

Aspectos Clínicos e Neurobiológicos do Transtorno Bipolar antes do 1º Episódio de Mania

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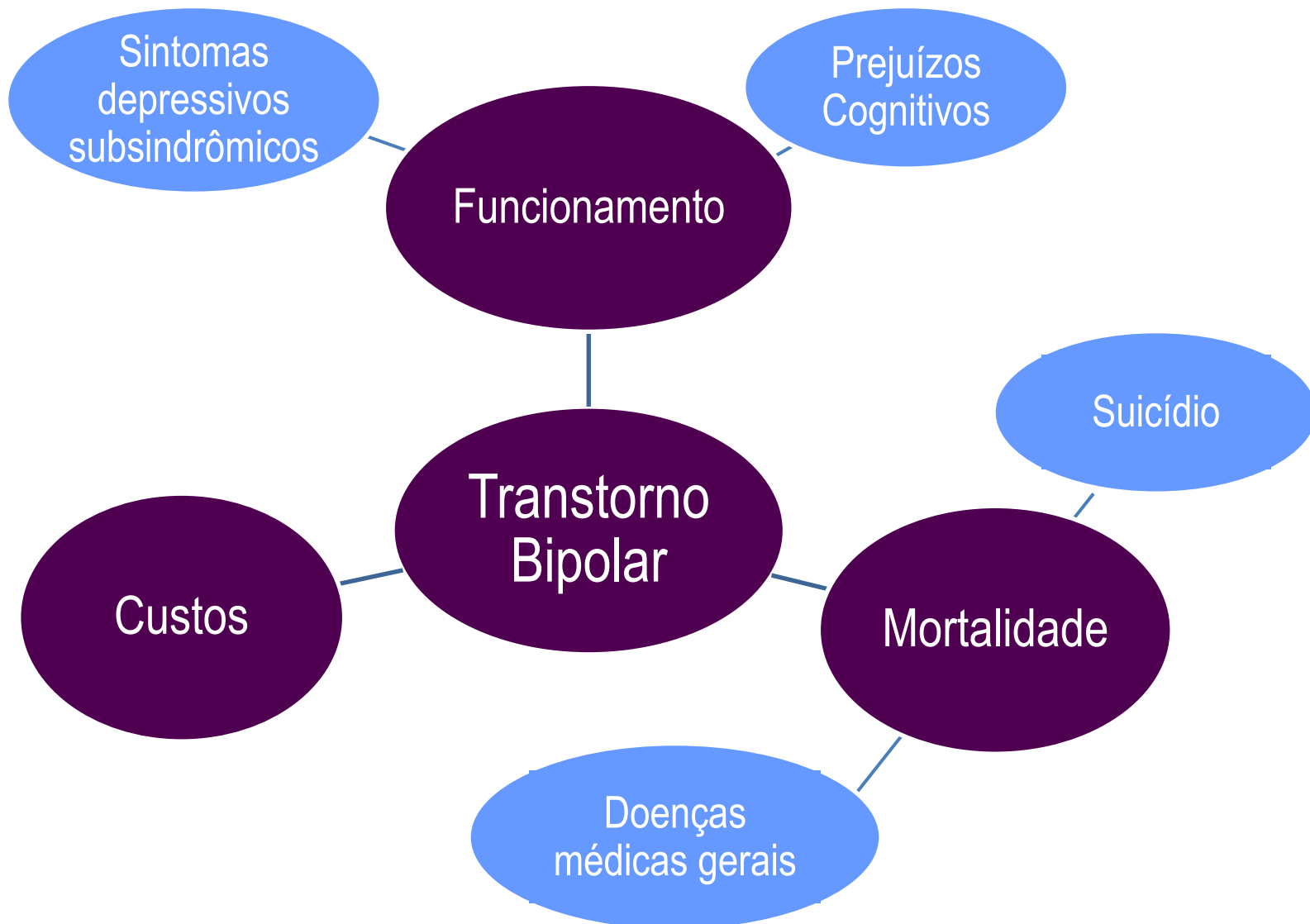


Declaração de Conflito de Interesse

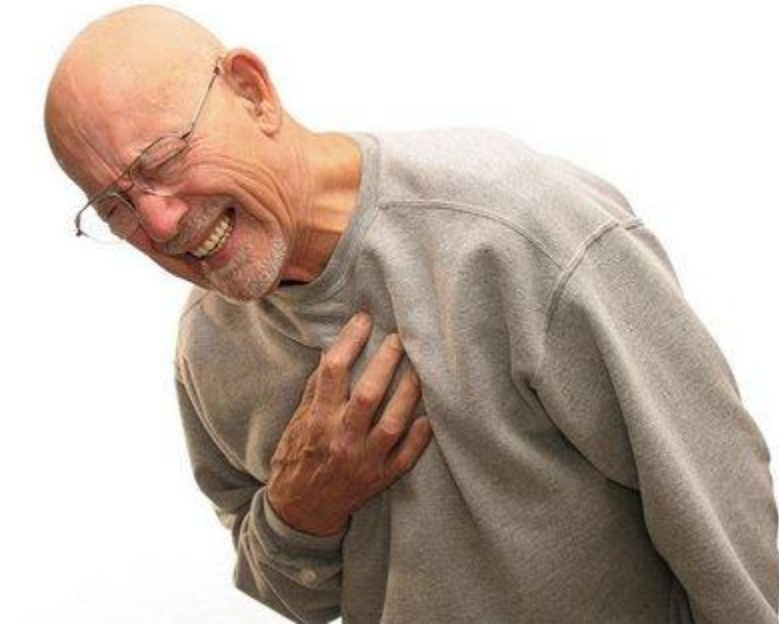
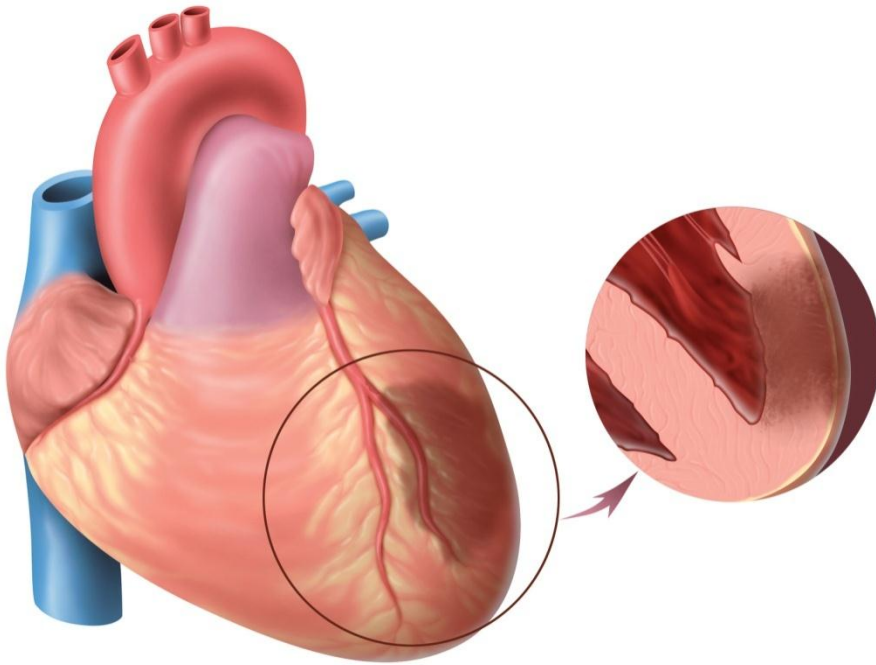


