La psychiatrie de demain et les avancées neurobiologiques ?

Pierre Marquet, PhD, MD

Titulaire de la chaire d'excellence en recherche du Canada sur la neurophotonique

Laboratoire de recherche en psychiatrie et neurophotonique, Centre de recherche CERVO

Département de psychiatrie et de neurosciences, Université Laval

SRMMB, 8 décembre 2018

COPL Centre d'optique, photonique et laser

CENTRE DE RECHERCHE CERVO BRAIN RESEARCH CENTRE QUÉBEC

Canada Excellence Research Chairs

Chaires d'excellence en recherche du Canada

UNIVERSITÉ LAVAL

Background

- Major psychoses (schizophrenia, bipolar disorder, major depression disorder) affect nearly 4% of the population
- Diagnoses based on clinical symptoms are made late and current treatments are largely palliative

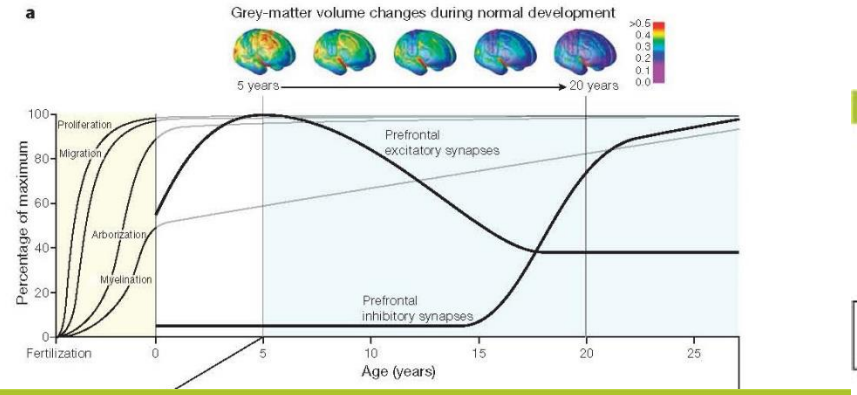
  Insufficient response with conventional pharmacological and manual-based psychosocial interventions

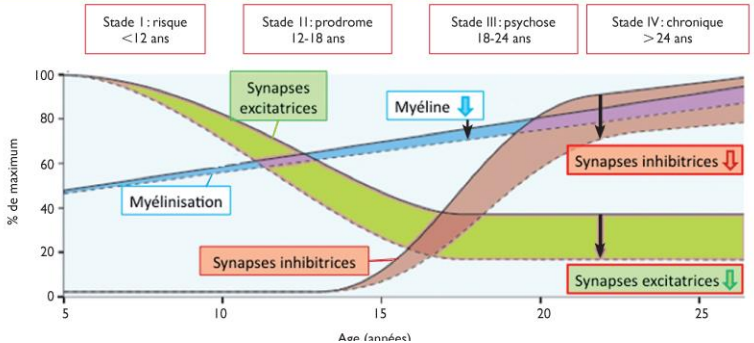
  Evidence of illness progression and acceleration

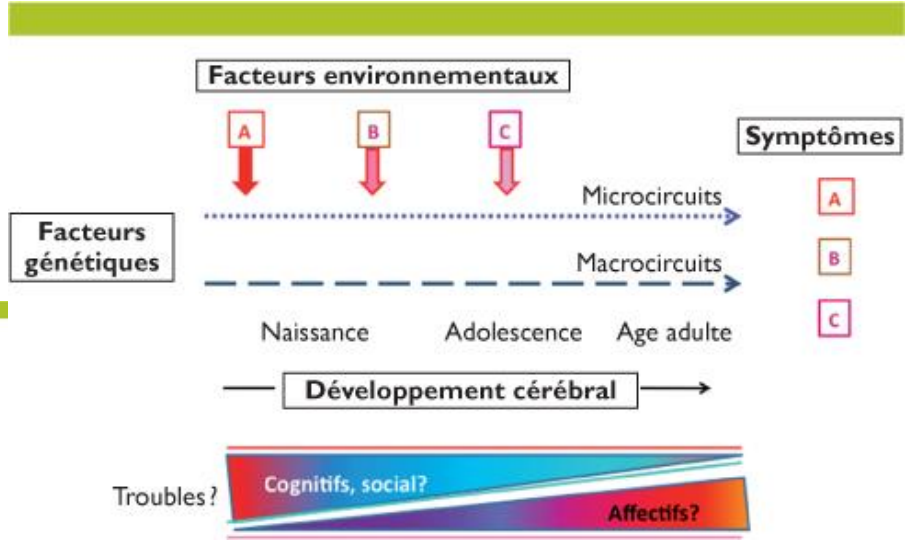
- Treatments targeting the period immediately preceding the onset of frank psychotic symptoms (the prodromal period) represent more effective interventions

The sooner the treatment – the better the outcome

Major psychoses have a neurodevelopmental component



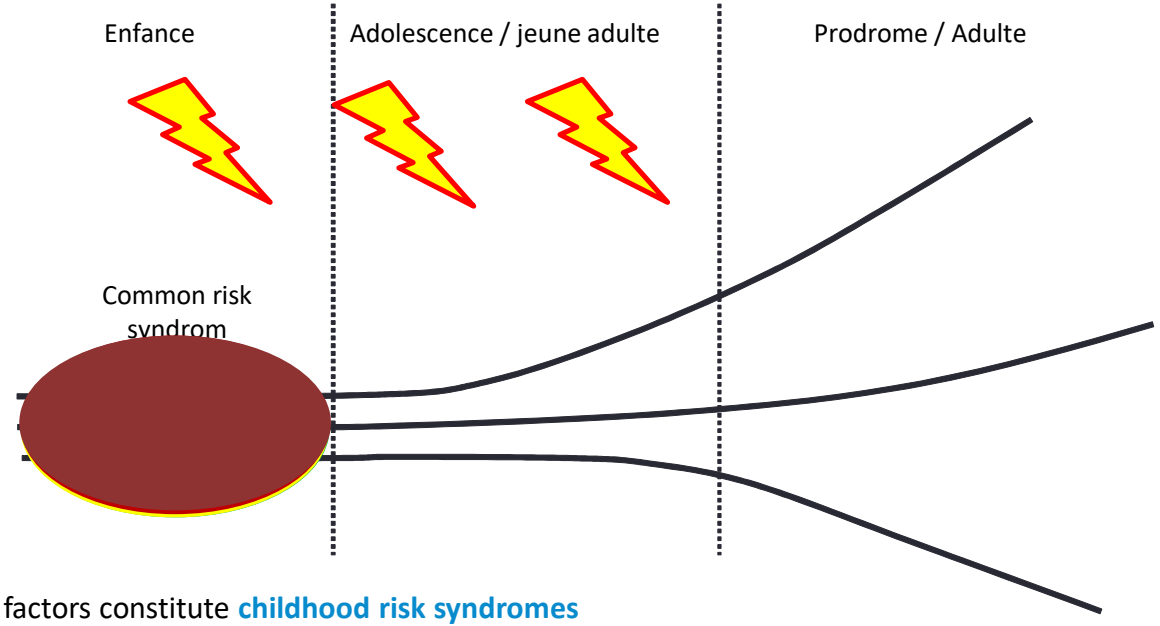




Adapted from T. Insel, Nature, 2010

Schizophrenia, bipolar disorder and recurrent depression share some common roots

- They share several causative mechanisms
- Particularly in their childhood determinants



- A combinatorial genetic and environmental factors constitute **childhood risk syndromes**
- The way environmental factors hit the genetic vulnerability may result in different developmental trajectories leading to the clinical phenotype recognized as SCh, BPD and MDD

Maziade & Paccalet, *Schizophr Res,* 2013
Maziade, M., Gilbert, E., Berthelot, N., & Paccalet, T. dans J-P. Raynaud, M. Hodes, & S.S-F. Gau (Eds) (2014)

