ALTERING THE COURSE OF SCHIZOPHRENIA: CHALLENGES AND OPPORTUNITIES

Mark J. Millan

Neuropsychiatry Department
Institut de Recherches Servier
Croissy-sur-Seine (Paris), France

SCHIZOPHRENIA AND ITS IMPACT: CORE ELEMENTS AND OVERVIEW OF TALK

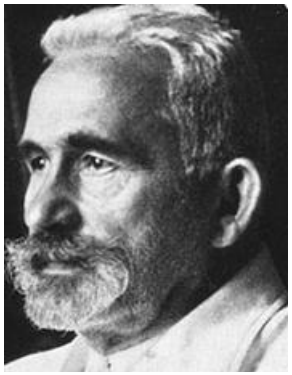
- **Severe, chronic and debilitating disorder with early onset (18-30), reduced life-expectancy and a high incidence of suicide (~10 %).**
- **Prevalence about 1% of the population with little geographical/cultural variation.**
- **Huge economic burden - inability to work, social support and hospitalisation. Cost is nearly 100 billion Euros per year for the EU (Wittchen et al, 2011).**
- **Clinically heterogeneous with a complex pattern of emotional, social and cognitive symptoms: incompletely understood causes and pathophysiology, but much recent progress.**
- **Symptomatic treatment of limited efficacy: neuroleptics (haloperidol…), clozapine, second-generation antipsychotics (risperidone…) and aripiprazole.**

This presentation discusses:

- **The new concept of course- alteration, preventing and stopping the progress of schizophrenia: key questions - whom to treat, when to treat, how to treat.**
- **Clinical and experimental data supporting course-alteration, and broader implications of the concept.**

SCHIZOPHRENIA: "BORN" IN GERMANY

*Emil Kraeplin (1890's)**



* « *Dementia Praecox* »

« Organic disorder »

Eugen Bleuler (1910's)

« Psychological dimension »

Positive Symptoms
Delusions (false beliefs - persecution, great powers)
Hallucinations (visual, auditory - hearing orders)

Negative Symptoms
↓Motivation,
↓Sociality,
↓Expression
(verbal and non-verbal)

Disorganisation:
Thought,
Speech,
Behaviour

Cognitive Symptoms (1980s/1990s)
Attention, Working memory
Executive function (planning)
Speed of processing

Co-morbid:
Depression
Anxiety…

Impaired Social Cognition* (2000+)
Use of social cues to assess emotions, intentions and mental states of others - and to guide ones own behaviour

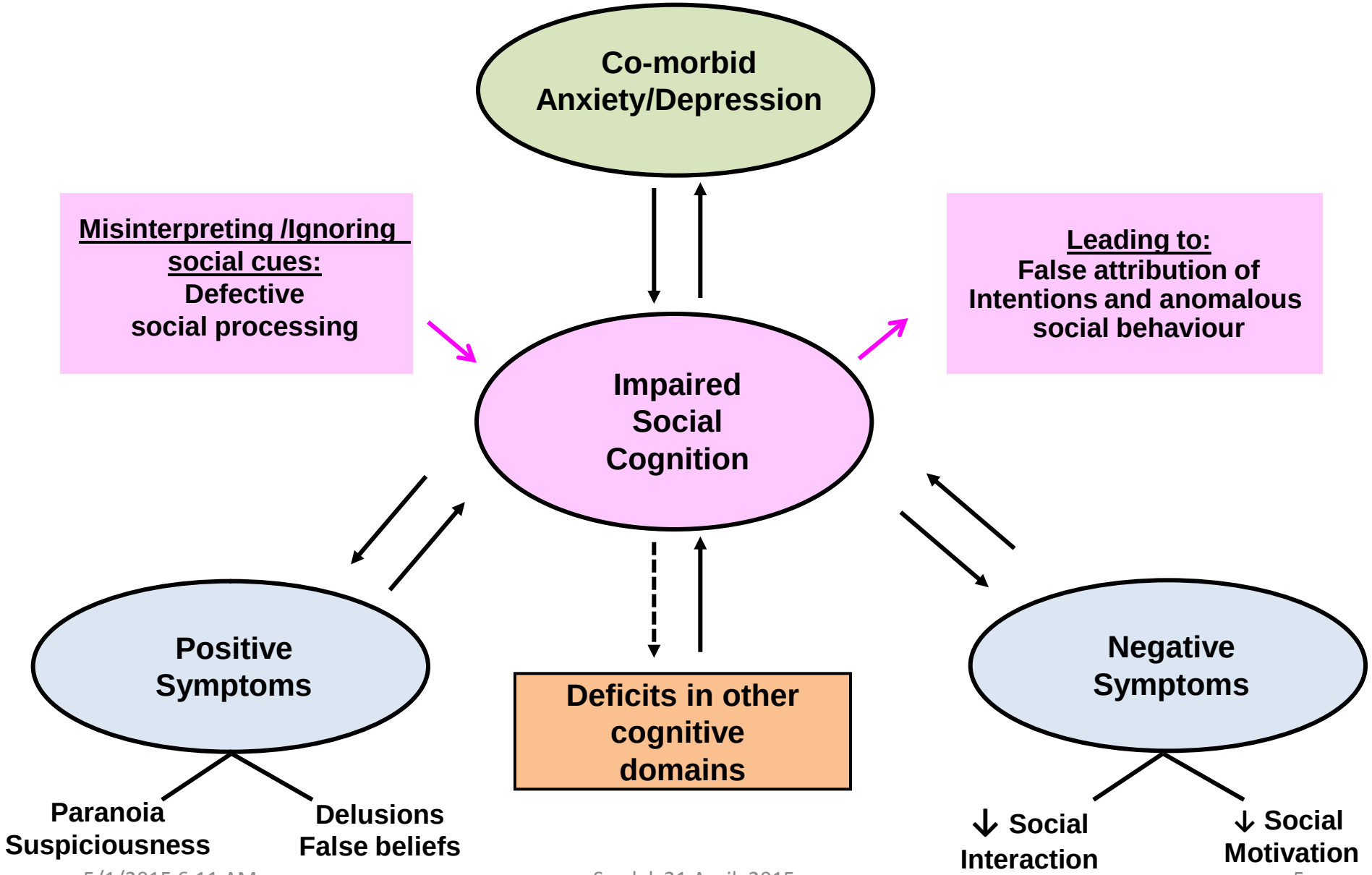
**Eye contact, gaze, facial expression, gestures…*