- Financiamento para pesquisa: CNPq e FAPESP
- Speaker: Janssen-Cilag, Pfizer, Libbs
- Redação de material científico: Astra-Zeneca, Janssen-Cilag, Eurofarma, Achè
- Consultoria: Libbs

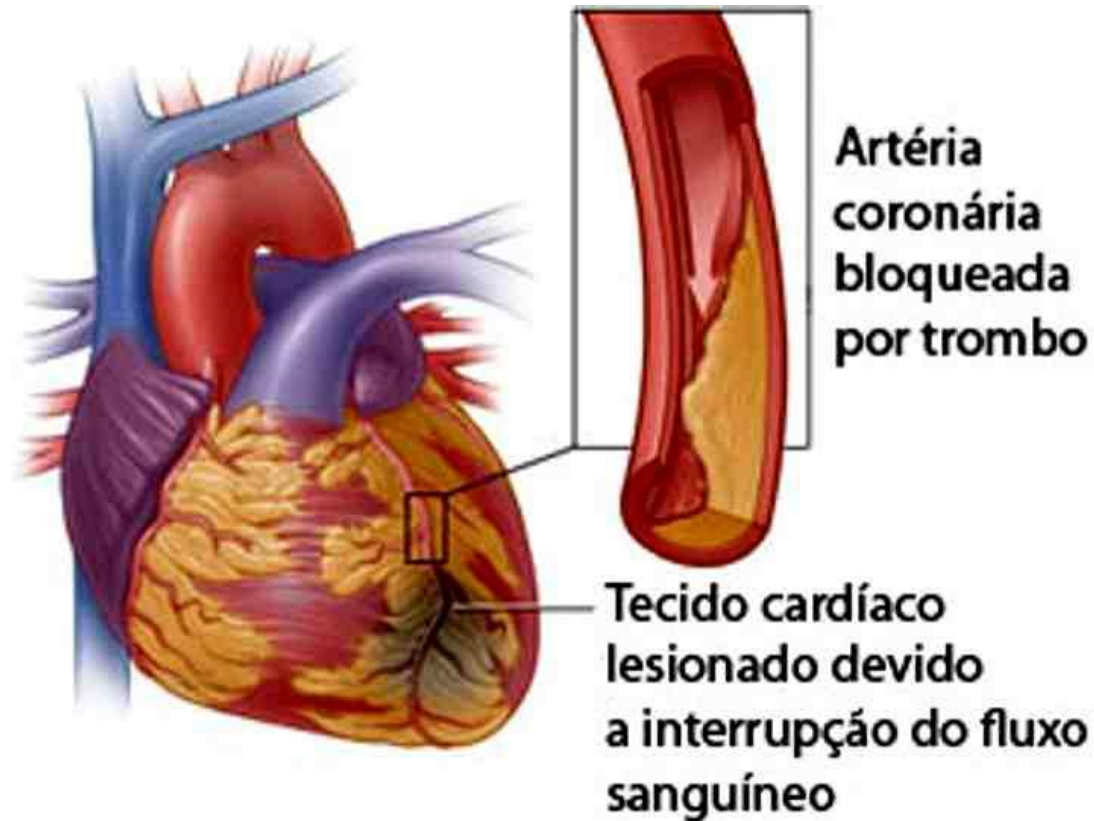