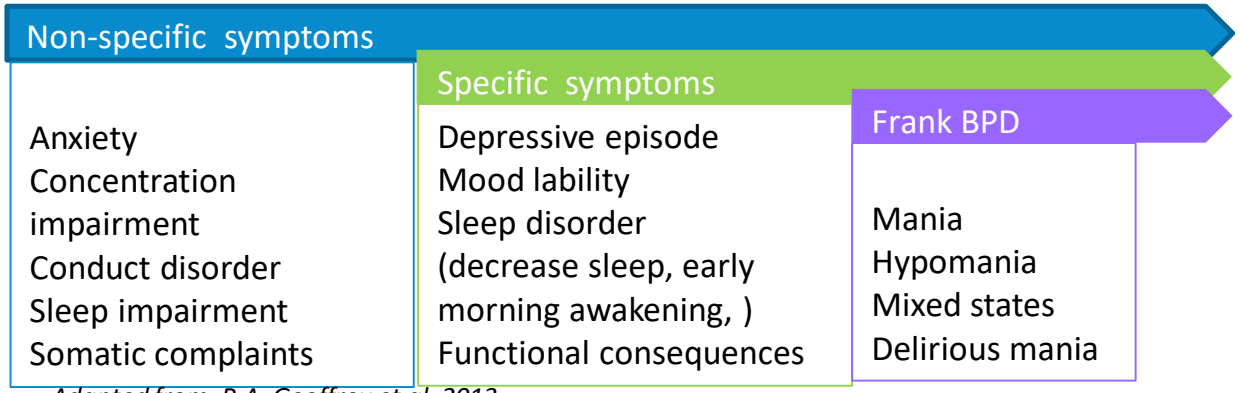
Aims

To define *childhood risk syndromes which are likely :*

- To develop earlier, safer and more effective interventions as well as a paradigm of primary prevention

- To improve our understanding of the pathophysiology or pathogenesis of these neurodevelopmental disorders

How can we define childhood risk syndromes ?



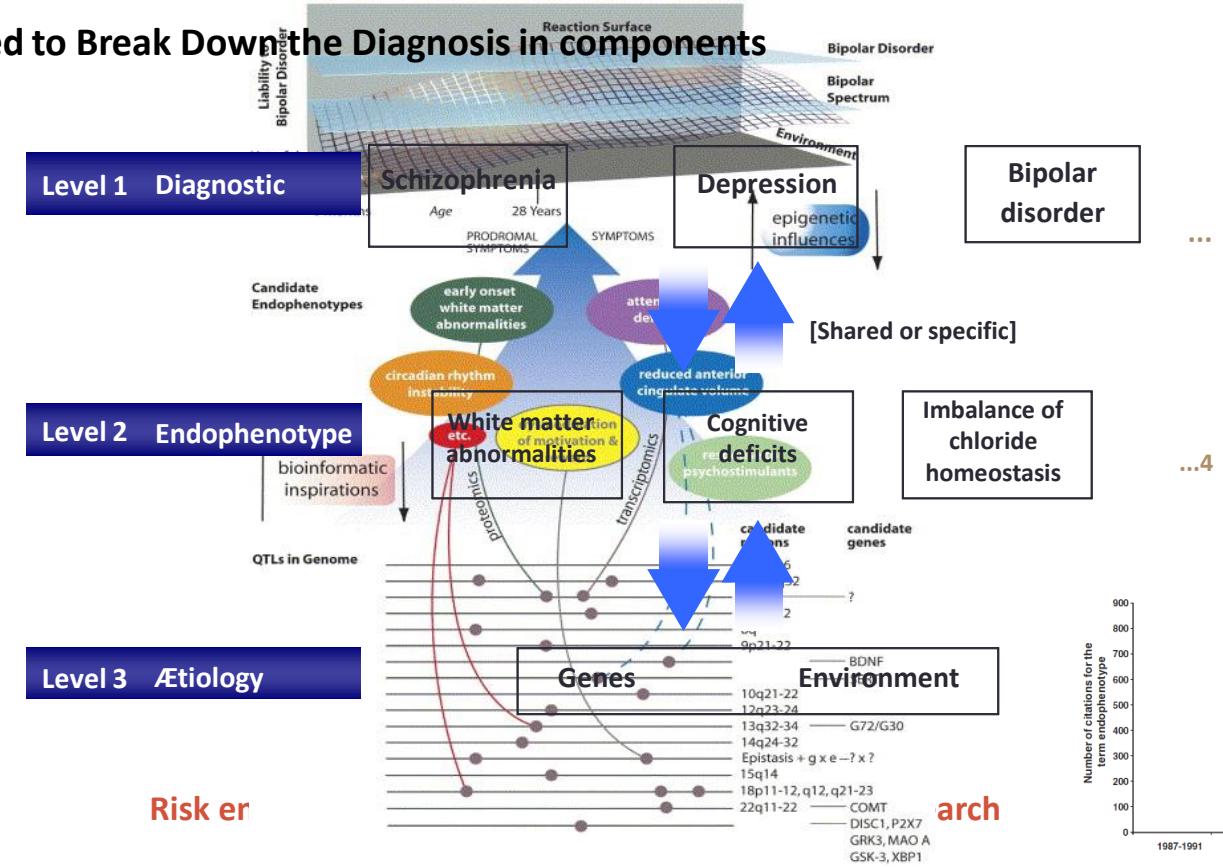
Adapted from P.A. Geoffroy et al. 2013

These early non-specific symptoms are episodic and change over time

An strategy based on the DSM criteria is not pertinent to define Childhood at-risk syndromes

Strategy: identifying risk endophenotypes

Need to Break Down the Diagnosis in components

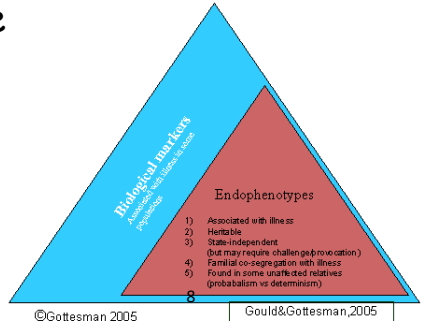


Definition of an endophenotype

Gottesman & Gould, Am J Psy 2003, Braff et al., Schiz Bull, 2007

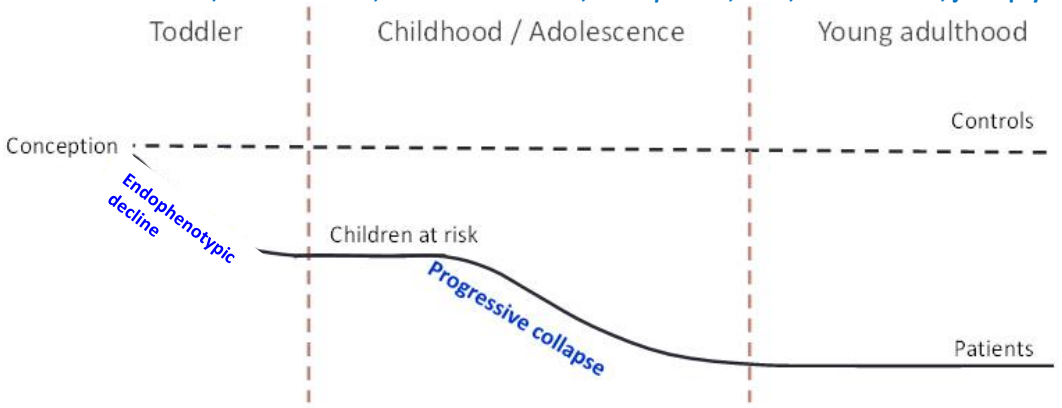
- The endophenotype is associated with illness in general population
- Endophenotype is heritable
- Endophenotype is primarily **state-independen**t (manisfests in a individual whether or not illness is active)
- Endophenotype is more frequent in a patient's **family members** than in the general population.
- Within families endophenotype and disease co-segregate

A risk endophenotype:
- **Present in both children at risk as well as their parents**
- **Can change along life courses (timing of expression, evolution)**



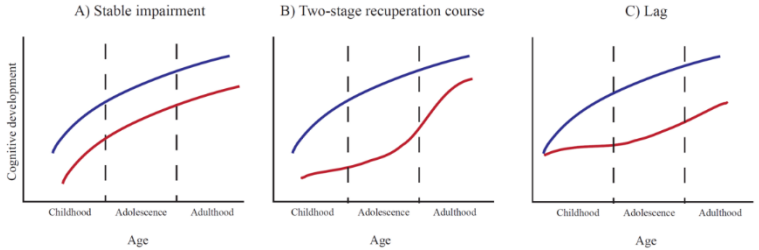
Tracing risk developmental trajectories composed of various endophenotypes or biomarkers