MOUNTAIN GORILLAS: SOCIAL COGNITION IN ACTION

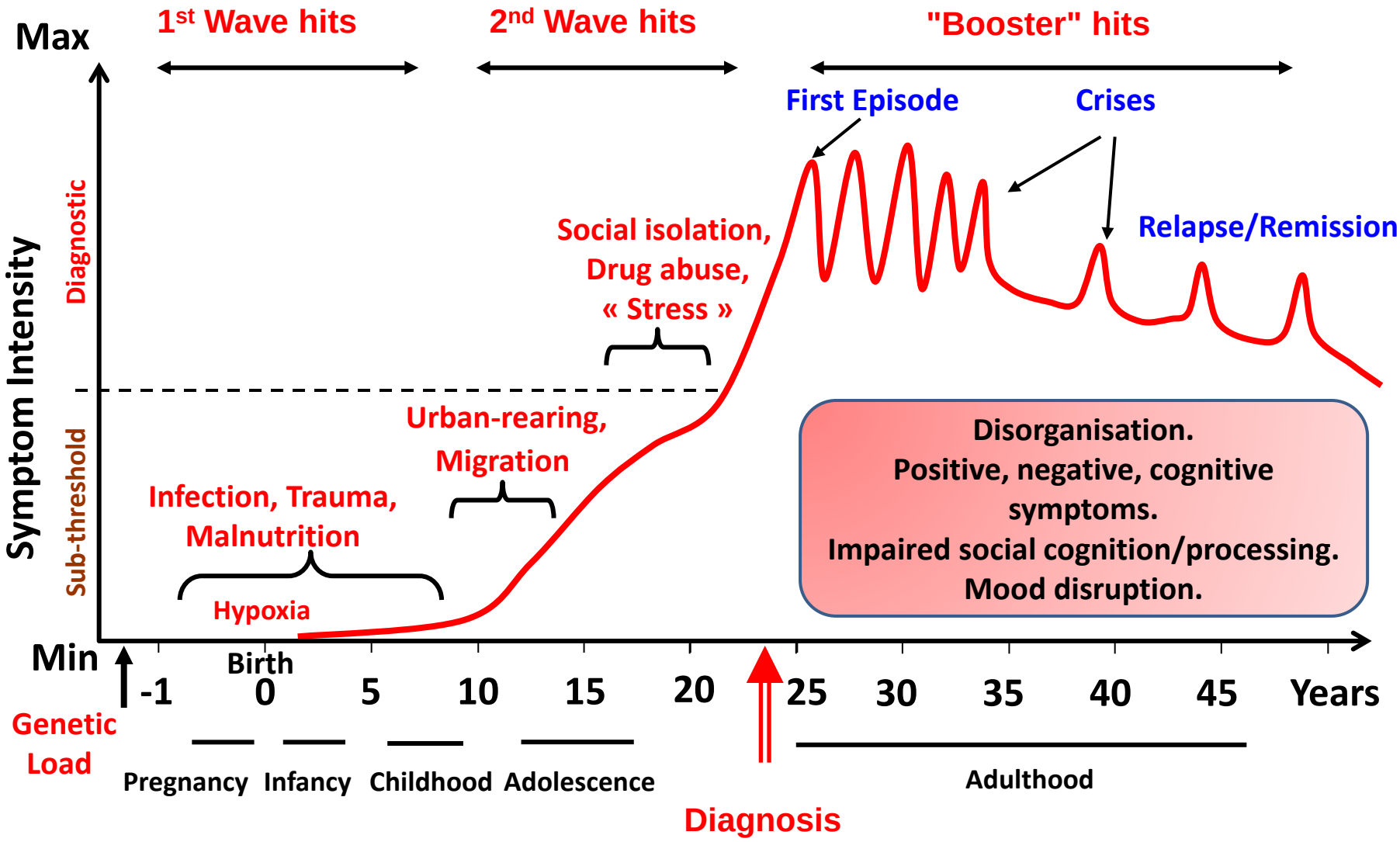
Subordinate male and female "interacting" and looking nervous :
WHAT'S GOING ON ? AND WHAT HAPPENED NEXT ?

