Prevention in Schizophrenia
– from Neuroscience to Community

Rodrigo A. Bressan
Professor, Department of Psychiatry, Un. Federal de São Paulo, Brazil
Honorary Visiting Professor, Institute of Psychiatry, King’s College London
Disease Burden by Illness

DALY - Disability Adjusted Life Year (15-44 anos)

Unipolar depressive disorders
Alcohol use disorders
Schizophrenia
Iron-deficiency anemia
Bipolar affective disorder
Hearing loss, adult onset
HIV/AIDS
Chronic OPD
Osteoarthritis
Road traffic accidents

Challenges for Prevention of Schizophrenia

• A – Limited biological knowledge
• B – Poor effectiveness of treatments
• C – Stigma
Schizophrenia – neurodevelopmental disease

Murray et al., Lancet 1985; Weinberger, Arch Gen Psychiatry 1987

ENVIRONMENT

Obstetric complications → Immigration/Urbanicity → Trauma Bullying → Cannabis → Schizophrenia

DNA Gene Expression → Citokines → Brain changes Structural/Funcional GENES → Dopamine sensitization

Murray et al., Lancet 1985; Weinberger, Arch Gen Psychiatry 1987
Multiphasic Approach

Risk during Neurodevelopment

“HIGH RISK”

“ULTRA-HIGH RISK”

1ST EPISODE PSYCHOSIS

SCHIZOPHRENIA

CHRONICITY or TREATMENT RESISTANCE
Multimodal Approach
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<th>Risk during Neurodevelopment</th>
<th>PRE-MORBID</th>
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Risk during Neurodevelopment:

- Pre-Morbid
- High Risk
- Ultra-High Risk

Psychosis Severity:

- Ultra-High Risk
- High Risk

Multiphasic – Multimodal Approach
Schizophrenia

Clinical: PANSS validation, prediction of Treatment Resistance

Cognition:

• MCCB Matrics validation in Brazil – Regular FAPESP

• Cognitive Rehabilitation – PRONEX
Plasma Ndel1 enzyme activity is reduced in patients with schizophrenia — A potential biomarker?

Ary Gadelha\textsuperscript{a}, Mauricio F.M. Machado\textsuperscript{b}, Camila M. Yonamine\textsuperscript{c}, João R. Sato\textsuperscript{d}, Maria A. Juliano\textsuperscript{b}, Vitor Oliveira\textsuperscript{b}, Rodrigo A. Bressan\textsuperscript{a}, Mirian A.F. Hayashi\textsuperscript{c,\textsuperscript{*}}
Reduced dorso-lateral prefrontal cortex in treatment resistant schizophrenia

- Compare cortical thickness between 61 treatment resistant SCZ, 67 non-resistant and 80 healthy controls.
- TR-SCZ presented widespread reduction in cortical thickness in frontal, temporal, parietal and occipital regions.
- TR-SCZ presented significant reduced DFPFC thickness than controls.
- Finding suggest cortical thickness of DLPFC a more severe form of the disease.

Figure: Decreased DLPFC (BA 46) in the TR-SCZ group.

Gene Modulation of Brain Structure

ZDHHC8 gene may play a role in cortical volumes of patients with schizophrenia.

• 282 patients and 379 controls were genotyped. 138 went to an MRI scan.
• **GG-genotypes carriers presented reduced frontal grey matter volume.**
Neurotrophins and Brain Structure

BDNF modulating cortical thickness in schizophrenia.

- BDNF and cortical thickness showed different patterns of correlation for patient and healthy control group in one cluster in the right hemisphere distributed across the supramarginal, post central, and inferior frontal cortices.

Figure: Blue shade represents significant cluster at $p<0.05$ for group*bdnf interaction. Lines represent Freesurfer parcelation regions.

