La psychiatrie de demain et les avancées neurobiologiques

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SRMMB, 8 décembre 2018
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
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?

<table>
<thead>
<tr>
<th>Non-specific symptoms</th>
<th>Specific symptoms</th>
<th>Frank BPD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anxiety</td>
<td>Depressive episode</td>
<td>Mania</td>
</tr>
<tr>
<td>Concentration</td>
<td>Mood lability</td>
<td>Hypomania</td>
</tr>
<tr>
<td>impairment</td>
<td>Sleep disorder</td>
<td>Mixed states</td>
</tr>
<tr>
<td>Conduct disorder</td>
<td>(decrease sleep, early morning awakening, )</td>
<td>Delirious mania</td>
</tr>
<tr>
<td>Sleep impairment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Somatic complaints</td>
<td>Functional consequences</td>
<td></td>
</tr>
</tbody>
</table>

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.

Adapted from P.A. Geoffroy et al. 2013
Strategy: identifying risk endophenotypes

Need to Break Down the Diagnosis in components

Level 1 Diagnostic
- Schizophrenia
- Depression
- Bipolar disorder

Level 2 Endophenotype
- White matter abnormalities
- Cognitive deficits
- Imbalance of chloride homeostasis

Level 3 Aetiology
- Genes
- Environment
The endophenotype is associated with illness in general population

Endophenotype is heritable

Endophenotype is primarily state-independent (manifests in an 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


- 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


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 Research 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

High-Risk Study

- Probands N=208
- Spouses N=202
- Offspring n=347

- BPD
  - N=81
- MDD
  - N=64
-Ctrls
  - N=63

- N=80
- N=60
- N=62
- N=145
- 115
- 112
### Offspring sample

<table>
<thead>
<tr>
<th>N Interviewed</th>
<th>127</th>
<th>210</th>
<th>232</th>
<th>246</th>
<th>142</th>
<th>129</th>
<th>71</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>76%</td>
<td>85%</td>
<td>88%</td>
<td>87%</td>
<td>72%</td>
<td>71%</td>
<td>73%</td>
</tr>
</tbody>
</table>

#### Diagnostic instruments
- K-SADS Dominique
- K-SADS Self-reports
- K-SADS Self-reports
- K-SADS Self-reports
- DIGS Self-reports
- DIGS Self-reports
- DIGS Self-reports

#### Age of follow-up
- 7
- 10
- 13
- 16
- 19
- 22
- 25

### 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.
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

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


** p < .01
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

<table>
<thead>
<tr>
<th>Clinical Status</th>
<th>SZ</th>
<th>CT</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SZ</strong></td>
<td>120 (80%)</td>
<td>21 (14%)</td>
</tr>
<tr>
<td><strong>CT</strong></td>
<td>30 (20%)</td>
<td>129 (86%)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>150</td>
<td>150</td>
</tr>
<tr>
<td><strong>OR=25</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**SZ Vs CT**
Sensitivity: 80%
Specificity: 86%

As predicted by the ERGs

<table>
<thead>
<tr>
<th>True Clinical Status</th>
<th>BP</th>
<th>CT</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>BP</strong></td>
<td>119 (79%)</td>
<td>18 (12%)</td>
</tr>
<tr>
<td><strong>CT</strong></td>
<td>31 (21%)</td>
<td>132 (88%)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>150</td>
<td>150</td>
</tr>
<tr>
<td><strong>OR=26</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**BP Vs CT**
Sensitivity: 79%
Specificity: 88%

As predicted by the ERGs

<table>
<thead>
<tr>
<th>True Clinical Status</th>
<th>SZ</th>
<th>BP</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SZ</strong></td>
<td>102 (88%)</td>
<td>11 (9%)</td>
</tr>
<tr>
<td><strong>BP</strong></td>
<td>14 (12%)</td>
<td>108 (91%)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>116</td>
<td>119</td>
</tr>
<tr>
<td><strong>OR=72</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**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