Transtorno Bipolar



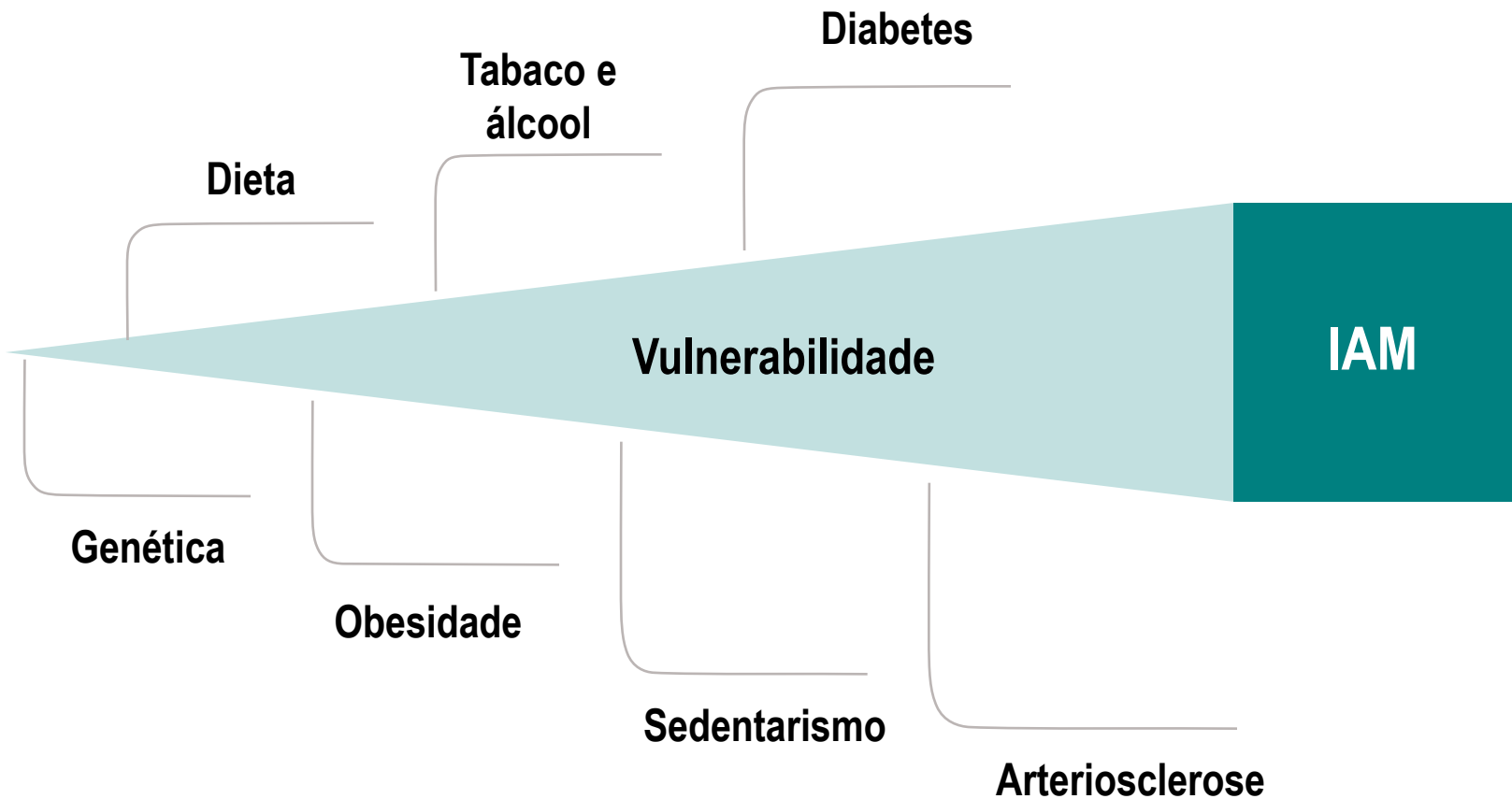
IAM



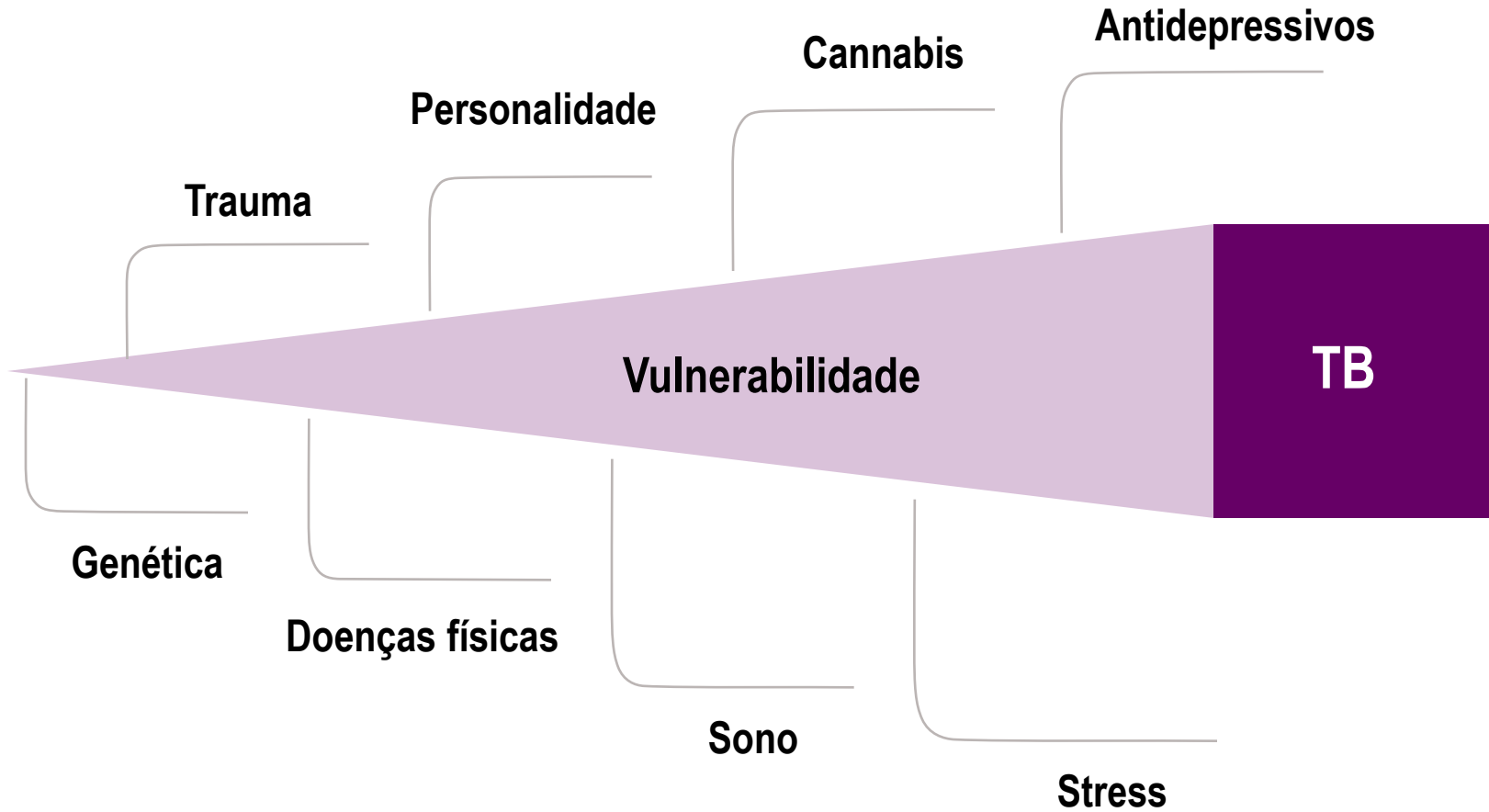
Quando começa um IAM...



Antes do IAM...



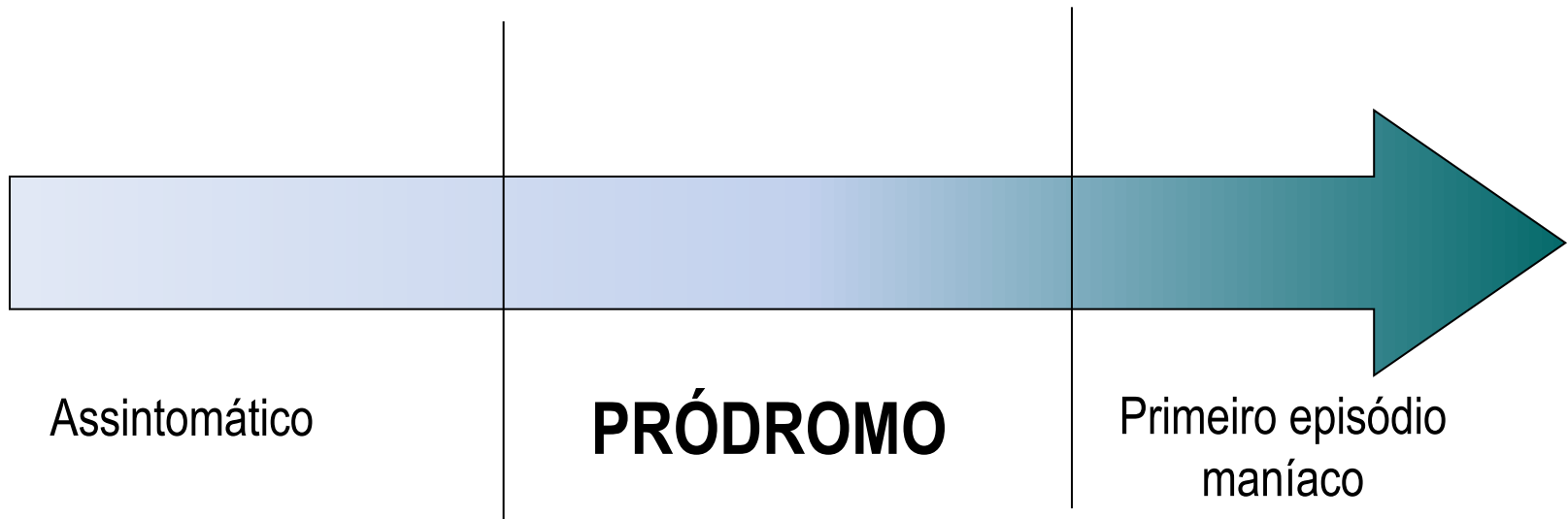
Antes do TB...