Zugman et al., submitted
First Episode Psychosis
Epigenetics: gene expression and methylation

• 175 drug-naïve 1st episode psychotic patients
First Episode Psychosis

Gene expression (RNA) – Risperidone treatment (2 months)
# Ultra-High Risk for Psychosis

## Transition Rates to Psychosis (2 years)

<table>
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<tr>
<th>Centre</th>
<th>Transition rate</th>
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<tr>
<td>PACE</td>
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<td>PRIME</td>
<td>38%</td>
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<td>TOPP</td>
<td>43%</td>
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<td>EDIE</td>
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<td>PIER</td>
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<td>22%</td>
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*… work in progress*

Fusar-Poli et al., 2012
## Conversion to psychosis – is it possible to prevent?

<table>
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<tr>
<th>Reference</th>
<th>Comparison Group</th>
<th>N</th>
<th>Outcome</th>
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<tr>
<td><strong>PACE</strong> McGorry et al., Am J Psychiatr 2002</td>
<td>1. CBT + risperidone 2. Support Therapy</td>
<td>31</td>
<td>1. ↓ conversion in 6 mo (9.7 vs. 35%), p=0.026 2. ↔ in 1 yr</td>
</tr>
<tr>
<td><strong>EDIE</strong> Morrison et al., Br J Psychiatr 2004</td>
<td>1. CBT 2. Monitoring</td>
<td>29</td>
<td>1. ↓ conversion in 1 yr (6% vs. 26%), p&lt;0.05 2. ↓ conversion in 3 yr</td>
</tr>
<tr>
<td><strong>PRIME</strong> McGlashan et al., Am J Psychiatr 2006</td>
<td>1. Olanzapine 2. Placebo</td>
<td>31</td>
<td>1. ↓ conversion (15% vs. 38%), p&gt;0.05 2. ↑ Side effects</td>
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<tr>
<td>Amminger et al., Arch Gen Psychiatr 2010</td>
<td>1. Omega 3 2. Placebo</td>
<td>41</td>
<td>1. ↓ conversion (4.9% vs. 27.5%), p=0.004</td>
</tr>
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</table>
Cytokines – new opportunities


Review Article

Cytokines in schizophrenia: Possible role of anti-inflammatory medications in clinical and preclinical stages

Rodrigo Barbachan Mansur, MD,1 André Zugman, MD,1 Elson de Miranda Asevedo, MD,1 Graccielle Rodrigues da Cunha, MD,1 Rodrigo Affonseca Bressan, MD, PhD1,2 and Elisa Brietzke, MD, PhD1,2*
Treatment: new opportunities

Elson Asevedo*, Graccielle R. Cunha, André Zugman, Rodrigo B. Mansur and Elisa Brietzke

N-acetylcysteine as a potentially useful medication to prevent conversion to schizophrenia in at-risk individuals
Review

Do sleep abnormalities and misaligned sleep/circadian rhythm patterns represent early clinical characteristics for developing psychosis in high risk populations?

Marcio Zanini\textsuperscript{a,*}, Juliana Castro\textsuperscript{a,c}, Fernando Morgadinho Coelho\textsuperscript{c}, Lia Bittencourt\textsuperscript{c}, Rodrigo A. Bressan\textsuperscript{a,b}, Sergio Tufik\textsuperscript{c}, Elisa Brietzke\textsuperscript{a,b}
Identifying Gene-Environment Interactions in Schizophrenia: Contemporary Challenges for Integrated, Large-scale Investigations

European Network of National Networks studying Gene-Environment Interactions in Schizophrenia (EU-GEI)*

*A full list of authors and affiliations appears in the Appendix.
Animal Model Schizophrenia (SHR) – preventive effects strategies

Enriched Environment – prevent schizophrenia like symptoms

Santos, CM - 2015
Animal Model Schizophrenia (SHR) – preventive effects strategies

~ adolescence

Canabidiol (CBD) – prevent schizophrenia like symptoms

~ adulthood

Peres FF, 2015
9,937 Children (6-12 yo)