Maziade et al., *PLoS ONE* 2011, Maziade & Paccalet, *Schizophr Res*, 2013, Maziade et al., jama psychiat



- **Specific trajectories for each risk endophenotype or biomarkers**

Maziade et al. *PLoS ONE* 2011 ; Maziade et Paccalet *Schizophr Res* 2013



Combined Versus isolated Risk Endophenotypes

A single risk endophenotype

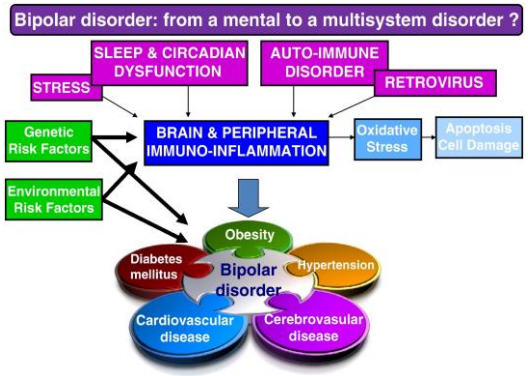
High frequency in the population

Multiple risk endophenotypes

Lower frequency in the population

Clustering of risk endophenotypes -> higher risk to convert

T. Paccalet et al. Schizophr Res. 2016 Aug;175(1-3):186-192.



Leboyer M, et al. Can bipolar disorder be viewed as a multi-system inflammatory disease? J Affect Disord. 2012 Dec 1;141(1):1-10.

Information From different modalities

Likely to reflect different underlying processes -> high capacity to determine distinct subtypes when combined

High risk cohorts: key aims

Eastern Quebec Kindred Study (EQKS): multigenerational families affected by schizophrenia and mood disorders (Dr M. Maziade)

- samples: adult family members (patients and their adults non-affective first-degree relatives) offspring (children/ adolescents and young adults) at risk for schizophrenia and mood disorders
    - Typical sample: 48 Kindred (1274 family members, 136 affected by schizophrenia and 205 by mood disorders) with 25-year follow-up

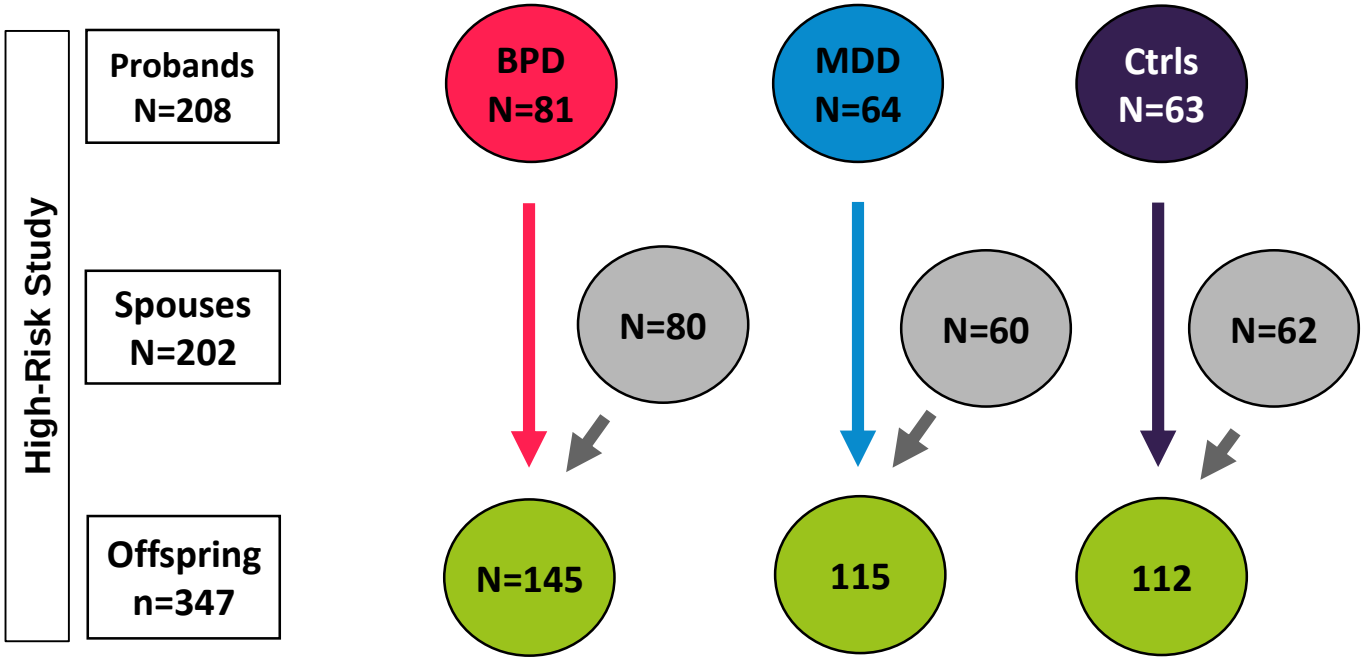
Le programme clinique « Horizon parent enfant » (HoPE)

Installing an **Joint International Reseach Unit** bringing together, **Université LAVAL, université de Lausanne** and **NCCR Synapsy***,

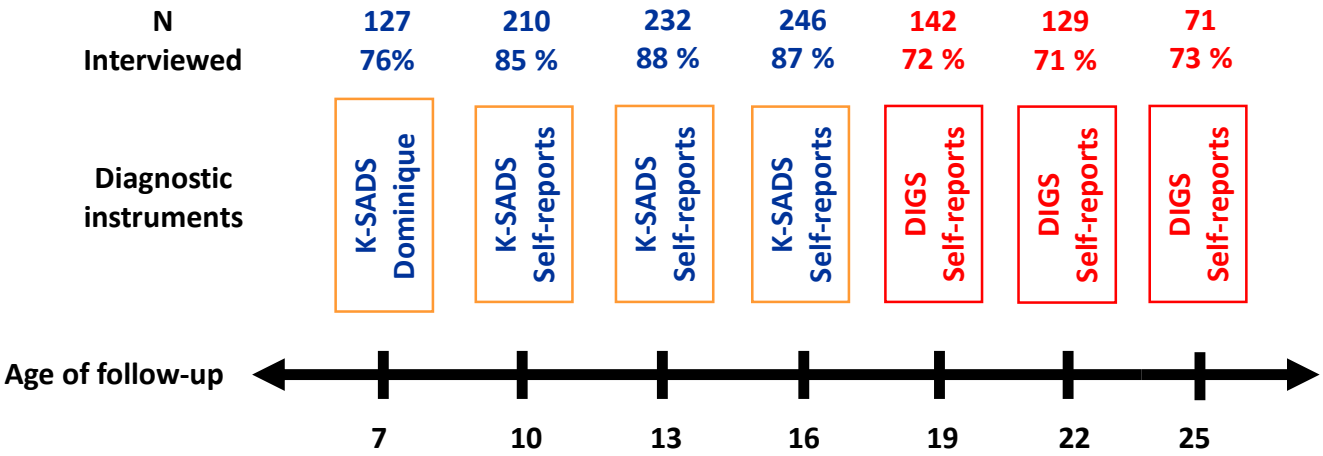
- To jointly carrying out and coordinating high risk cohort studies**
- To accelerate the identification of endophenotypes and their corresponding high risk trajectories in offspring
- To allow for researcher mobility as well as PhD student and resident exchanges

* National Center of Competence in Research for Brain Research and Psychiatry
**Lausanne-Geneva high risk Mood Cohort (300 offspring, 200 probands, 15-year follow-up)

Lausanne-Geneva High-Risk Mood Cohort



Offspring sample



Evaluation of early life stressors

Probands:

- Systematic evaluation of early life stressors including the age of stressful events;
- CTQ at current follow-up.

Offspring:

- Prospective and repetitive evaluation of life stressors at each follow-up;
- CTQ at current follow-up.