Photo from RW Byrne Aberdeen, 2007

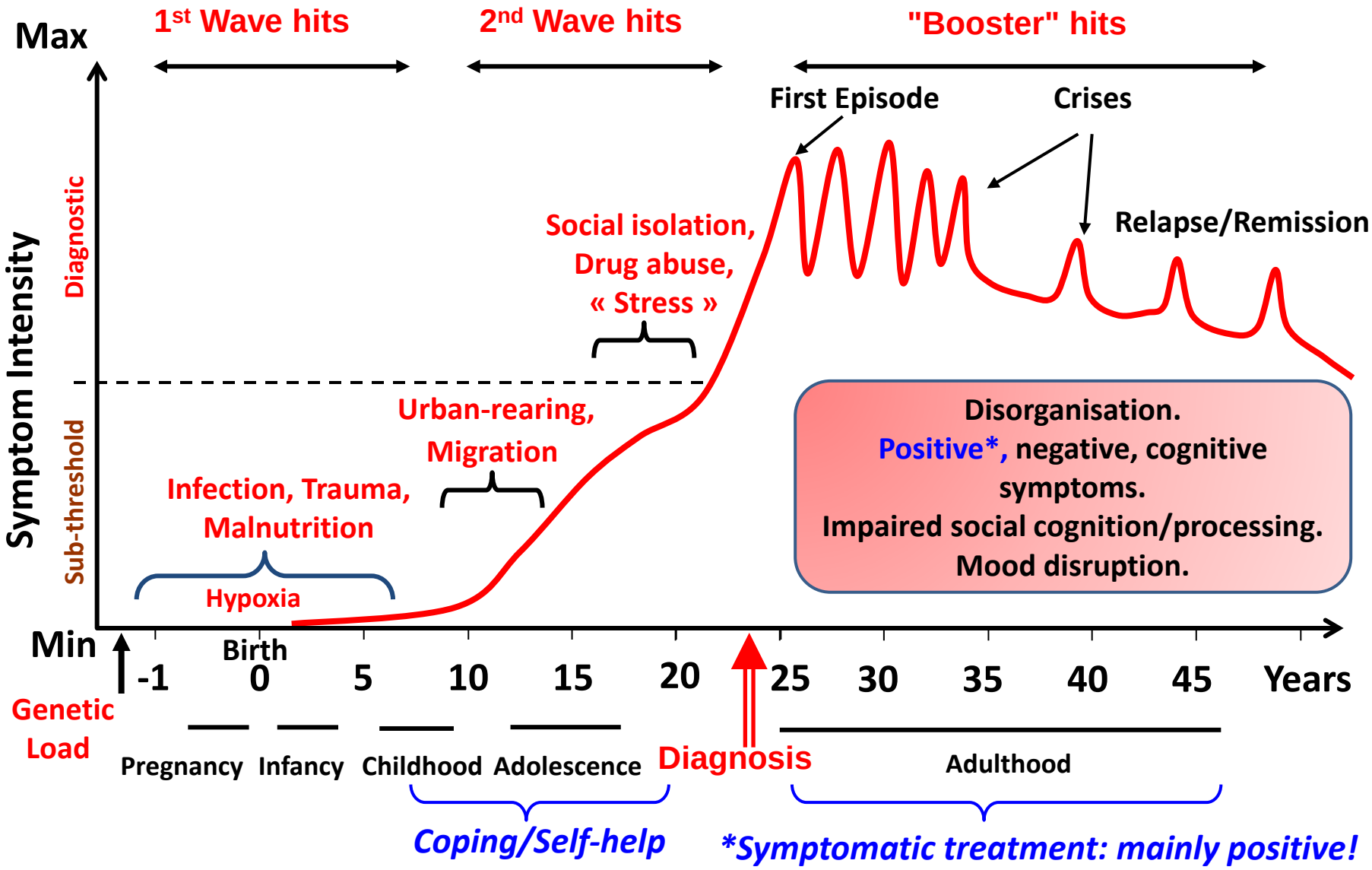
IMPAIRED SOCIAL COGNITION MAY DRIVE OTHER SYMPTOMS OF SCHIZOPHRENIA



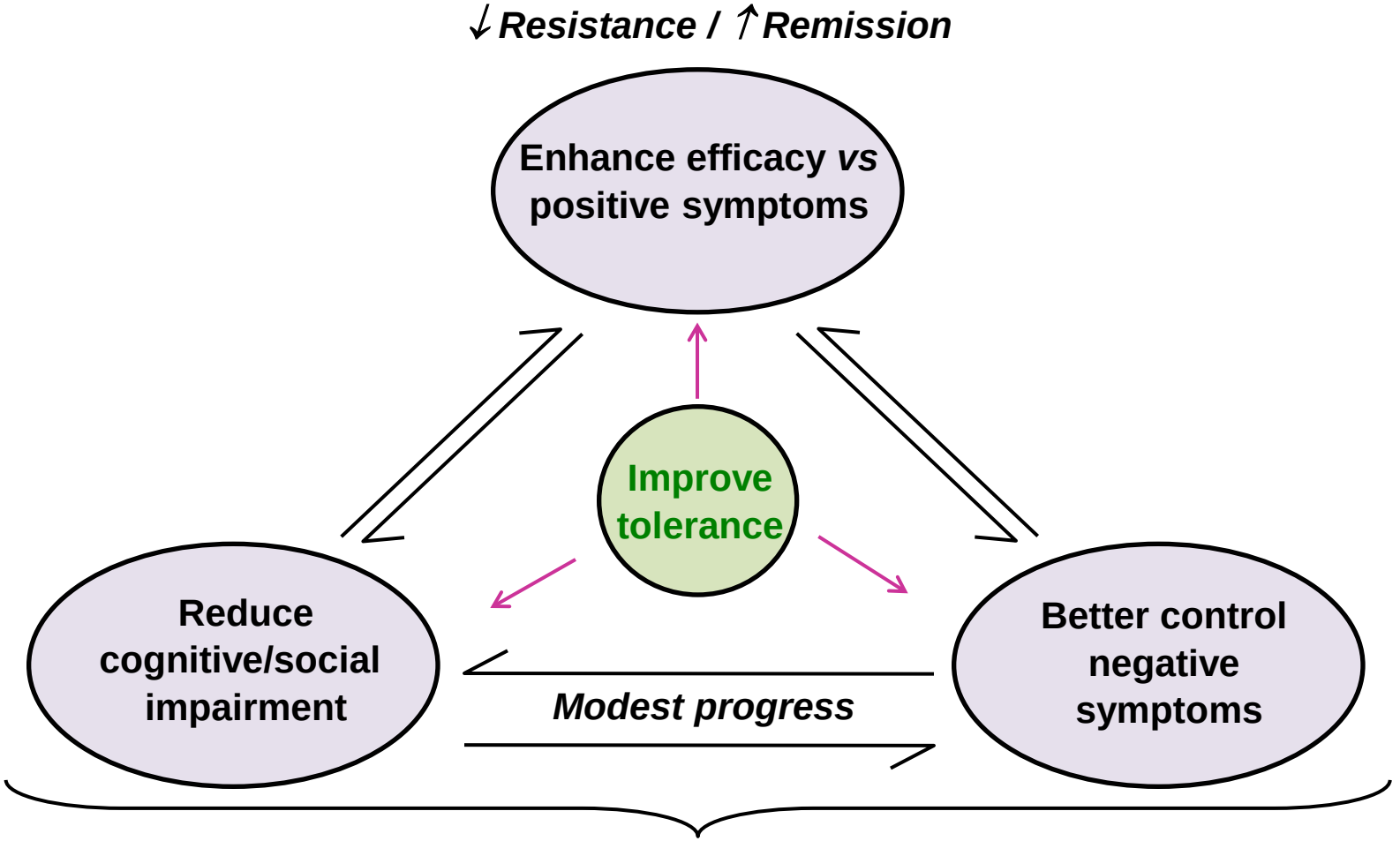
CORE CHARACTERISTICS, CUMULATIVE CAUSES AND CHRONIC COURSE OF SCHIZOPHRENIA



CHARACTERISTICS, CAUSES, COURSE AND CONTROL OF SCHIZOPHRENIA TODAY



IMPROVING EFFICACY OF SYMPTOMATIC TREATMENT OF SCHIZOPHRENIA
LITTLE SUCCESS DURING 60 YEARS !



Chlorpromazine, haloperidol - neuroleptics (1952 on): Only positive symptoms, motor side-effects

Clozapine (1989): still Gold Standard for efficacy !! - but safety issues and *not* cog/social nor negative.

Second-generation agents (1994 on), risperidone, aripiprazole… *not* more efficacious.

FROM SYMPTOMATIC TREATMENT TO COURSE-ALTERATION FOR SCHIZOPHRENIA: A NEW WAY OF THINKING

- **Precedents from other domains - "Disease-modification"**

  - Statins for reducing excess cholesterol and risk of cardiovascular disorders.
  - Attempts to block beta-amyloid and progression of Alzheimer's disease.
  - Rescuing functional (GABA) deficits in autism-related disorders like Down Syndrome.