O TB antes do 1º episódio de mania



O TB antes do 1º episódio de mania



E. Kraepelin, 1909



“O início das doenças mentais geralmente é **gradual**; muito raramente começa de forma súbita, sem sintomas precursores... O início dos sintomas pode **preceder em anos ou até décadas**, o início da doença. O início da doença parece relacionar-se a períodos específicos da vida, especialmente aos **relacionados ao desenvolvimento.**”



Vinheta



João, 16 anos, com história familiar de Transtorno Bipolar

Queixa: inquietude há 3 meses

Vinheta



10 anos

Choro frequente, irritabilidade, fugas de casa, apatia e recusa em permanecer na escola.

Depressão: risperidona (não tolerou) e sertralina (agitação).

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Humor deprimido, isolamento, retardo psicomotor, recusa alimentação, enurese.

Depressão grave: imipramina

Vinheta



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11 anos	Humor deprimido, isolamento, retardo psicomotor, recusa alimentação, enurese.	Depressão grave: imipramina
12 anos	Isolamento social, irritabilidade, dificuldade de concentração.	TDAH desatento: metilfenidato QI médio-inferior

Vinheta



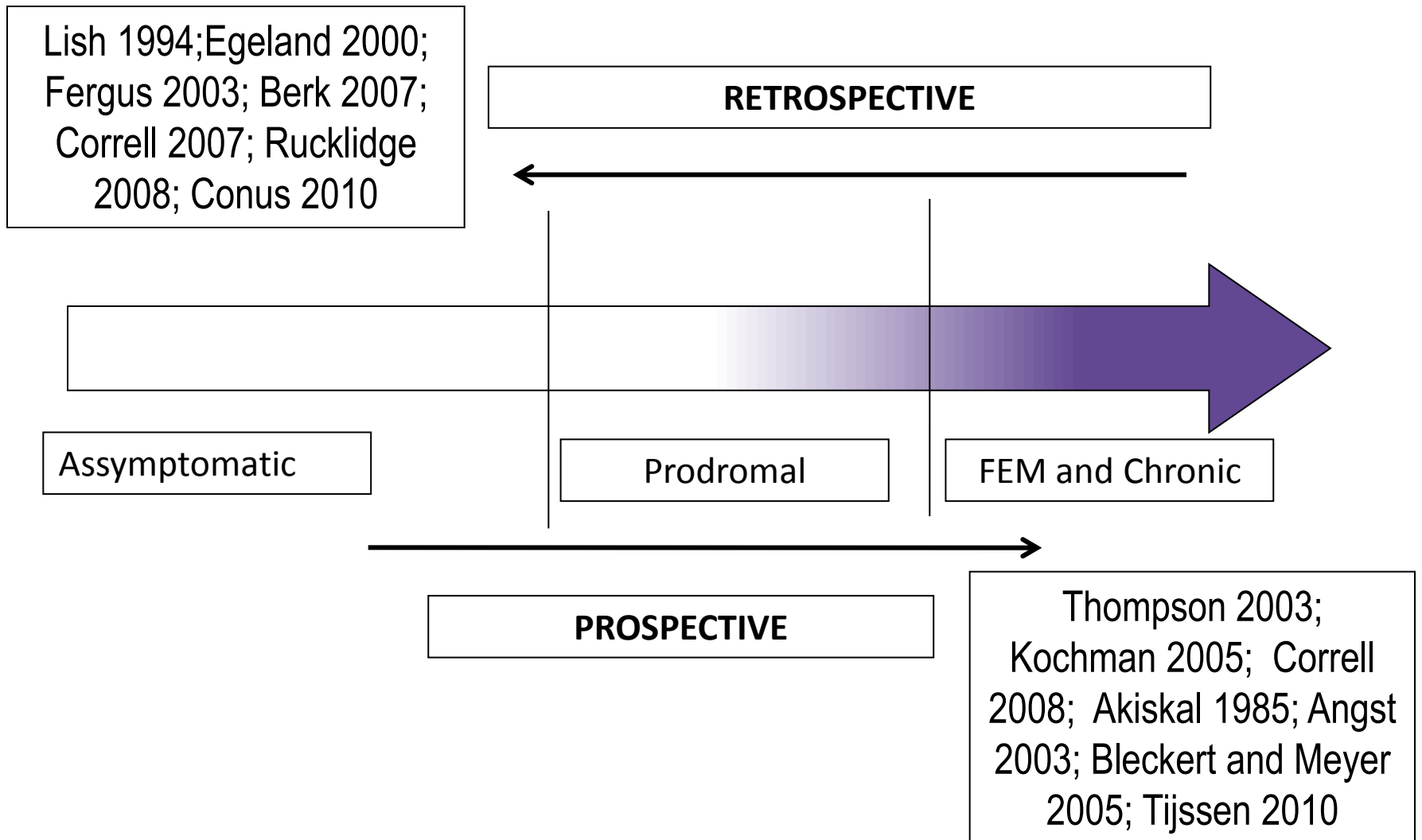
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16 anos	Após 4 meses com leve inquietude, apresenta episódio de verborragia, discurso com conteúdo sexual, agitação, redução da necessidade de sono, delírios de grandeza.	Mania com psicose: olanzapina e lítio QI limítrofe