FONDS NATIONAL SUISSE
SCHWEIZERISCHER NATIONALFONDS
FONDO NAZIONALE SVIZZERO
SWISS NATIONAL SCIENCE FOUNDATION

Plateforme de phénotypage

Plateforme comportementale

Psychiatrique
Entrevues cliniques et semi-structurées

Neuropsychologique
Batteries consensuelles d'évaluations

Intégration intermodale
Batteries consensuelles d'évaluations

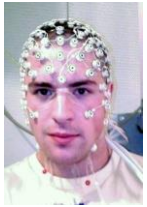
Plateforme de neuroimagerie

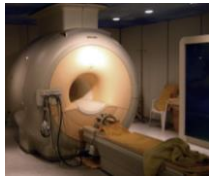
Imagerie RMN structurelle quantitative

Imagerie RMN fonctionnelle

Électroencéphalographie

Électrorétinographie



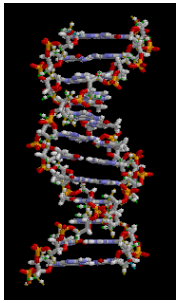


Plateforme génétique et neurobiologique

Marqueurs biochimiques candidats

Biomarqueurs transcriptionnels candidats

Rythmes circadien de l'activité



Plateforme neurophotonique

Microscopie optique multimodale à haute résolution et spectroscopie

&

Reprogrammation cellulaire humaine pour créer des cellules dérivées du patient

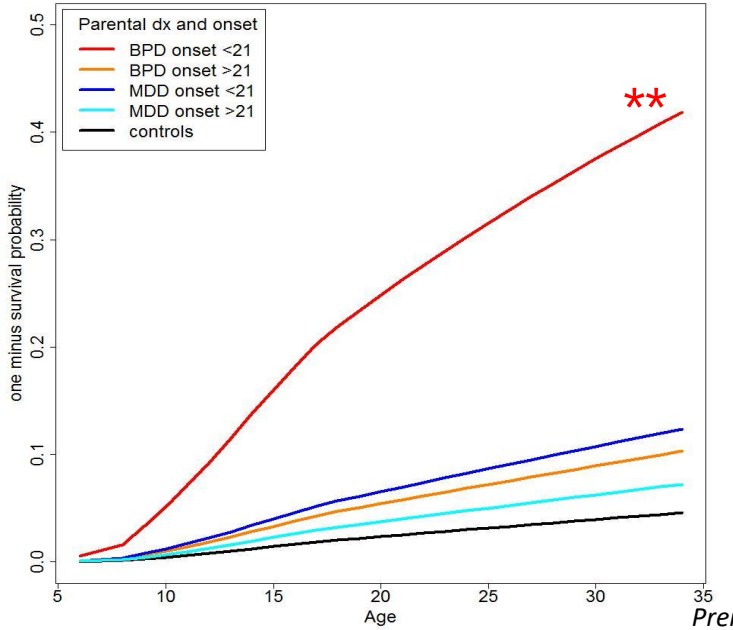
↓

Biomarqueurs de la dynamique cellulaire
- Homéostasie des chlorures (cotransporteurs)
- Stress métabolique
- Stress oxydatif

Intégration des biomarqueurs de risque et des endophénotypes

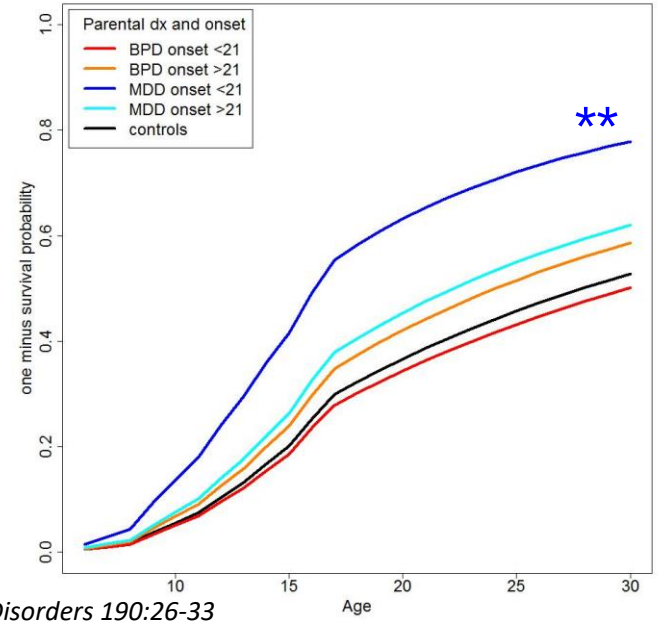
Subtyping of mood disorders : Age of onset

Risk of BPD in offspring as a function of proband mood disorder onset



** p < .01

Risk of MDD in offspring as a function of proband mood disorder onset

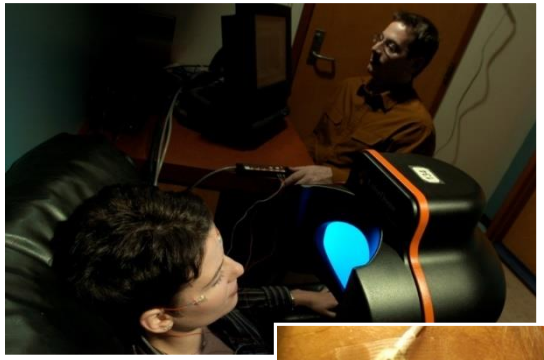


** p < .01

Preisig M. et al (2016) J Aff Disorders 190:26-33

ERG: A Novel Biomarker of Psychiatric Disorders

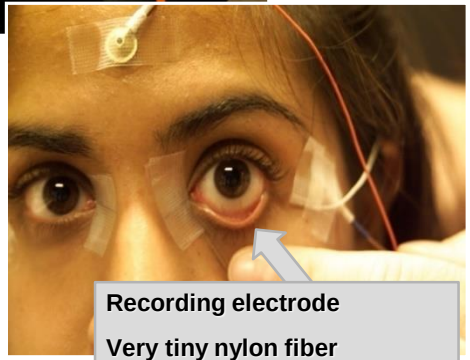
Collaboration with Prof. Marc Hebert, Centre Cervo, Université Laval, Québec

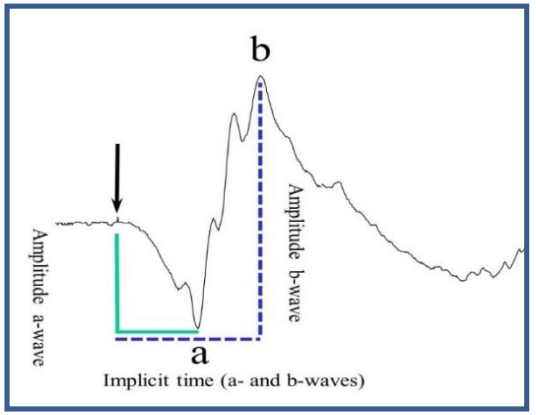


Rationale:

The Retina as an approachable part of the brain

Cone and rod ERGs can be obtained. The waveform is composed of a negative component known as the **a-wave** and a positive component known as the **b-wave.** Both the amplitude and implicit time are measured for each component.





Logistic regression analyses were performed entering all ERG parameters yielding to prediction models for: SZ, BP and SZ Vs. BP diagnosis

As predicted by the ERGs	Clinical Status		
	SZ	CT	
SZ	120 (**80%**)	21 (14%)	
CT	30 (20%)	129 (**86%**)	
Total	**150**	**150**	**OR=25**

SZ Vs CT
Sensitivity: 80%
Specificity: 86%

As predicted by the ERGs	True Clinical Status		
	BP	CT	
BP	119 (**79%**)	18 (12%)	
CT	31(21%)	132 (**88%**)	
Total	**150**	**150**	**OR=26**

BP Vs CT
Sensitivity: 79%
Specificity: 88%

As predicted by the ERGs	True Clinical Status		
	SZ	BP	
SZ	102 (**88%**)	11 (9%)	
BP	14 (12%)	108 (**91%**)	
Total	**116**	**119**	**OR=72**

SZ Vs BP
Sensitivity: 88%
Specificity: 91%

Hébert M, et al., Electroretinographic anomalies in medicated and drug free patients with major depression: Tagging the developmental roots of major psychiatric disorders. Prog Neuropsychopharmacol Biol Psychiatry. 2017 Apr 3;75:10-15