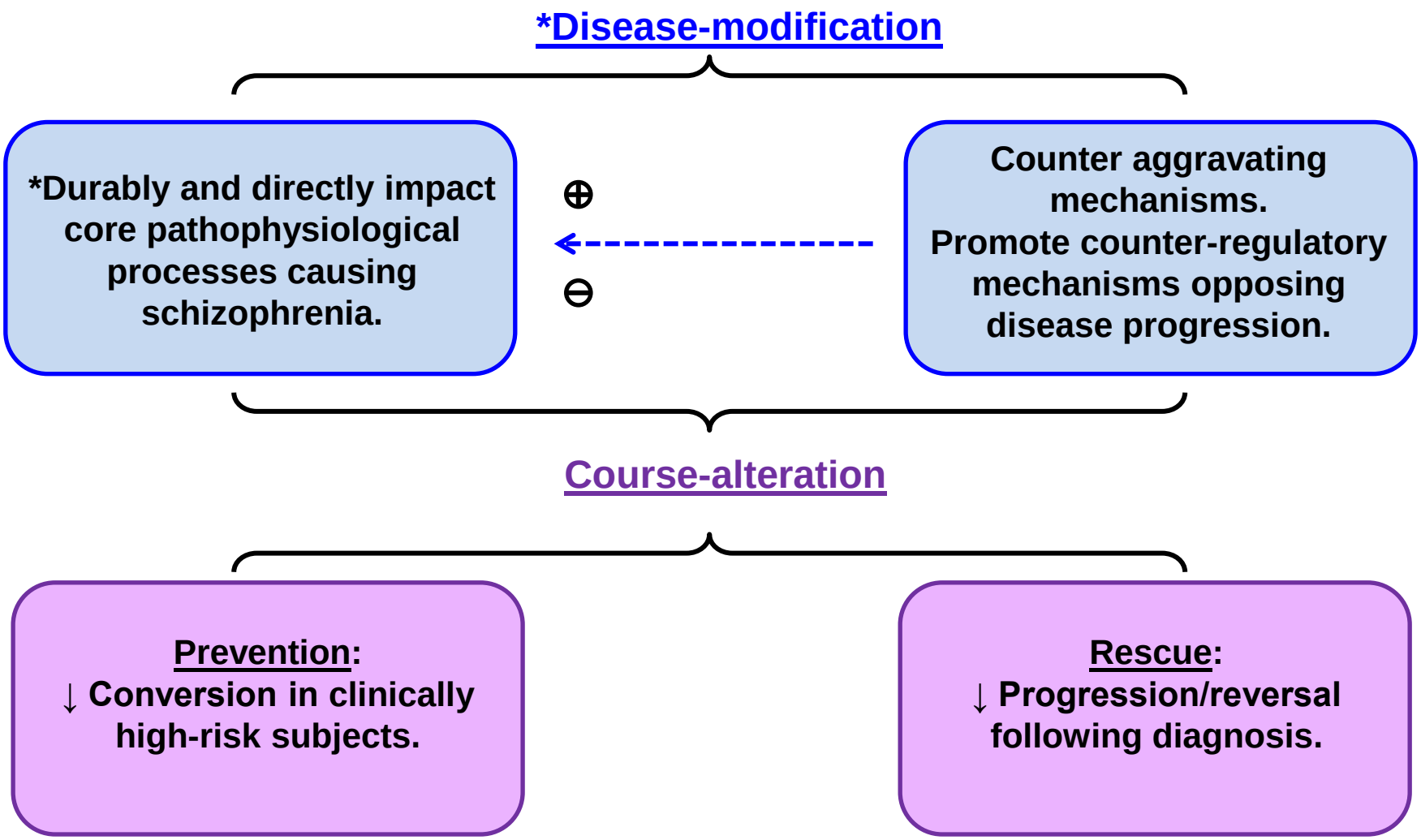
- **Recent emergence for schizophrenia - "Course-alteration"**

  - Rethinking schizophrenia
  Tom Insel (Director of National Inst. Mental Health, US), Nature 2010

  - A new beginning for a broken mind: reversing synaptic dysfunction
  Marin and Rico, Neuron, 2013

  - Prediction and prevention of psychosis in youth at clinical high-risk
  Stafford MR et al (National Health Service, UK), Br Medical Journal, 2013

DISEASE-MODIFICATION AND COURSE-ALTERATION: GENERAL CONSIDERATIONS



Biomarkers: Readouts of pathophysiological processes

COURSE-ALTERATION AS A POTENTIAL PARADIGM SHIFT FOR SCHIZOPHRENIA:

THREE CRUCIAL AND INTERRELATED ISSUES

WHEN TO TREAT ?

WHOM TO TREAT ?

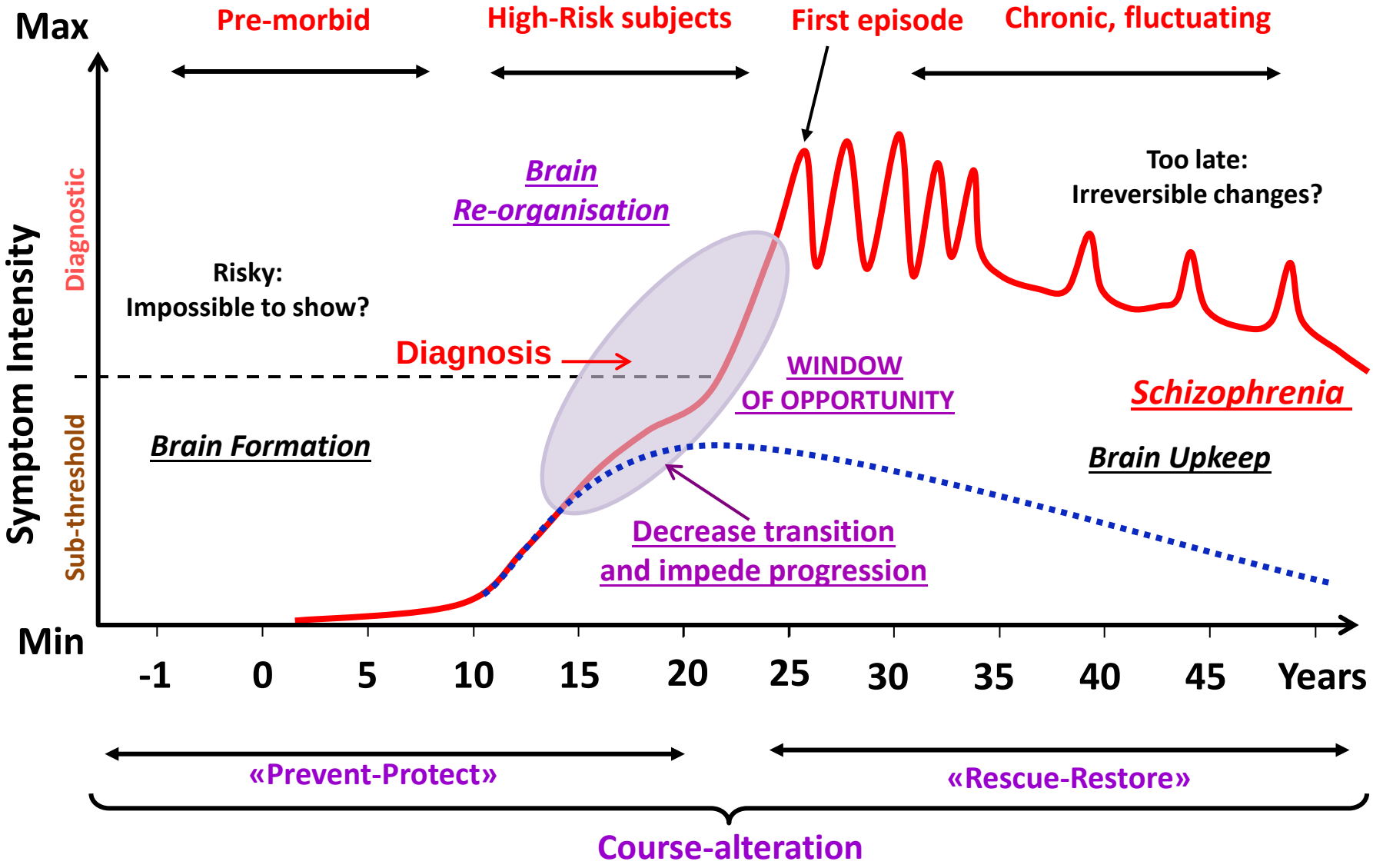
HOW TO TREAT ?