The Prodrome of BD



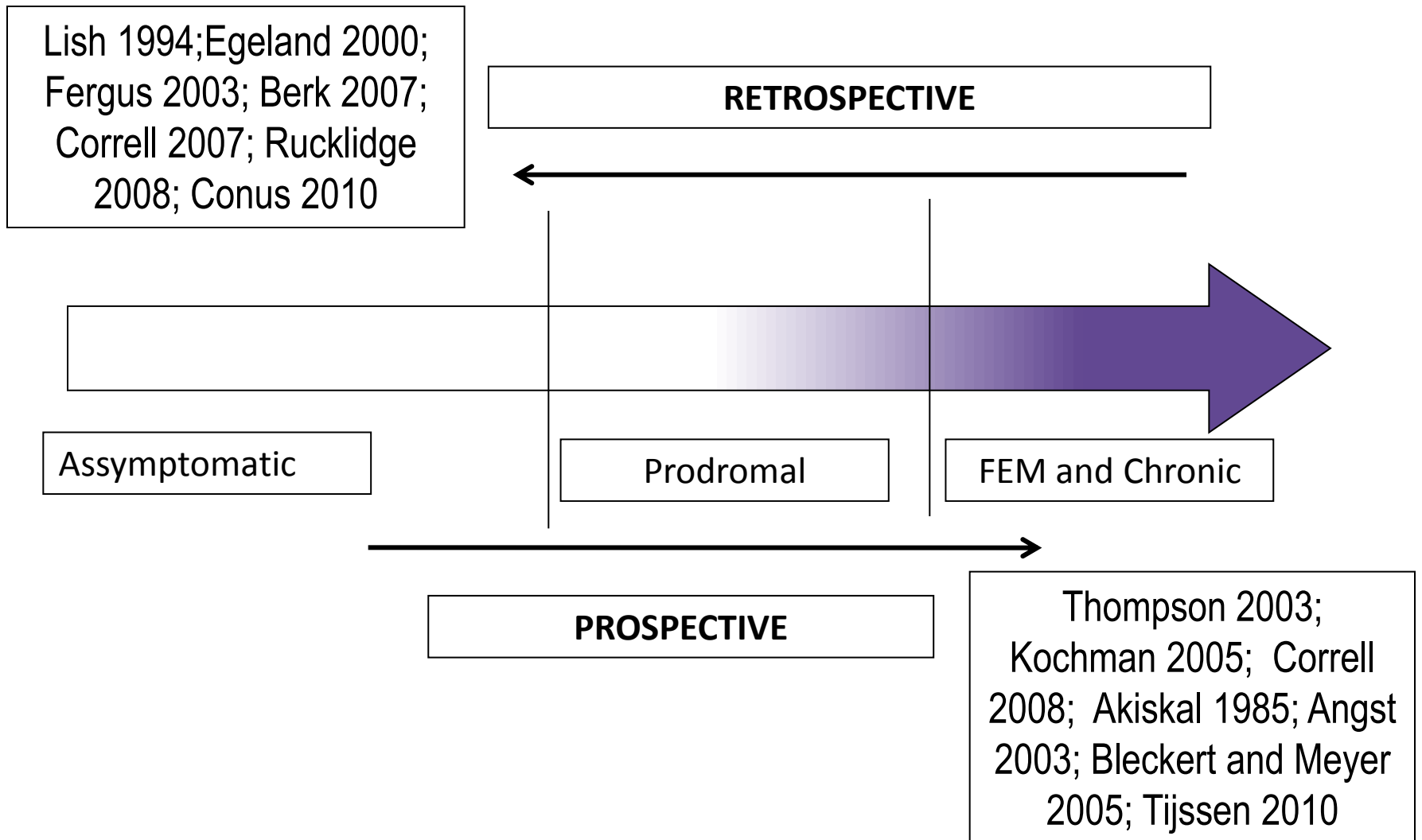
Retrospective studies

- **Correll et al., 2007:**
 - N= 50 BD 1, 7-21 yo, evaluated with the BPSS-R.
 - Mean duration of mania prodrome: 1.8 years.
 - Prodrome with less than 1 month occurred in only 3.8% of the sample.
 - Symptoms: irritability (61.1%), depressed mood (55.6%), decreased functioning (55.6%), anger (55%), social isolation (55%), racing thoughts (50%), mood swings (50%), oppositionality (50%).
- **Conus et al., 2010:**
 - N= 22 (15 BD1), 15-29 yo, evaluated with the Initial Prodrome Questionnaire (IMPQ).
 - Mean duration: 20.9 weeks and 18% had prodrome with less than 1 month.
 - Symptoms: disrupted sleep (83%), increased stress (77.8%), impairment functioning (66.7%), dysphoric mood/hopelessness (66.7%), reduced sleep or need for sleep (61%), concentration problems (61%), anxiety (61%), elevated mood (55.6%), irritability (55.6%), grandiosity (50%), disinhibited (50%), disturbed appetite (50%).

Retrospective studies

- **Noto et al., 2013 (unpublished data):**
 - N= 43; euthymia or mild depression; BD 1 or 2 (32/11), 16-60 yo (mean 33.7 yo; SD: 8.8), evaluated with the BPSS-R.
 - First mood episode: depressive 51.2%, manic 34.9%, hypomanic 2.3%, mixed 11.6%.
 - Median of duration of mania prodrome: 5 months.
 - Symptoms:
 - All the severity levels: anxiety (74.4%), depressed mood (53.5%), irritability (58.1%),
 - Influence of childhood maltreatment
 - CM X NCM: duration similar
 - At least one CM: social isolation, decline of functioning, anhedonia, excessive joy, self confidence and increases in creativity (FDE), strange ideas (FME).
 - Sexual abuse: feeling worthless or guilty, dangerous behavior, suspiciousness, hallucinations (FME).

The Prodrome of BD



Prospective Studies

Studies in Community Samples

- Tijessen et al. (2010):
 - 1,902 random sample of adolescents (12-24 yo) in the Munich area.
 - 21 people developed BD in a mean follow-up of 8 years.
 - Converters: load and persistence of manic and depressive symptoms.
- Pan et al. (2013):
 - 2,512 children between 7-14 yo from São Paulo and Porto Alegre, Brazil.
 - Risk score composed by symptoms and family history
 - Agregation of biomarkers in a subsample (750): BDNF, Oxidative stress

Prospective Studies

First Depressive Episodes Studies

- **Akiskal et al. (1995)**

- 559 FDE in 11 years follow-up
- 8.6% converted to BD 2; 3.9% converted to BD 1.
- Predictive symptoms for BD 2: mood lability, energy–activity and day-dreaming.

- **Kochman et al. (2005)**

- 80 FDE children in 2 years follow-up
- 43% converted to BD (cyclothymic temperament measured at the baseline).

Prospective Studies Offspring Studies

- **Akiskal et al. (1985):**
 - 68 offspring of BD1 referred for treatment
 - Mean age of mood symptoms: 15.9 years
 - A half of them had bipolarity signs at 3 year follow up
 - The converter group presented more frequently hypomanic, dysthymic or cyclothymic.
- **Hillegers et al. (2005):**
 - 129 genetically defined high-risk adolescents
 - Increase from 3 to 10% of prevalence in 5 years
 - 12/13 participants had a MDE prior to FEM
- **Duffy et al. (2010):**
 - 207 with genetic risk (ages 8-25)
 - 67 met DSM-IV criteria for at least one mood episode
 - Depressive polarity: 89% in first mood episode, 68% in the second, 78% in the third, 58% in the fourth.

Akiskal et al., Arch Gen Psychiatry 1985;
Hillegers et al. *Bipolar Disord* 2005;
Duffy et al. *Br J Psychiatry* 2009.