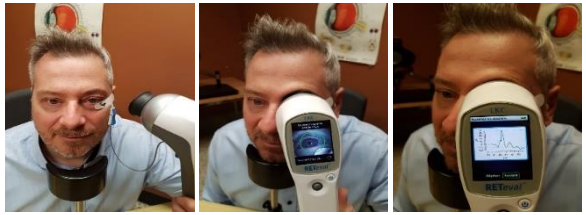
Hébert M, et al., Light evoked potentials measured by electroretinogram may tap into the neurodevelopmental roots of schizophrenia. Schizophr Res. 2015 Mar;162(1-3):294-5

Hébert M, Gagné AM, Paradis ME, Jomphe V, Roy MA, Mérette C, Maziade M. Retinal response to light in young nonaffected offspring at high genetic risk of neuropsychiatric brain disorders. Biol Psychiatry. 2010 Feb 1;67(3):270-4

ELECTRORETINOGRAPHY IN THE LAUSANNE-GENEVA HIGH-RISK COHORT

Marie-Pierre F. Strippoli, Martin Preisig, Marc Hébert , Pierre Marquet

Ambulatory portable device

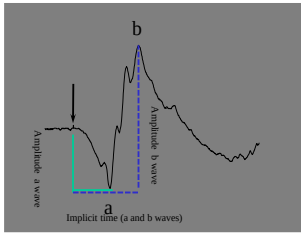


A **B** **C**

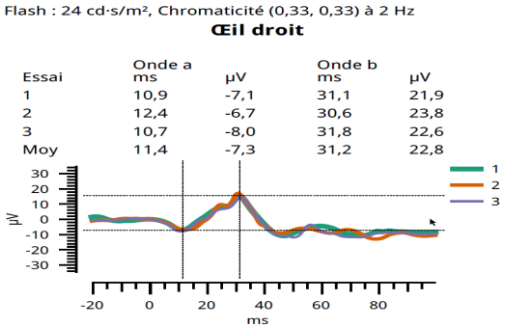
A) Skin electrode positioning and connection
B) Eye tracking during recording
C) Average final ERG response display

LKC RET eval

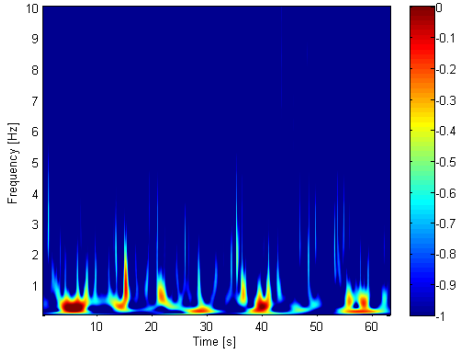
Typical ERG response



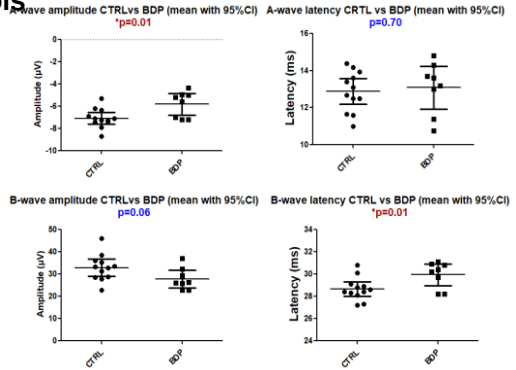
Example of recordings



Time – Frequency – Wavelet Analysis



ERG response (7.5 cd/m².s) among BPD and controls



Plateforme de phénotypage

Plateforme comportementale

Psychiatrique
Entrevues cliniques et semi-structurées

Neuropsychologique
Batteries consensuelles d'évaluations

Intégration intermodale
Batteries consensuelles d'évaluations

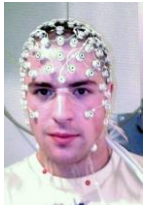
Plateforme de neuroimagerie

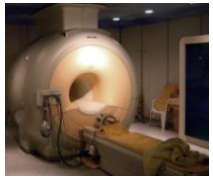
Imagerie RMN structurelle quantitative

Imagerie RMN fonctionnelle

Électroencéphalographie

Électrorétinographie



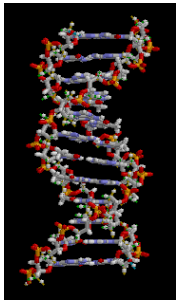


Plateforme génétique et neurobiologique

Marqueurs biochimiques candidats

Biomarqueurs transcriptionnels candidats

Rythmes circadien de l'activité



Plateforme neurophotonique

Microscopie optique multimodale à haute résolution et spectroscopie

&

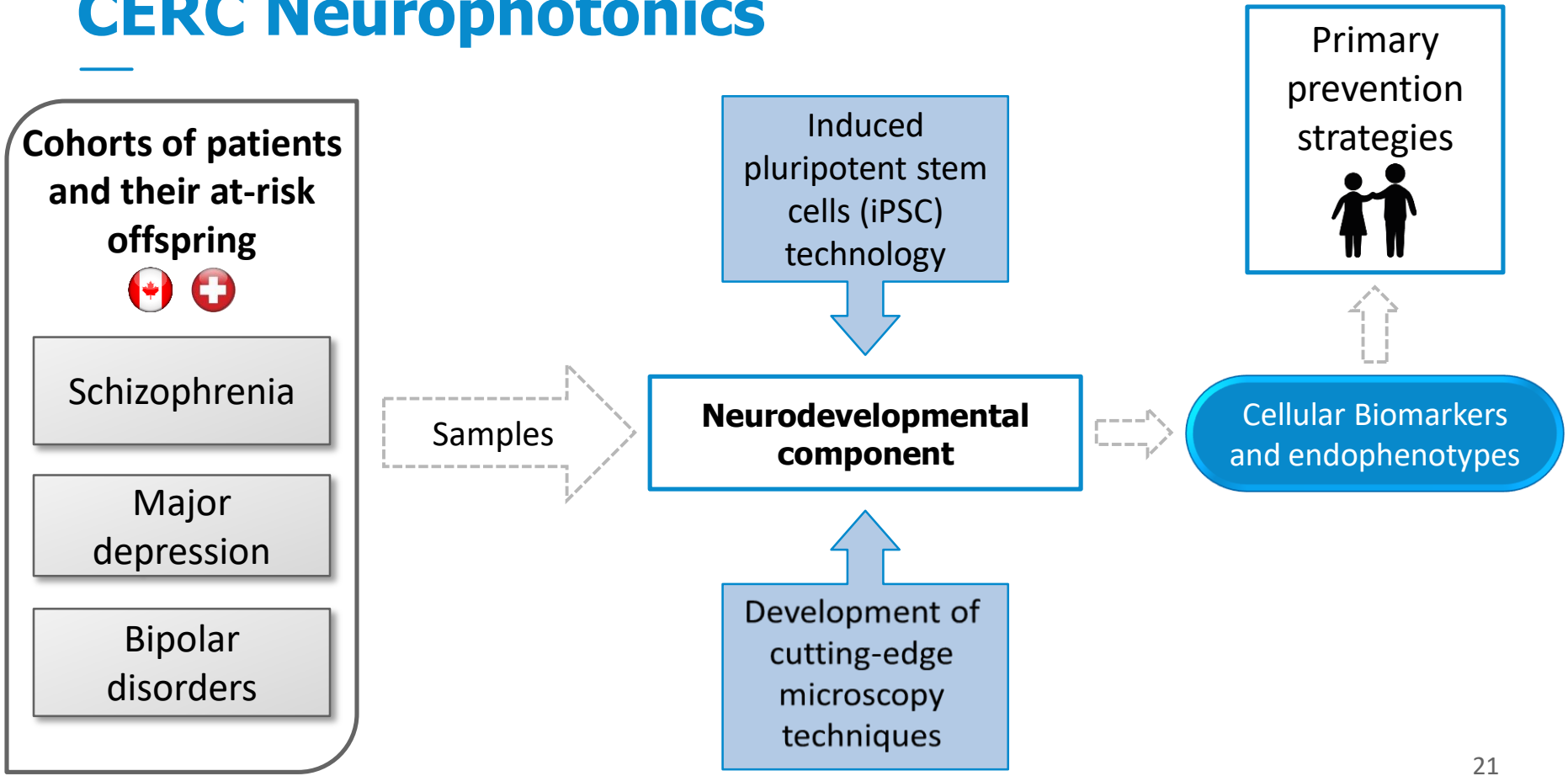
Reprogrammation cellulaire humaine pour créer des cellules dérivées du patient