COURSE-ALTERATION AS A POTENTIAL PARADIGM SHIFT FOR SCHIZOPHRENIA :

***WHEN* TO TREAT ?**

AT WHAT PHASE OF THE DISORDER RELATIVE TO DIAGNOSIS ?

COURSE-ALTERATION FOR SCHIZOPHRENIA: WHEN TO TREAT ?

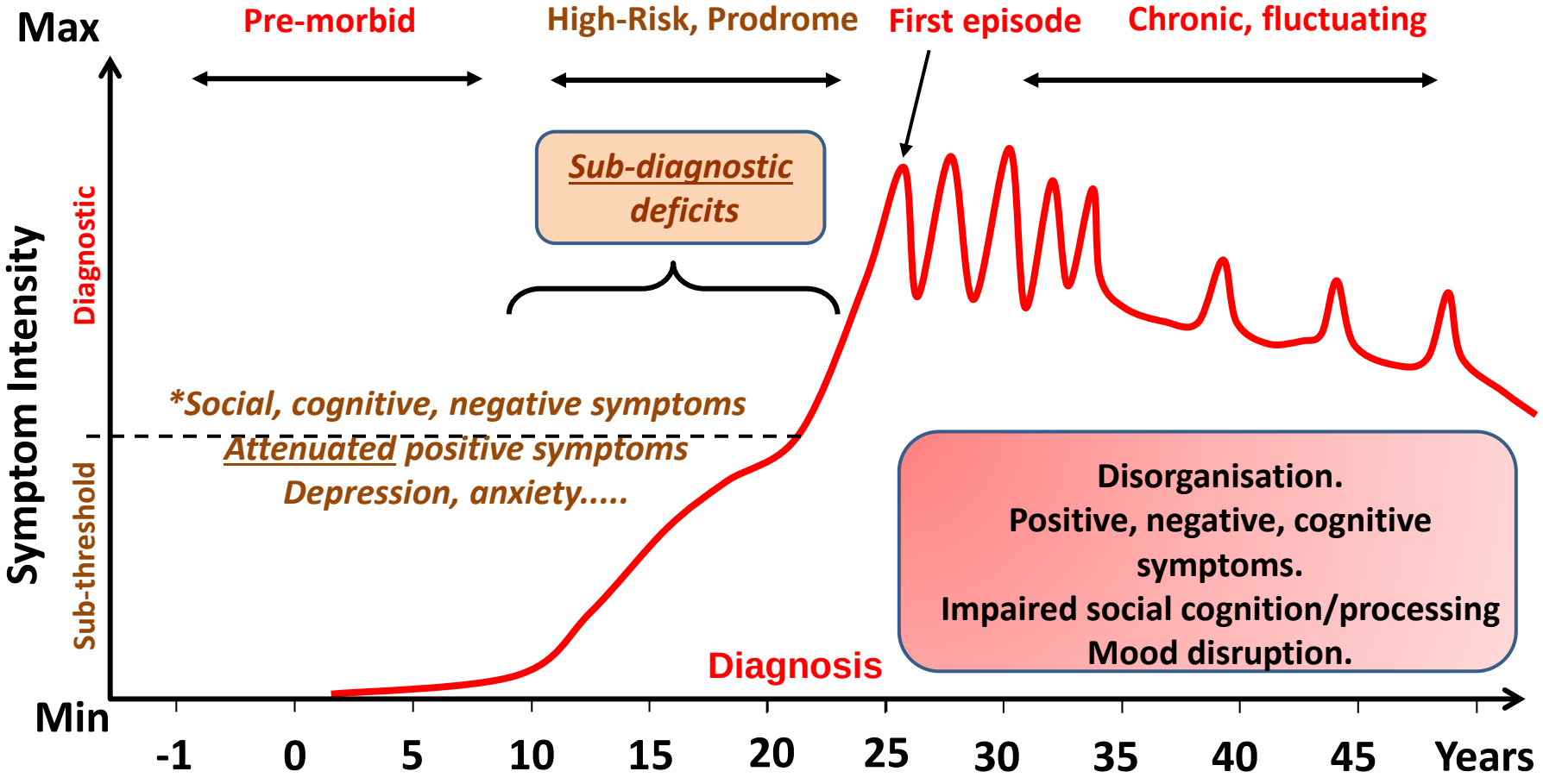


COURSE-ALTERATION AS A POTENTIAL PARADIGM SHIFT FOR SCHIZOPHRENIA :