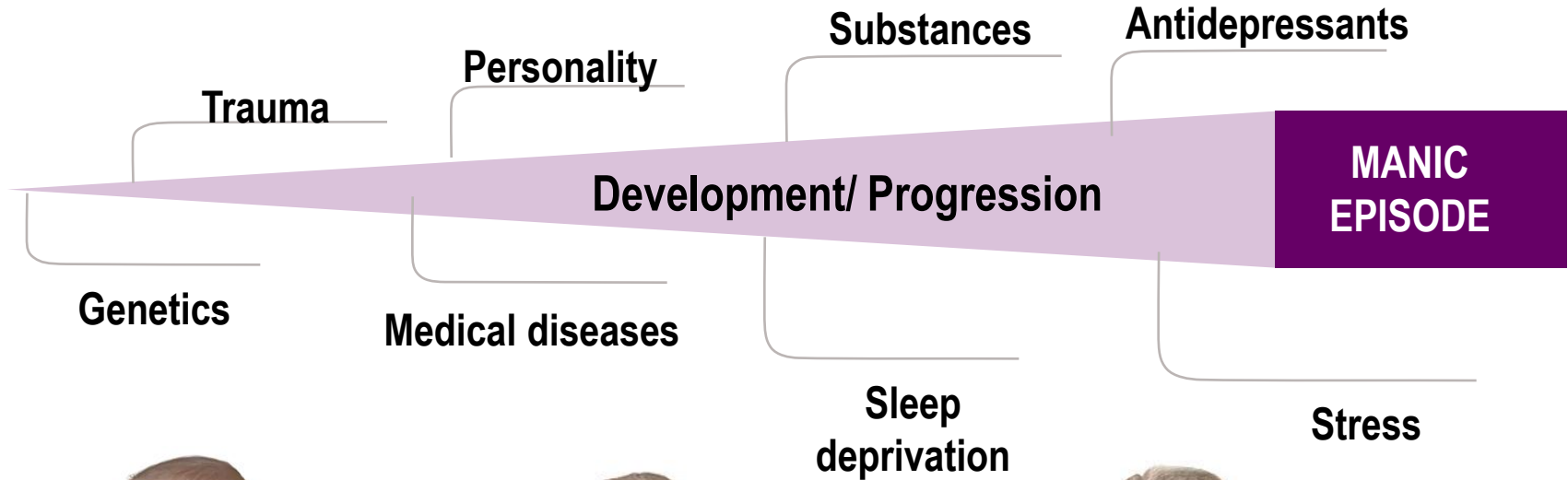
Prospective Studies Ultra High Risk

- UHR: surpass limitations of previous approaches
 - Community samples: low rates of conversion, normal distribution of symptoms in general population
 - Offspring: a minority of patients have an affected 1st-degree relative; select a subtype with strong genetic load.
 - FDE: does not include those with first episode with manic polarity



Low rates of conversion
Long follow up
Large sample sizes

Development and Prodrome of BD



Excessive crying
Anxiety
Temperamental
Increased energy
Sleep disturbances
Enuresis

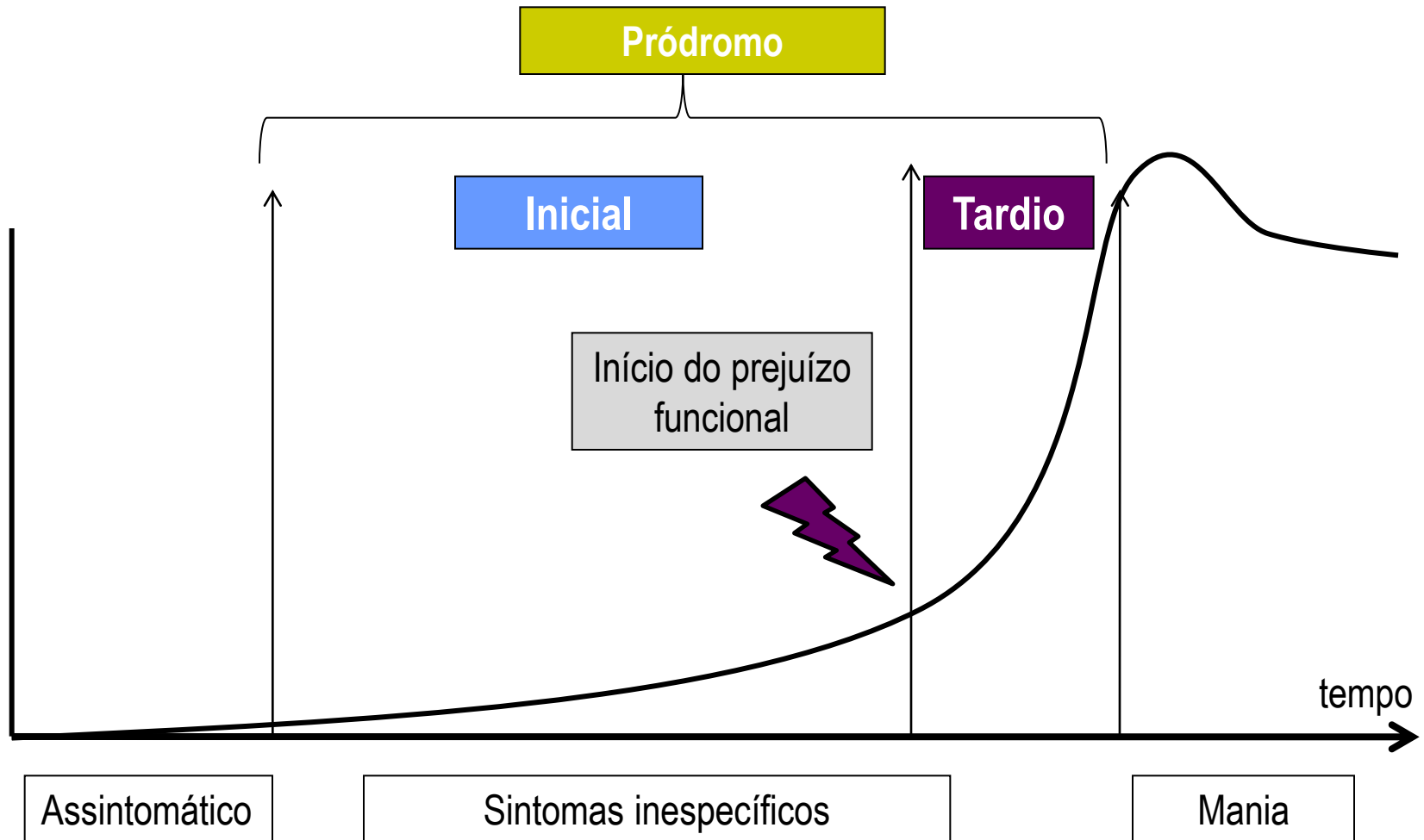


Irritable
Sensitive
Demanding
Conduct problems
"Do not listen"
Fast speech



Cognitive complains
Irritability
Mood swings
Grandiosity
Suicidal thoughts
Craving for sweets
Depression

Evolução do Pródromo



Lessons from Psychosis Field

- **Concept:** UHR, CHR, Basic Symptoms
- **Operational criteria**
 - Age 15-25 years
 - Help seeking
 - Distress and functional impairment
 - Severity, frequency and duration
- **3 possible groups:**
 - Attenuated positive symptoms
 - Brief, limited and intermittent psychotic symptoms
 - Trait risk (family history or schizotypal personality)
+ functional decline in the last year).