↓

Biomarqueurs de la dynamique cellulaire
- Homéostasie des chlorures (cotransporteurs)
- Stress métabolique
- Stress oxydatif

Intégration des biomarqueurs de risque et des endophénotypes

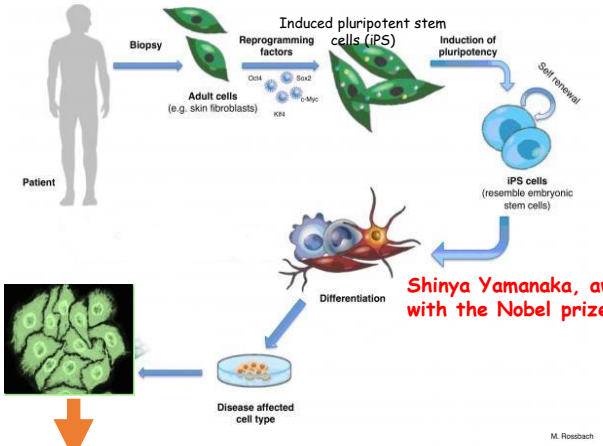
CERC Neurophotonics



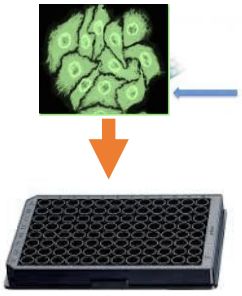
neurophotonics

- **Identify disease-specific cellular phenotypes**
- **Personalized medicine**

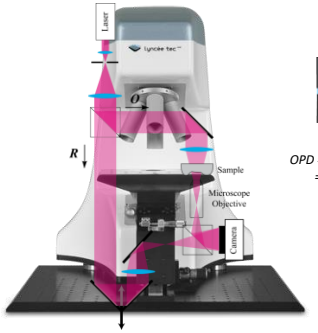
Human Cellular Reprograming
to Create Patient-derived Cells

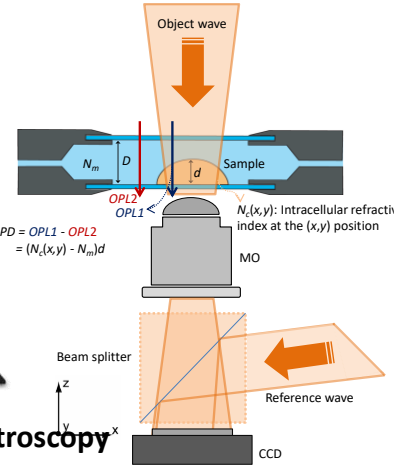


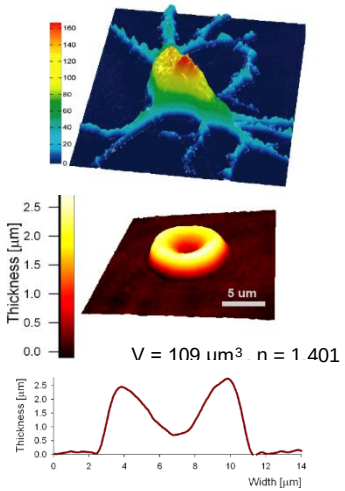
Shinya Yamanaka, awarded with the Nobel prize in 2012



Screening capability:
Automation and parallelization



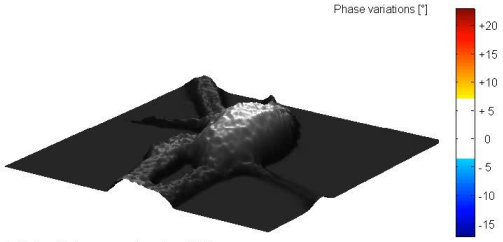




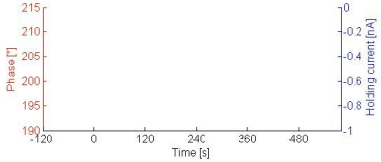
High resolution multimodal optical microscopy and spectroscopy
To analyze cell dynamics at the nanoscale

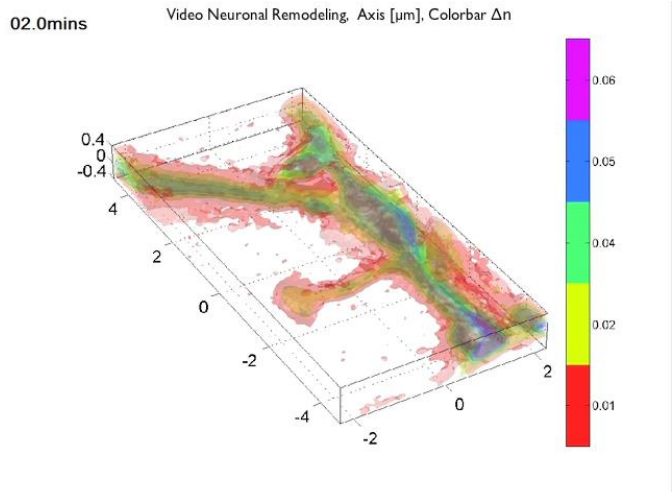
Digital Holographic microscopy

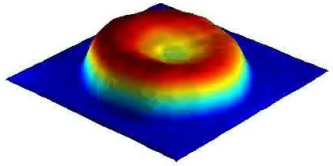
ın invasive monitoring of electrical neuronal activity by measuring transmembrane water movements

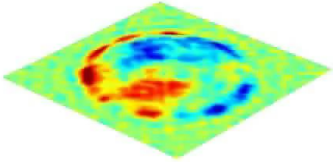


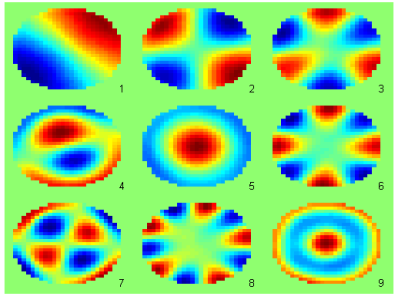
Initial cell phase contrast = 197°

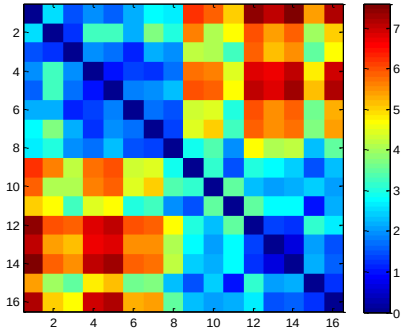






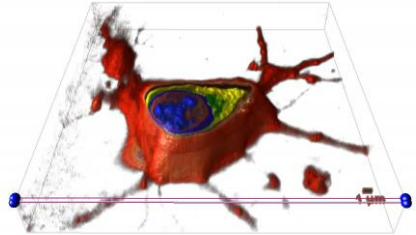






j = 1..8 Healthy subjects

i = 8..16 Diabetic patients



ct j are.
ergy

gy distribution

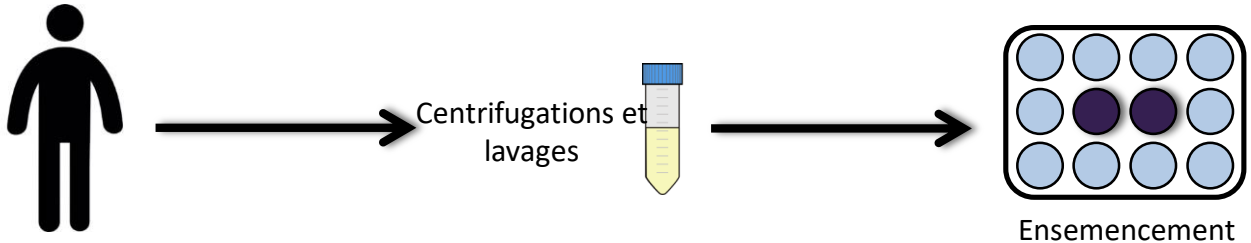
PROTOCOL

Generation of human induced pluripotent stem cells from urine samples

Ting Zhou[1,7], Christina Benda[1,7], Sarah Dunzinger[2], Yinghua Huang[1], Jenny Cy Ho[3], Jiayin Yang[1], Yu Wang[1], Ya Zhang[1], Qiang Zhuang[1], Yanhua Li[1], Xichen Bao[1], Hung-Fat Tse[3–5], Johannes Grillari[2,6], Regina Grillari-Voglauer[2,6], Duanqing Pei[1] & Miguel A Esteban[1,4,5]

[1]Key Laboratory of Regenerative Biology, Chinese Academy of Sciences, and Guangdong Provincial Key Laboratory of Stem Cells and Regenerative Medicine, South China Institute for Stem Cell Biology and Regenerative Medicine, Guangzhou Institutes of Biomedicine and Health, Guangzhou, China. [2]Aging and Immortalization Research, Department of Biotechnology, University of Natural Resources and Life Sciences, Vienna, Austria. [3]Cardiology Division, Department of Medicine, Queen Mary Hospital, Li Ka Shing Faculty of Medicine, University of Hong Kong, Hong Kong, China. [4]Guangdong Stem Cell and Regenerative Medicine Research Centre, University of Hong Kong, Hong Kong. [5]Guangzhou Institutes of Biomedicine and Health, Guangzhou, China. [6]Evercyte, Vienna, Austria. [7]These authors contributed equally to this work. Correspondence should be addressed to M.A.E. (esteban@gibh.org).