WHOM TO TREAT ? I

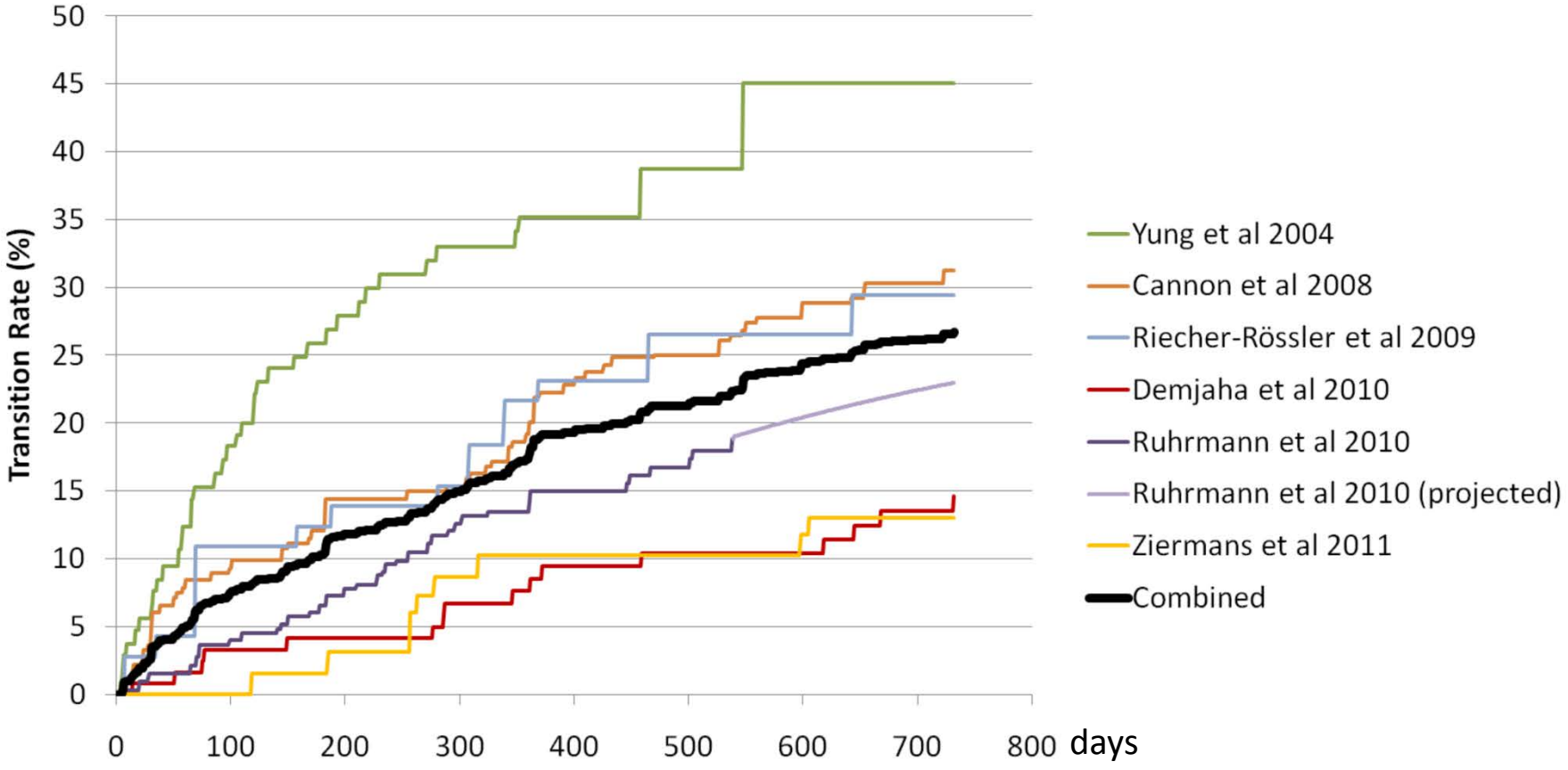
HOW TO IDENTIFY PEOPLE AT HIGH RISK ?

COURSE-ALTERATION FOR SCHIZOPHRENIA: PEOPLE AT HIGH RISK SHOW MODEST SYMPTOMS *PRIOR* TO DIAGNOSIS



TRANSITION OVER TIME IN HIGH-RISK PEOPLE: ONLY A *THIRD* CONVERT TO SCHIZOPHRENIA WITHIN 2-5 YEARS

Meta-analysis of Kaplan-Meier estimates of transition from High-Risk state (n = 984).



Another third transit to depression, bipolar depression, anxiety….

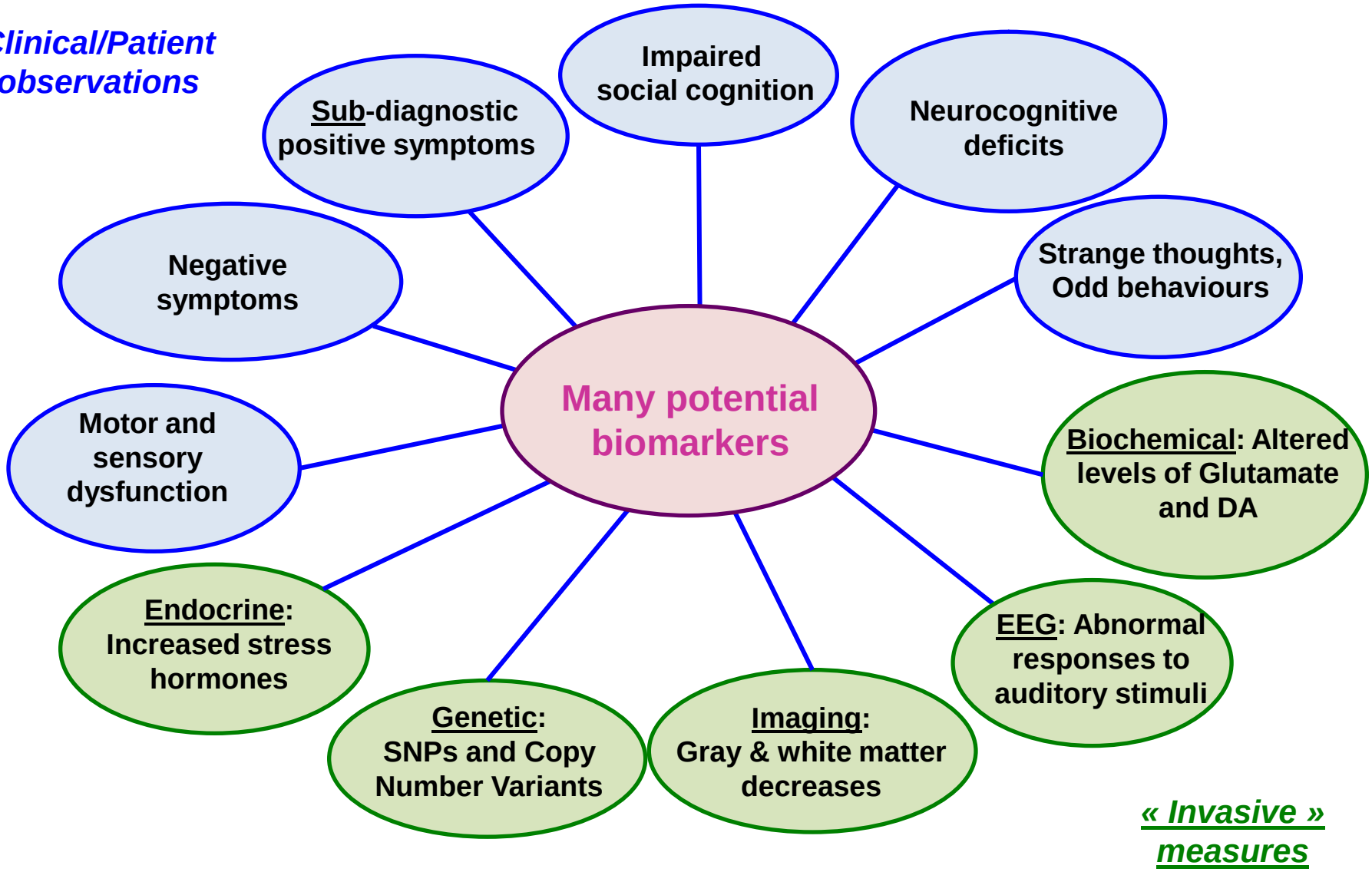
Fusar-Poli P. et al, Arch Gen Psy, 2012

“COURSE-ALTERATION” AS A POTENTIAL PARADIGM SHIFT FOR SCHIZOPHRENIA :

WHOM TO TREAT ? II

ARE THERE RELIABLE BIOMARKERS PREDICTING CONVERSION TO SCHIZOPHRENIA?