2,500 children
- Psychopathology
- Risk factors
- Cognition
- Learning/speech
- DNA

750 children
- MRI
- DNA & RNA
- Peripheral biomarkers

Phase II – 3-year follow-up (9-15 yo)

22 schools in Porto Alegre
35 schools in São Paulo

Phase III – 6-year Follow-up

Salum et al., Intl J Meth Psychiatr Res, 2014
Dimensional Psychopathology

Manic Symptoms in Youth: Dimensions, Latent Classes, and Associations With Parental Psychopathology

Pedro Mario Pan, MD, Giovanni Abrahão Salum, MD, PhD, Ary Gadelha, MD, Tais Moriyama, MD, Hugo Cogo-Moreira, PhD, Ana Soledade Graeff-Martins, MD, PhD, Maria Conceição Rosario, MD, PhD, Guilherme Vanoni Polanczyk, MD, PhD, Elisa Brietzke, MD, PhD, Luís Augusto Rohde, MD, PhD, Argyris Stringaris, MD, PhD, MRCPsych, Robert Goodman, PhD, FRCPsych, Ellen Leibenluft, MD, Rodrigo Affonso Bressan, MD, PhD
Structural Brain Trajectories – hippocampus

Left Hippocampus - Male

Left Hippocampus - Female

Right Hippocampus - Male

Right Hippocampus - Female

Andre Zugman, Sato, Bressan, Jackowsky et al., in preparation
Genetic determinants of brain morphology

Common genetic variants influence subcortical brain volumes in ancestrally diverse adolescents

Patrick MA Sleiman\textsuperscript{1,2}, Theodore Satterthwaite\textsuperscript{3}, Sintia L Belangero\textsuperscript{4,5}, John Connolly\textsuperscript{1}, Frank Mentch\textsuperscript{1}, Haijun Qiu\textsuperscript{1}, Xiao Chang\textsuperscript{1}, Cecilia Kim\textsuperscript{1}, Renata Pellegrino-Silva\textsuperscript{1}, Kelly Thomas\textsuperscript{1}, Andrea P Jackowski\textsuperscript{4}, Helena P Brentani\textsuperscript{6,7}, Euripedes CM Filho\textsuperscript{6,7}, Giovanni A Salum\textsuperscript{7,8}, Ary Gadelha\textsuperscript{4}, Mackenzie Behr\textsuperscript{1}, Rosetta Chiavacci\textsuperscript{1}, Rueben C Gur\textsuperscript{3}, Rodrigo A Bressan\textsuperscript{5}, Raquel E Gur\textsuperscript{3} and Hakon Hakonarson\textsuperscript{1,2}.

GWAS study of subcortical brain volumes (MRI) of 1957 individuals

- Philladephia Neurodevelopmental Cohort (age 8-21 years)
- Brazilian High Risk Cohort Study (age 7-15 years).
- 2 loci associated with brain volume also associate with neurocognitive tests
- For the first time that genetic variants associated with intermediate phenotypes such as brain imaging data can be predictive of a behavioral phenotype.

Sleiman et al., submitted
Age effects on the default mode and control networks in typically developing children

João Ricardo Sato a, c, h, *, Giovanni Abrahão Salum b, h, Ary Gadelha c, h, Felipe Almeida Picon b, h, Pedro Mario Pan c, h, Gilson Vieira e, g, André Zugman c, h, Marcelo Queiroz Hoexter c, d, h, Mauricio Anés b, h, Luciana Monteiro Moura c, h, Marco Antonio Gomes Del'Aquila c, h, Edson Amaro Junior g, Philip McGuire f, Nicolas Crossley f, Acíoly Lacerda c, h, Luis Augusto Rohde b, h, Euripedes Constantino Miguel d, h, Rodrigo Affonseca Bressan c, h, Andrea Parolin Lackowski c, h
Decreased centrality of subcortical regions during the transition to adolescence: A functional connectivity study