Published online 8 November 2012; doi:10.1038/nprot.2012.115



Maturation of neural stem cells

NPCs expansion **NPCs maturation**

Neural rosettes NPCs Mature neurons

d0 d10 d15 d21

Neural rosettes (N-cadherin, PKC-λ, PLZF, PAX-6)

NPCs (Nestin)

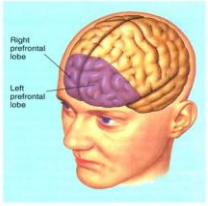
Mature neurons (βIII Tubulin, MAP-2)

Dopaminergic neurons (TH)

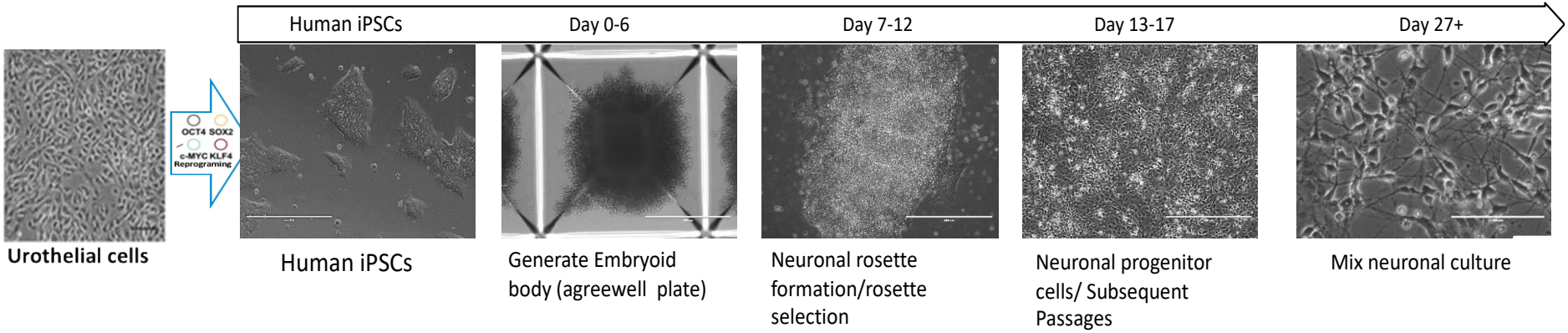
GABAergic neurons (GAD-1)

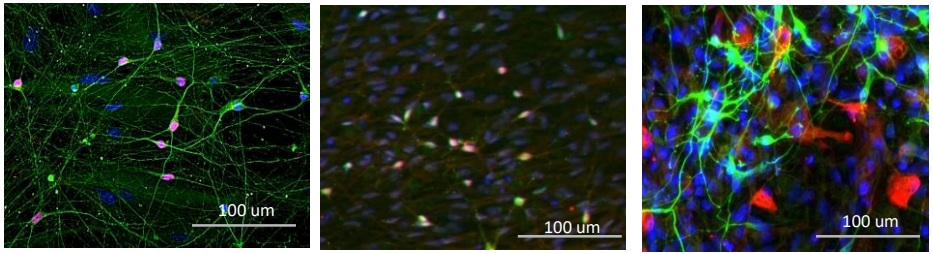
Astrocytes (GFAP)

► Prefrontal Lobes



A process to generate neuronal cells from iPSCs in-vitro



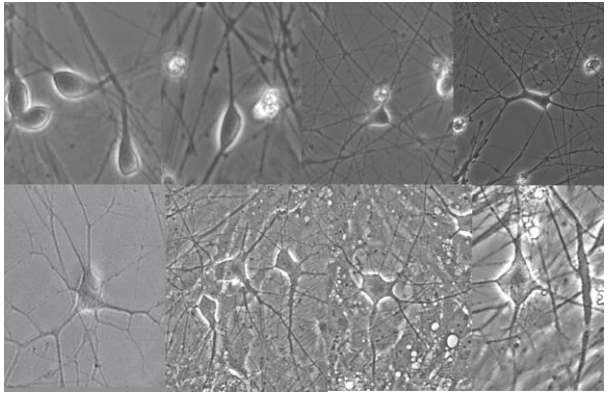


TBR-1/ Beta3 tubulin (Cortical neurons)

Neu-N/ GABA (matuere neurons)

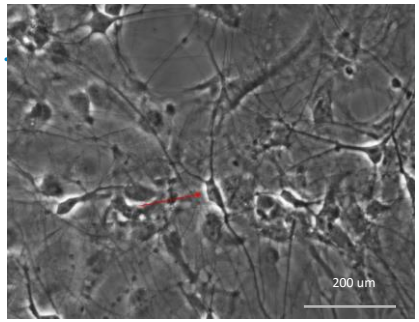
GFAP/ MAP2 (glial cells)

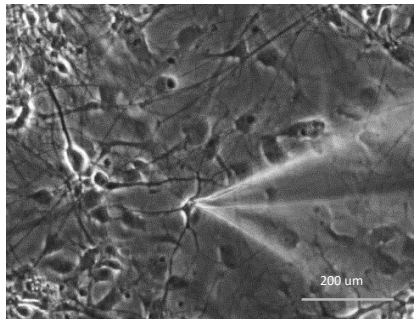
Fig: Immunocytochemistry and FACS analysis data shows the majority of cells exhibited cortical neurons marker TBR-1 (40-50%), Mature neurons marker NeuN (50-70%) and Glial cells marker GFAP (10-15%) at week-5 (Control n=4).



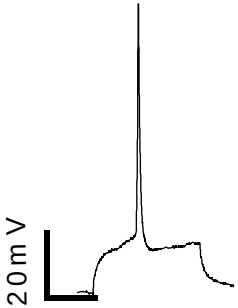
Identification of different neuronal morphologies

Whole cell patch Clamp analysis

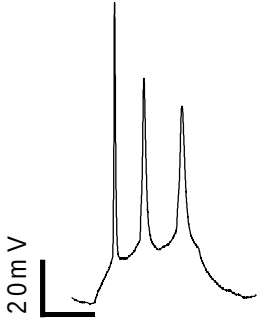




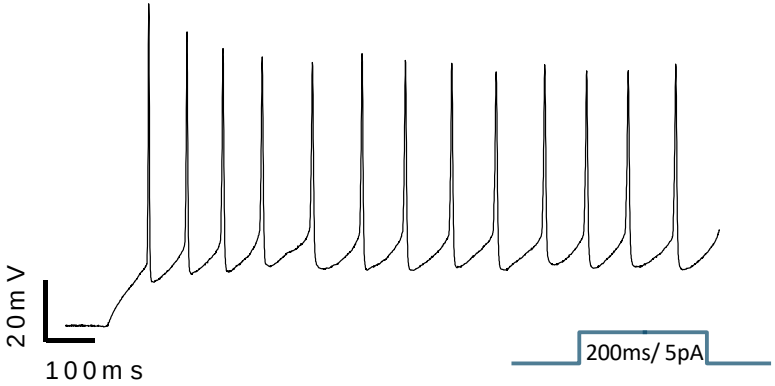
Spontaneous neuronal activity



Single evoked APs (week-3)



Adoptive evoked APs (week-5)