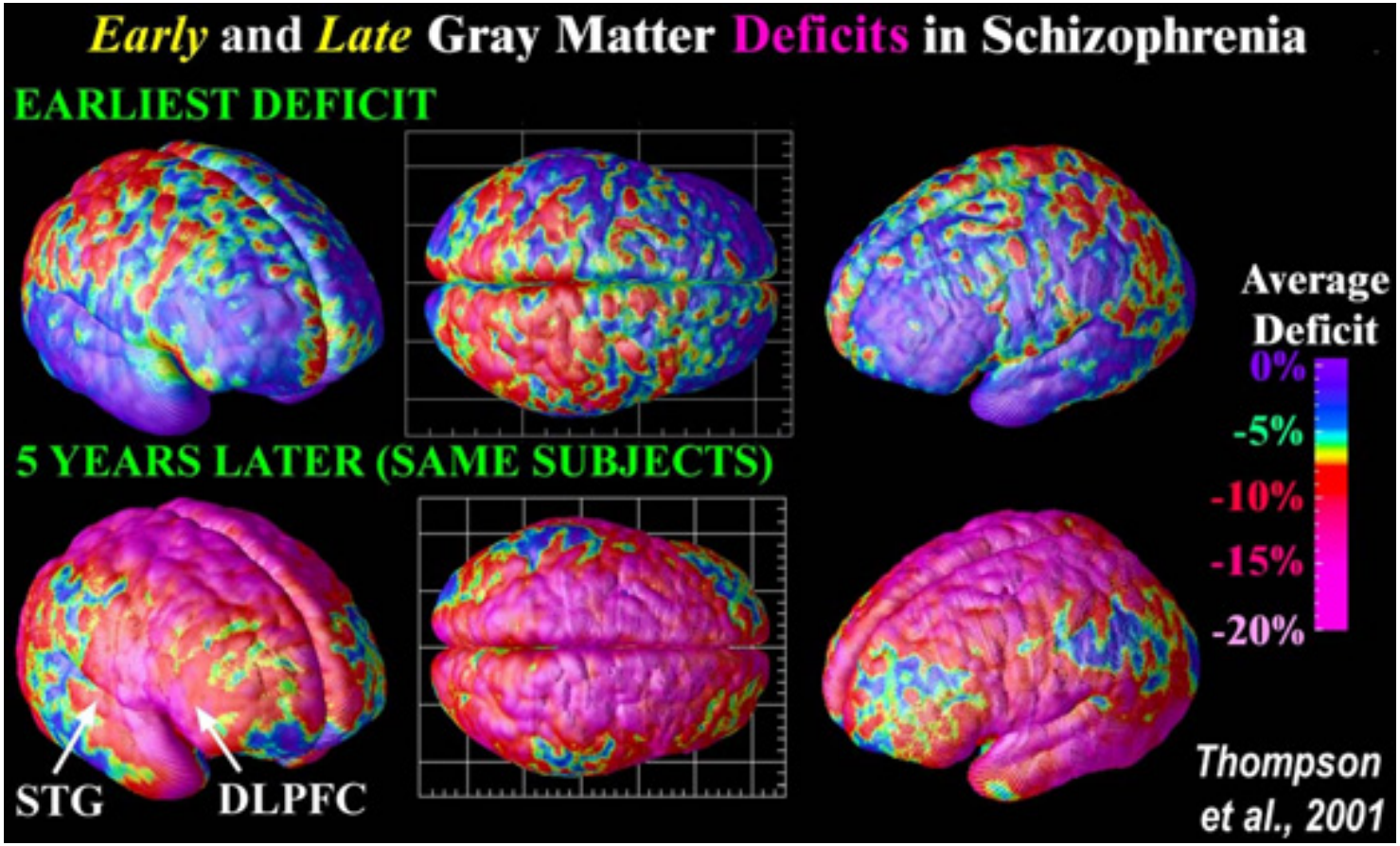
DIVERSE READOUTS FOR PREDICTING RISK OF TRANSITION TO SCHIZOPHRENIA



PROGRESSIVE LOSS OF GRAY MATTER IN SCHIZOPHRENIA: THE EXAMPLE OF EARLY-ONSET CASES

Magnetic Resonance Imaging

Differences to normal, young subjects



13 years

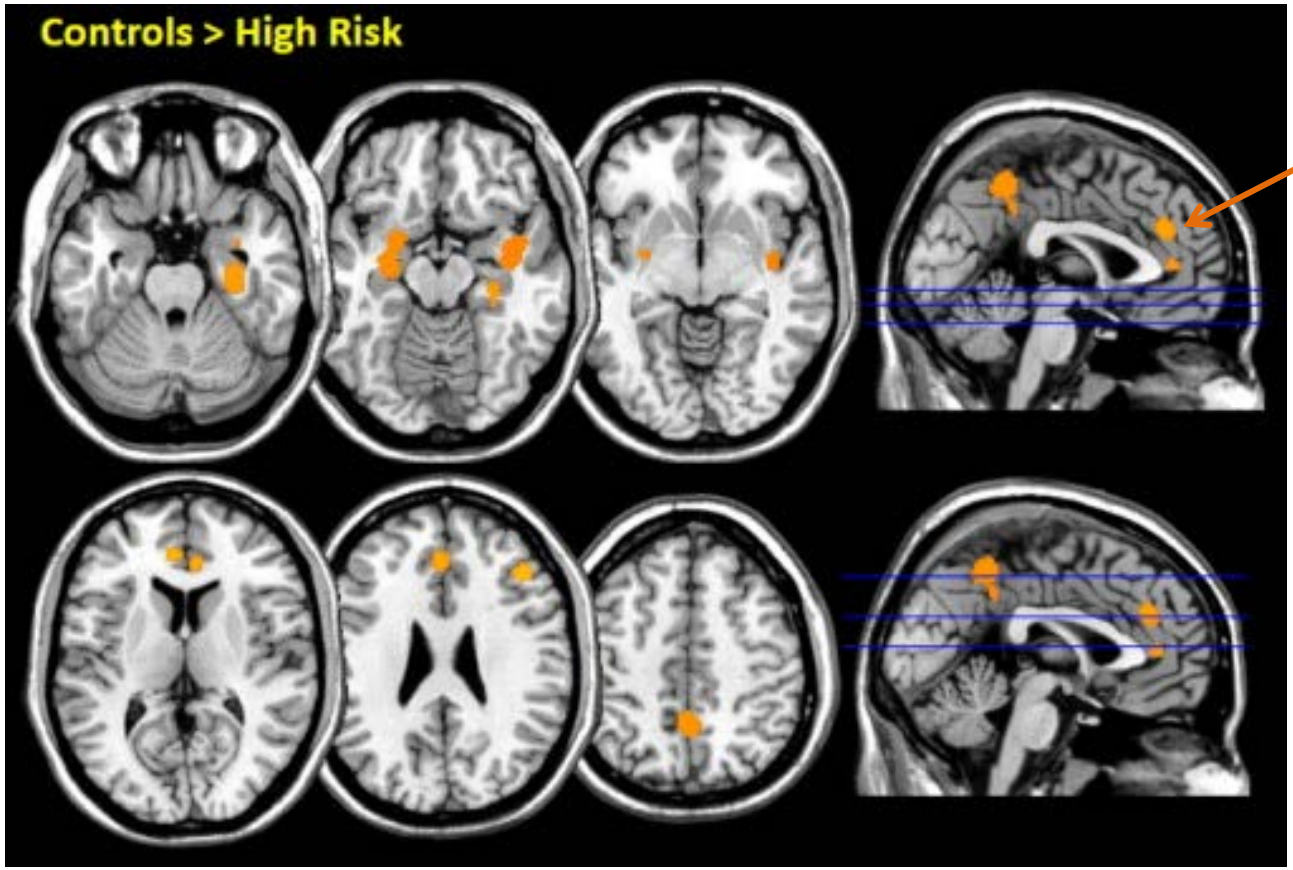
PINK, Major loss

18 years

STG, Superior temporal gyrus; DLPFC, Dorsolateral prefrontal cortex

Thomson PM et al, PNAS 2001