ELECTRORETINOGRAPHY IN THE LAUSANNE-GENEVA HIGH-RISK COHORT

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

Ambulatory portable device

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

Typical ERG response

Example of recordings

Time – Frequency – Wavelet Analysis

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

LKC RET eval
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Intégration des biomarqueurs de risque et des endophénotypes
CERC Neurophototonics

Cohorts of patients and their at-risk offspring

- Schizophrenia
- Major depression
- Bipolar disorders

Primary prevention strategies

Cellular Biomarkers and endophenotypes

- Samples
- Induced pluripotent stem cells (iPSC) technology
- Neurodevelopmental component
- Development of cutting-edge microscopy techniques
Human Cellular Reprograming to Create Patient-derived Cells

- Identify disease-specific cellular phenotypes
- Personalized medicine

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

Each \( t_{i,j} \)-value \((i,j)\) in the matrix indicates how similar the energy distribution of the PCA modes between subject \( i \) and subject \( j \) are. The lower this \( t \)-value, the more similar the energy distribution is. Healthy and diabetic populations can be distinguished. Correlation between mode energy distribution and HbAc1 fraction is currently analyzing.

Cotte et al. Nature Photonics, 2013

Digital Holographic microscopy
Generation of human induced pluripotent stem cells from urine samples

Ting Zhou1,7, Christina Benda1,7, Sarah Dunzinger2, Yinghua Huang1, Jenny Cy Ho3, Jiayin Yang1, Yu Wang1, Ya Zhang1, Qiang Zhuang1, Yanhua Li1, Xichen Bao1, Hung-Fat Tse3-5, Johannes Grillari2,6, Regina Grillari-Voglauer2,6, Duanqing Pei1 & Miguel A Esteban4,5

1Key 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. 2Aging and Immortalization Research, Department of Biotechnology, University of Natural Resources and Life Sciences, Vienna, Austria. 3Cardiology Division, Department of Medicine, Queen Mary Hospital, Li Ka Shing Faculty of Medicine, University of Hong Kong, Hong Kong, China. 4Guangdong Stem Cell and Regenerative Medicine Research Centre, University of Hong Kong, Hong Kong. 5Guangzhou Institutes of Biomedicine and Health, Guangzhou, China. 6Evrycta, Vienna, Austria. 7These 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

- Neural rosettes
  - NPCs expansion
  - NPCs maturation

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

- NPCs
  - (Nestin)

- Mature neurons
  - (βIII Tubulin, MAP-2)

- GABAergic neurons
  - (GAD-1)

- Astrocytes
  - (GFAP)
A process to generate neuronal cells from iPSCs in-vitro

### Human iPSCs

- **Day 0-6**: Generate Embryoid body (agree well plate)
- **Day 7-12**: Neuronal rosette formation/rosette selection
- **Day 13-17**: Neuronal progenitor cells/ Subsequent Passages
- **Day 27+**: Mix neuronal culture

### Immunocytochemistry and FACS analysis data shows

- **TBR-1/ Beta3 tubulin (Cortical neurons)**
- **Neu-N/ GABA (mature 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).
Whole cell patch Clamp analysis

Spontaneous neuronal activity

Single evoked APs (week-3)
Adaptive evoked APs (week-5)
Repetitive evoked Aps (week-8)

<table>
<thead>
<tr>
<th></th>
<th>AP amplitude (mV)</th>
<th>Threshold (mV)</th>
<th>AP duration (ms)</th>
<th>RMP (mV)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control n=15</td>
<td>70.58 ±23.67</td>
<td>32.29 ±3.18</td>
<td>10.63±1.75</td>
<td>36.08±7.23</td>
</tr>
</tbody>
</table>

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:

- **Plate preparation**
  - Patient-derived cells

- **Chemical Library**

- **Digital Holographic Microscope**
  - Screening capability: Automation and parallelization

- **Online Image reconstruction**
  - QP signal depends allows to measure a large number of cell parameters
  - Numerical reconstruction

- **Image processing**
  - Machine learning

- **Identification of new cell biomarkers of diseases**

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Linda René