CAARMS
COMPREHENSIVE ASSESSMENT OF AT RISK MENTAL STATES

A. Yung, L. Phillips, M.B. Simmons, J. Ward, K. Thompson, P. French, P. McGorry

NOME: _____

Número do Documento de Identificação _____

Classificador: _____

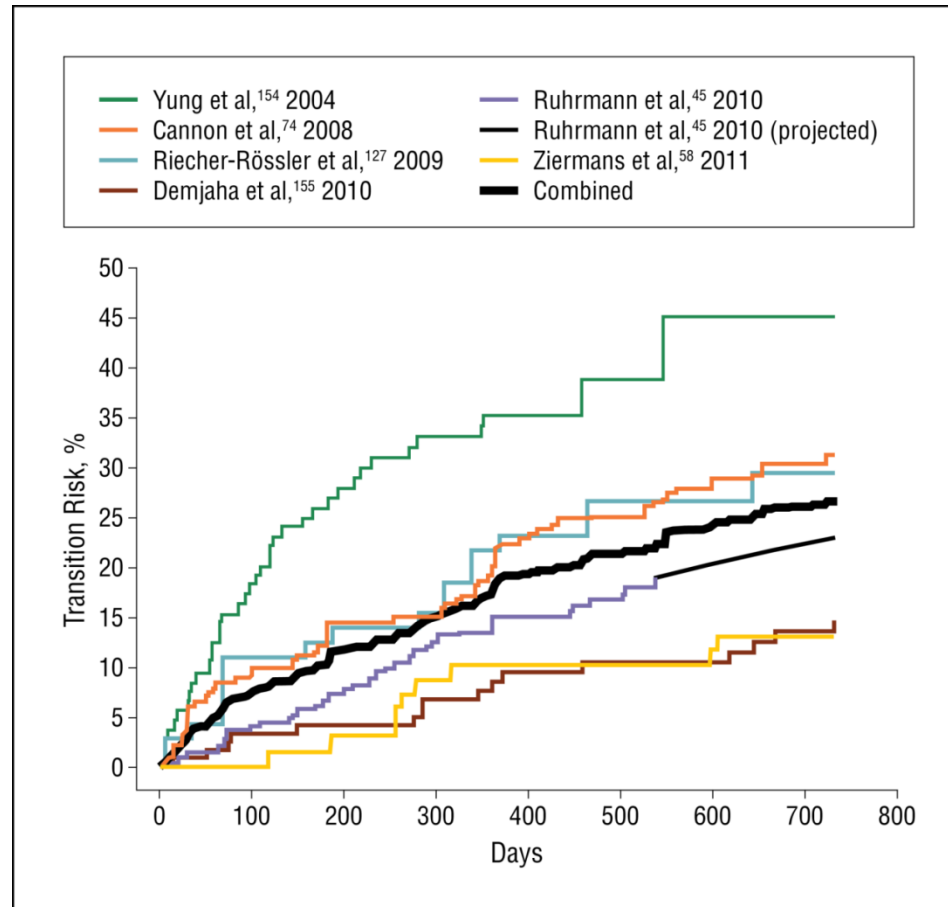
Data: ____ / ____ / ____

the PACE Clinic
ORYGEN Research Centre
University of Melbourne
Department of Psychiatry
Parkville Victoria, Australia

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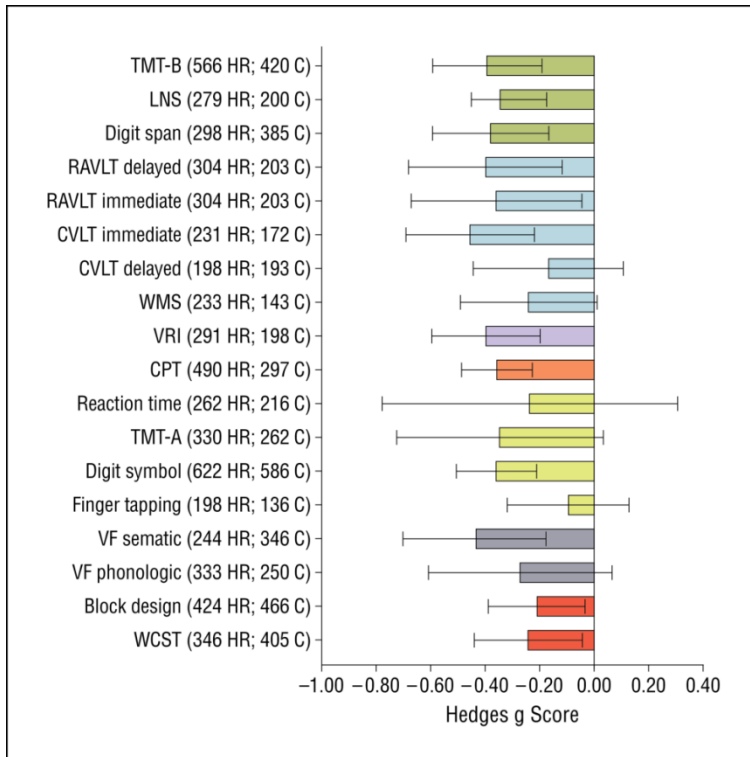
Lessons from psychosis field

