Rôle des cellules transitoires dans l'assemblage des circuits corticaux et l'étiologie des troubles psychotiques (PI A Pierani)

C. Selected Peer-reviewed Publications

Total number of publications: **256 in pub med Web of science: h-index : 42 ;** Times Cited without self-citations : 6314; Citing Articles: 5624 - 55 reviews or book chapter. One book : Signes Précoces de schizophrénie. Dunod, Paris **2015**. pp 224

List of the five major selected peer-reviewed publications in the scope of the current application

1. Chaumette B, Kebir O, Pouch J, Ducos B, Selimi F; ICAAR study group, Gaillard R, Krebs MO. Longitudinal Analyses of Blood Transcriptome During Conversion to Psychosis. Schizophr Bull. 2018 Feb 17. doi: 10.1093/schbul/sby009.
2. Kebir O*, Chaumette B*, Rivollier F, Miozzo F, Lemieux Perreault LP, Barhdadi A, Provost S, Plaze M, Bourgin J; ICAAR team., Gaillard R, Mezger V, Dubé MP, Krebs MO. Methylomic changes during conversion to psychosis. Mol Psychiatry. 2016 Apr 26. doi: 10.1038/mp.2016.53. [Epub ahead of print] PubMed PMID: 27113994.
3. Millan MJ, Andrieux A, Bartzokis G, Cadenhead K, Dazzan P, Fusar-Poli P, Gallinat J, Giedd J, Grayson DR, Heinrichs M, Kahn R, Krebs MO, Leboyer M, Lewis D, Marin O, Marin P, Meyer-Lindenberg A, McGorry P, McGuire P, Owen MJ, Patterson P, Sawa A, Spedding M, Uhlhaas P, Vaccarino F, Wahlestedt C, Weinberger D. Altering the course of schizophrenia: progress and perspectives. Nat Rev Drug Discov. 2016 Jul;15(7):485-515. doi: 10.1038/nrd.2016.28. Review. PubMed PMID:26939910.
4. Chan MK, Krebs MO, Cox D, Guest PC, Yolken RH, Rahmoune H, Rothermundt M, Steiner J, Leweke FM, van Beveren NJ, Niebuhr DW, Weber NS, Cowan DN, Suarez-Pinilla P, Crespo-Facorro B, Mam-Lam-Fook C, Bourgin J, Wenstrup RJ, Kaldate RR, Cooper JD, Bahn S. Development of a blood-based molecular biomarker test for identification of schizophrenia before disease onset. Transl Psychiatry. 2015 Jul 14;5:e601. doi: 10.1038/tp.2015.91. PubMed PMID: 26171982; PubMed Central PMCID: PMC5068725.
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