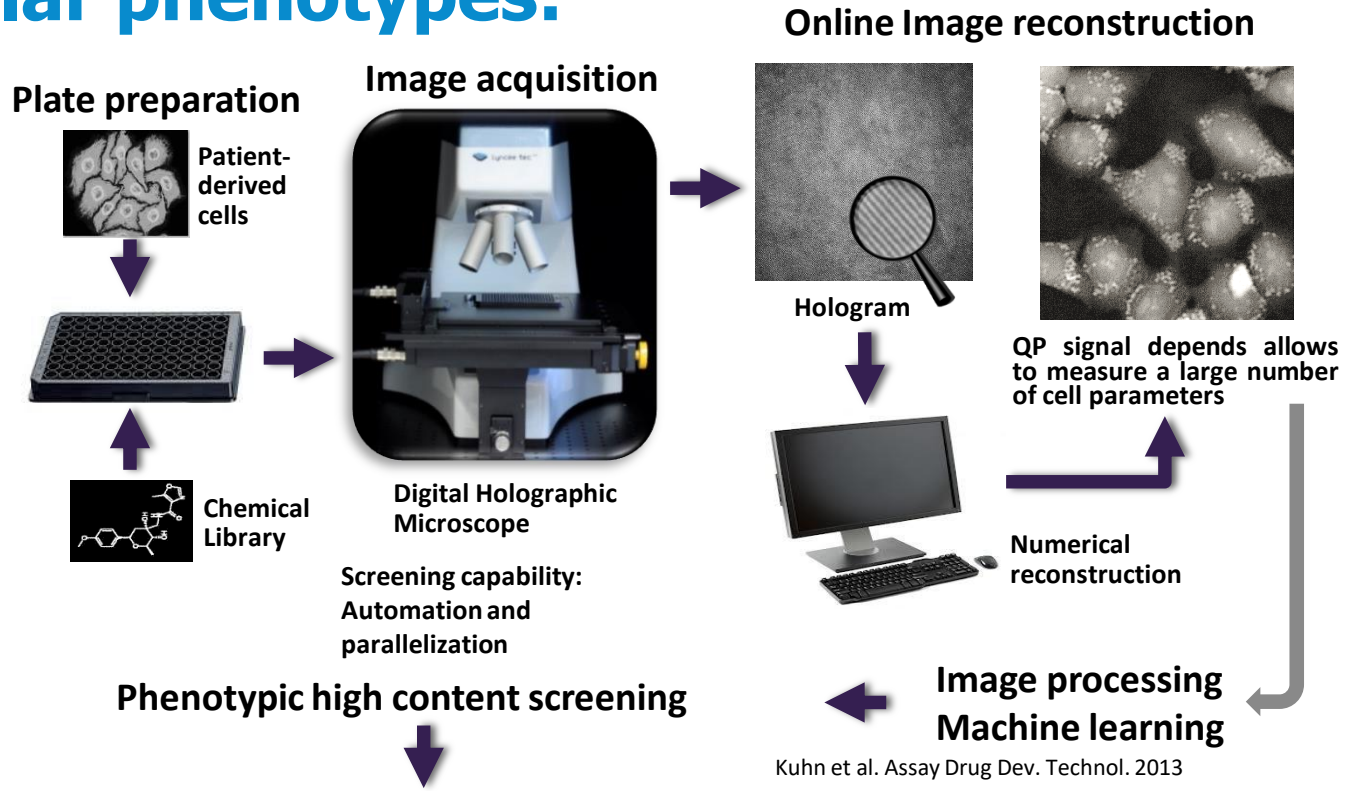


Repetitive evoked Aps (week-8)

	AP amplitude (mV)	Threshold (mV)	AP duration (ms)	RMP (mV)
Control n=15	70.58 ±23.67	32.29 ±3.18	10.63±1.75	36.08±7.23

Fig: Functional activity and maturation process of iPSCs derived neurons at different neuronal developmental days. At day week-3 neurons were start showing spontaneous activity and week-8 neurons were start showing repetitive evoked action potential (AP) a conformation of fully matured neurons.

A DHM based high-content screening (HCS) approach to non-invasively identify specific cellular phenotypes:



Kuhn et al. Assay Drug Dev. Technol. 2013

L'équipe de Lausanne

Neurophotonics group, UNIL , CHUV
Kaspar Rothenfusser
Kévin Bourgeaux
Carine Adiba
Pierre Marquet

Brain and Mind Institute, EPFL
Pascal Jourdain
Christian Depeursinge
Pierre J. Magistretti

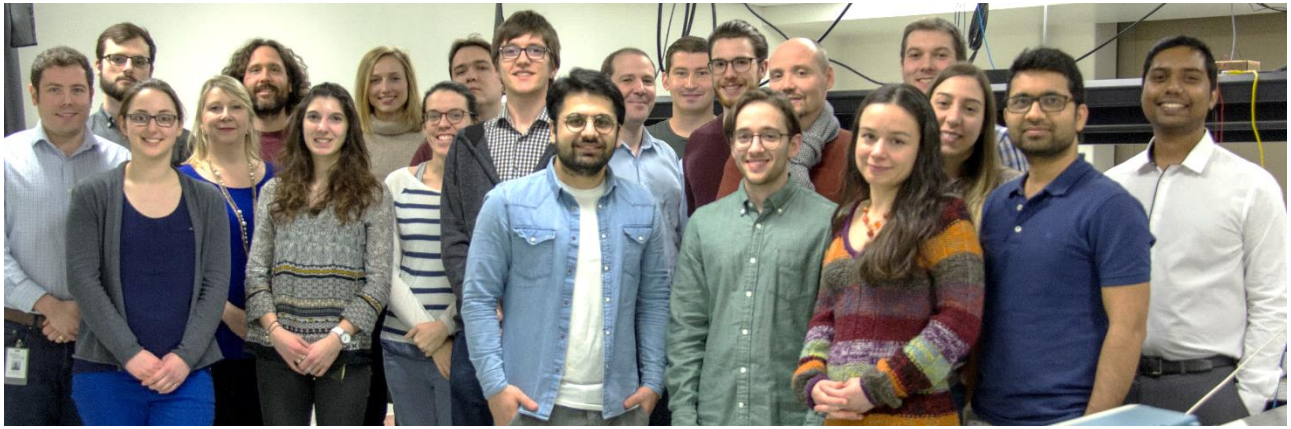
Biomolecular Screening Facility, EPFL
Gerardo Turcatti
Benjamin Rappaz

Lyncée Tec SA
Etienne Cuche
Tristan Colomb
Yves Emery

Centre for Psychiatric Epidemiology and Psychopathology, CHUV

Martin Preisig
Caroline Vandeleur
Marie-Pierre

L’équipe de Québec



Laboratoire de recherche en neurophotonique et psychiatrie (Dr. Pierre Marquet)

Erik Bélanger, PhD
Ana Sofia Correia, PhD
Antoine Godin, PhD
Sébastien Lévesque, PhD
Martin Roy, PhD
Hélène Leblond
Nathalie Van Houtte

Pierre-Louis Gagnon
Fariborz Khademian
Sara Mattar
Niraj Patel
Charles Pichette
Jean-Michel Mugnes, PhD
Lijo Thomas, Ph.D.
François Paquet-Mercier, Ph.D.

Philippe Bilodeau
Bertrand de Dorlodot
Andréanne Deschenes
Antoine Grégoire
Pauline Lavergne
Christophe Perron
Kanza Salem

Philippe de Tilleux
Émile Rioux-Pellerin
Valérie Watters

CIUSSS-CN Centre de neuromédecine personnalisée et du développement de l’enfant (Dr. Michel Maziade)

Elsa Gilbert, PhD
Thomas Paccalet, PhD
Byanka Lagacé, B.Sc.inf
Joanne Lavoie, M.Sc. Inf.
Valérie Beaupré Monfette
Emilie Binet
Marie-Claude Boisvert
Daphné Lussier
Linda René

Centre intégré universitaire de santé et de services sociaux de la Capitale-Nationale
Québec

LRNP

COPL
Centre d'optique, photonique et laser

CENTRE DE RECHERCHE CERVO
BRAIN RESEARCH CENTRE
QUÉBEC

UNIVERSITÉ LAVAL

Canada Excellence Research Chairs
Chaires d’excellence en recherche du Canada