- Transition rates

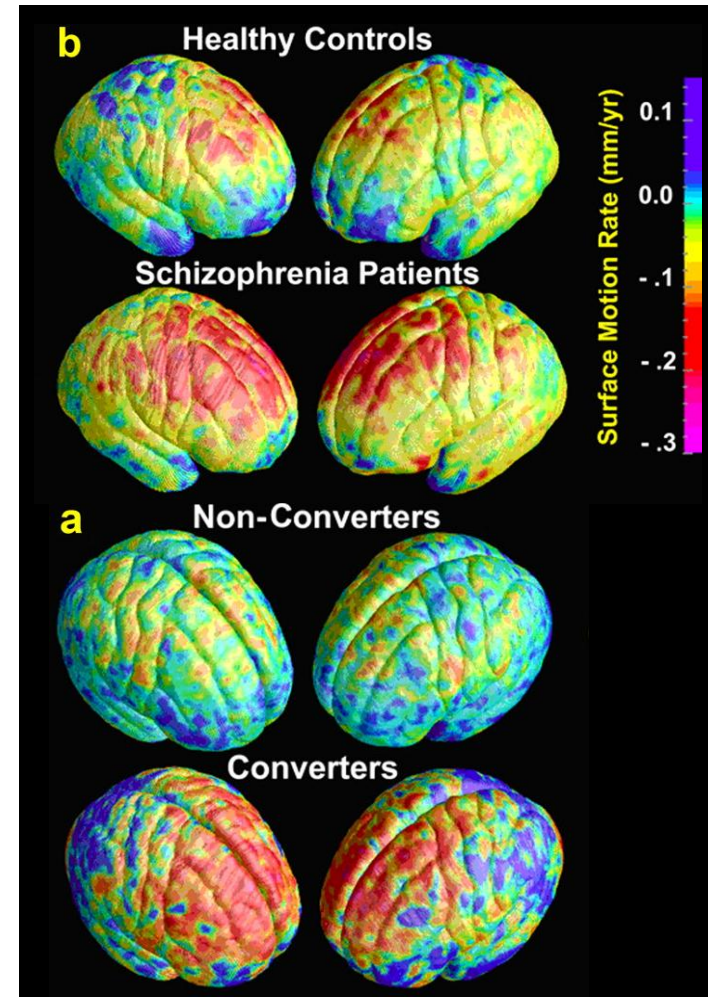


Lessons from psychosis field

- Specific neurobiology
 - Cognition



– Brain Structure

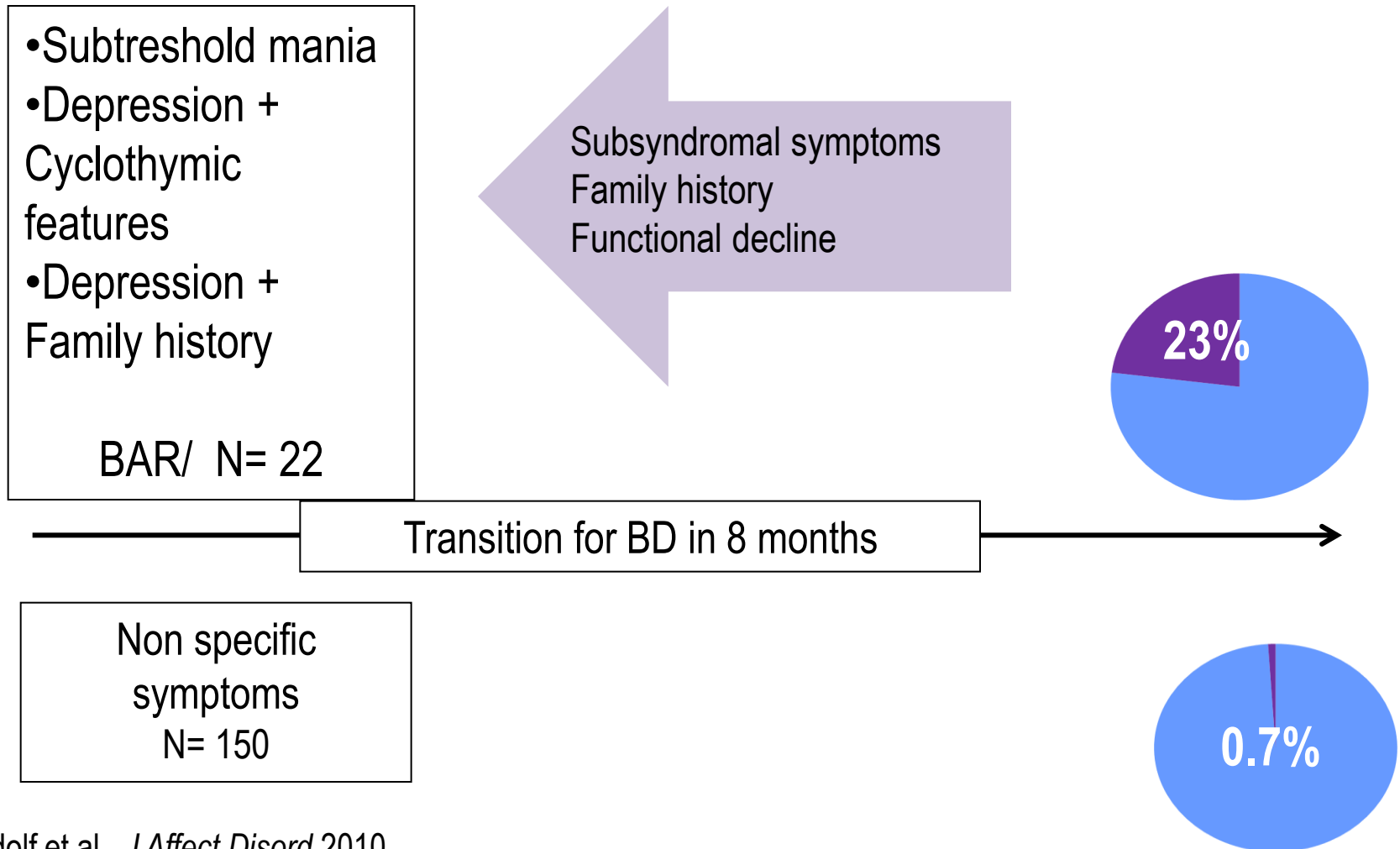


Pantelis et al., *Int Rev Psychiatry* 2007;
 Karlsgodt K H et al. *Curr Direc Psychol Sci* 2010.

Lessons from psychosis field

- Interventions
 - Risperidone, Olanzapine, Aripiprazole (ongoing)
 - Omega 3
 - CBT

Is it possible to define UHR for BD?



Summary

1. What evidence do we have about the existence of a prodromal stage in BD?

- Clinical experience
- Retrospective studies
- Prospective studies

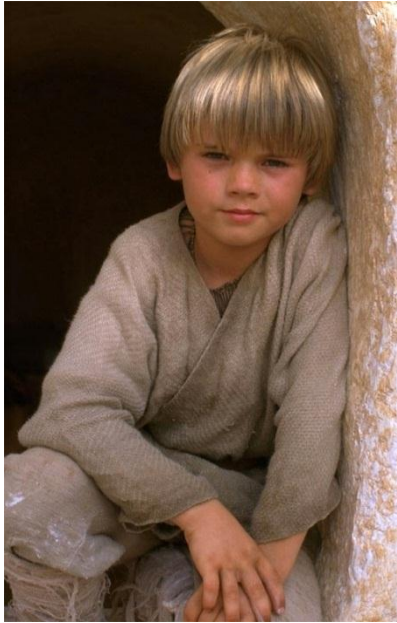
2. How can prodrome be characterized?

- Mild and non differentiated symptoms
- Distress, functional impairment, help seeking
- Family history

3. What do we not know yet about the prodrome of BD?

- Criteria
- Conversion rates
- Neurobiology
- Interventions





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