João Ricardo Sato a,c,h,* , Giovanni Abrahão Salum b,h , Ary Gadelha c,h , Gilson Vieira e,g , André Zugman c,h , Felipe Almeida Picon b,h , Pedro Mario Pan c,h , Marcelo Queiroz Hoexter c,d,h , Mauricio Anés b,h , Luciana Monteiro Moura c,h , Marco Antonio Gomes Del’Aquilla c,h , Nicolas Crossley f , Edson Amaro Junior g , Philip Mcguire f , Acioly L.T. Lacerda c,h , Luis Augusto Rohde b,h , Euripedes Constantino Miguel d,h , Andrea Parolin Jackowski c,h , Rodrigo Affonsoeca Bressan .

- ↑ centrality angular gyrus during the transition to adolescence
- ↓ many subcortical and cerebellar regions.
Functional Brain Trajectories

Altered neurodevelopment trajectory identified using a combination of graph theory and one-class support vector machine to analyze neuroimaging data.

- Assessed brain networks rsfMRI of 622 children and adolescents with increased risk for psychiatric disorders (7-15 y/o)

- Subjects with atypical brain network organization had higher levels of psychopathology

Figure: Box-plots of EVC at each node with significant mean difference (p<0.05) between the OC-SVM labels (typical vs atypical), CBCL Total and age.
Psychotic experiences: ↓ cortical thickness

- Findings may indicate subtle deviant brain maturation processes that may represent risk for schizophrenia

Ary Gadelha et al., in preparation
Translation to Community School Mental Health

- Mental Health Literacy for teachers
- RCT 80 Special Teachers (PMECs)
- Outcome measures:
  - Literacy
  - Stigma
  - Attitude towards MH
- Scale up: **472 PMCs teachers**

Apolinario et al., 2014; Simões et al., Cad Saud Publ, 2015
Mental Health in Schools – what teachers should know
Conclusions

- Multistage research approach – synergistic
- Multimodal – new questions may be answered
- Challenges:
  - Databank integration
  - Data analysis methodology
- Prevention: work in progress...
Agradecimentos
SÃO PAULO SCHOOL OF ADVANCED SCIENCE FOR PREVENTION OF MENTAL DISORDERS
## Disclosure

### Private Companies

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The angular gyrus become more central during this maturation period, while the caudate, cerebellar tonsils, pyramis, thalamus, fusiform, parahippocampal and inferior semilunar lobe become less central.

Conclusion: *increasing centrality of the angular gyrus during the transition to adolescence, with a decreasing centrality of many subcortical and cerebellar regions.*

*Sato et al., Neuroimage 2015*
Schizophrenia – neurodevelopmental disease

Murray et al., Lancet 1985; Weinberger, Arch Gen Psychiatry 1987
Schizophrenia –
neurodevelopmental disease

ENVIRONMENT

GENES

Obstetric complications
Bullying
Immigration/Urbanicity
Suspiciousness
Dopamine sensitization
Cannabis

Murray et al., Lancet 1985; Weinberger, Arch Gen Psychiatry 1987
Schizophrenia – neurodevelopmental disease

**ENVIROMENT**

- Obstetric complications
- Bullying
- Immigration/Urbanicity
- Cannabis
- DNA Gene Expression
- Brain changes Structural/Funcional
- Citokines
- Dopamine sensitization

Schizophrenia

Murray et al., Lancet 1985; Weinberger, Arch Gen Psychiatry 1987
The High-Risk State

Contributions of early cortical processing and reading ability to functional status in individuals at clinical high risk for psychosis
Ricardo E. Carrión, Barbara A. Cornblatt, Danielle McLaughlin, Jeremy Chang, Andrea M. Ather, Ruth H. Olsen, Daniel C. Javitt

Studies at the First Episode

Effects of depression on the cytokine profile in drug naïve first-episode psychosis
Cristiano Noto, Vanessa Kyomi Ota, Marcos Leite Santoro, Bruno B. Ortiz, Lucas B. Rizzo, Cinthia Hiroko Higuchi, Quirino Cordeiro, Sintia Iole Belangero, Rodrigo Affonsoa Bressan, Ary Gadelha, Michael Maes, Elsa Brietzke

Genetics

Integration of gene expression and GWAS results supports involvement of calcium signaling in Schizophrenia
L. Hertzberg, P. Katsel, P. Roussos, V. Haroutunian, E. Domany

Altered prefrontal cortical MARCKS and PPP1R9A mRNA expression in schizophrenia and bipolar disorder
Glenn T. Konopaske, Sivan Subburaju, Joseph T. Coyle, Francine M. Benes

ACE I/D genotype-related increase in ACE plasma activity is a better predictor for schizophrenia diagnosis than the genotype alone
Ary Gadelha, Camila M. Yonamine, Vanessa K. Ota, Vitor Oliveira, João Ricardo Sato, Sintia I. Belangero, Rodrigo A. Bressan, Mirian A.F. Hayashi
Clinical Findings

Brain tumor in a patient with attenuated psychosis syndrome.

Zugman A, Pan PM, Gadelha A, Mansur RB, Asevedo E, Cunha GR, Silva PF, Brietzke E, Bressan RA.
Psychotic Experiences (CBCL) vs. Brain Maturation

- Are PE associated with cortical thickness? (720 children, 7-15 year-old)

- CBCL Psychotic Experiences scores and cortical thickness:
  - Negative correlation with frontal and temporal cortices
  - Positive correlations with the occipital cortices

Ary Gadelha et al., in preparation
Gene Modulation of Brain Structure

PRODH polymorphisms, cortical volumes and thickness in schizophrenia.

• Investigation the effect of 12 polymorphisms of PRODH in 192 patients with schizophrenia.
• One polymorphism associated with schizophrenia (rs2904552) with the G-allele
Analysis of brain network disruptions in First Episode Psychosis: an approach based on graph analyses of structural covariance

Chronic SCZ: 143
First-episode psychosis: 32
Controls: 82

Zugman et al., submitted
Deep Belief Networks are modelos generativos de redes de arquitetura híbrida com múltiplas camadas ocultas.

**Etapa 1 - Autoencoder**

- **Autoencoder Raso**
  - Decodificação
  - Reconstrução
  - "Gargalo"
  - Entrada

- **Autoencoder Profundo**
  - Codificação
  - Entrada

**Etapa 2 - Classifier**

- **Unidades do topo**
- **Rótulos**
- **Unidades ocultas**
- **Memória associativa**
- **Pesos de reconhecimento**
- **Pesos generativos**
- **Camada visível**
- **Camada oculta**
- **Vetor de entrada**
Results

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<th>Differences between groups</th>
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<th>Layer 1</th>
<th>Layer 2</th>
<th>Layer 3</th>
<th>Layer 4</th>
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<td>(SCZ-FEP) – (FEP-HC)</td>
<td>0.114</td>
<td>0.039</td>
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<td>(SCZ-FEP) – (SCZ-HC)</td>
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<td>0.237</td>
<td>0.87</td>
<td>1.776</td>
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<tr>
<td>(FEP-HC) – (SCZ-HC)</td>
<td>0.009</td>
<td>0.027</td>
<td>0.0030</td>
<td>0.99</td>
<td>&lt;0.001</td>
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Integrative Neuroscience

• Hierarchical feature representation with deep learning of schizophrenia MRI data

• Walter H. L. Pinaya; Ary Gadelha a; Cristiano Noto a; Joana B. Balardin; Quirino Cordeiro c; Sintia I. O. Belangero b; Rodrigo A. Bressan a; Andrea P. Jackowski a; João Ricardo Sato a, d
3 groups of genes:

- Genes expressed in immune-system
- Neurodevelopment
- Transcription Factors

N=170

Gadelha et al., to be submitted