DECREASES IN CEREBRAL GRAY MATTER VOLUME IN HIGH-RISK *VERSUS* CONTROL SUBJECTS



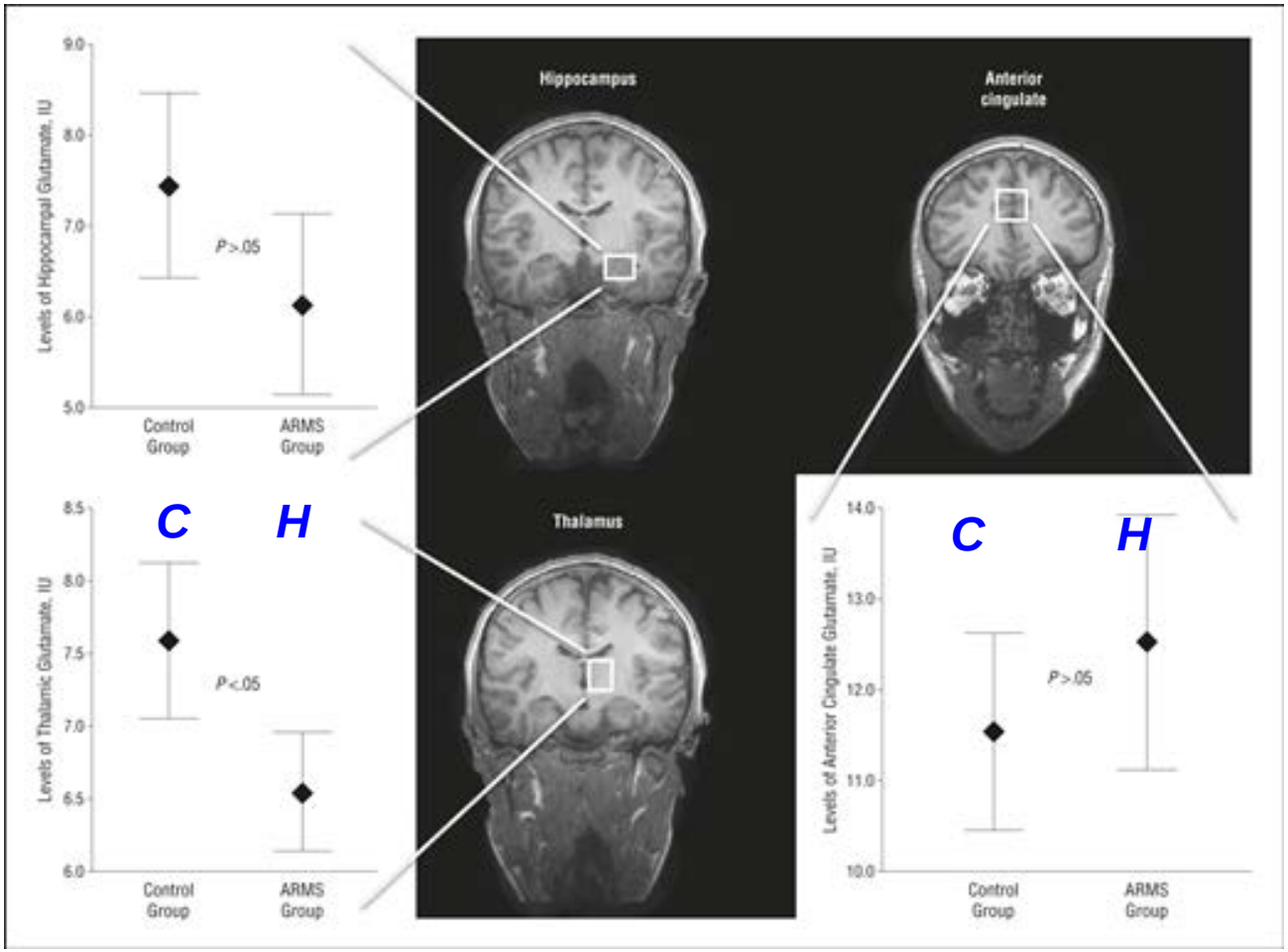
Differences in volume in temporal, frontal and parietal cortex, also hippocampus.

Magnetic Resonance Imaging, Meta-Analysis

Fusar-Poli, P. et al, Neurosci Biobehav Rev 2011

ALTERATIONS IN CEREBRAL LEVELS OF GLUTAMATE IN HIGH-RISK (H) *VERSUS* CONTROL (C) SUBJECTS

Hippocampus



Cingulate cortex

Robust decrease in Thalamus

Cingulate cortex

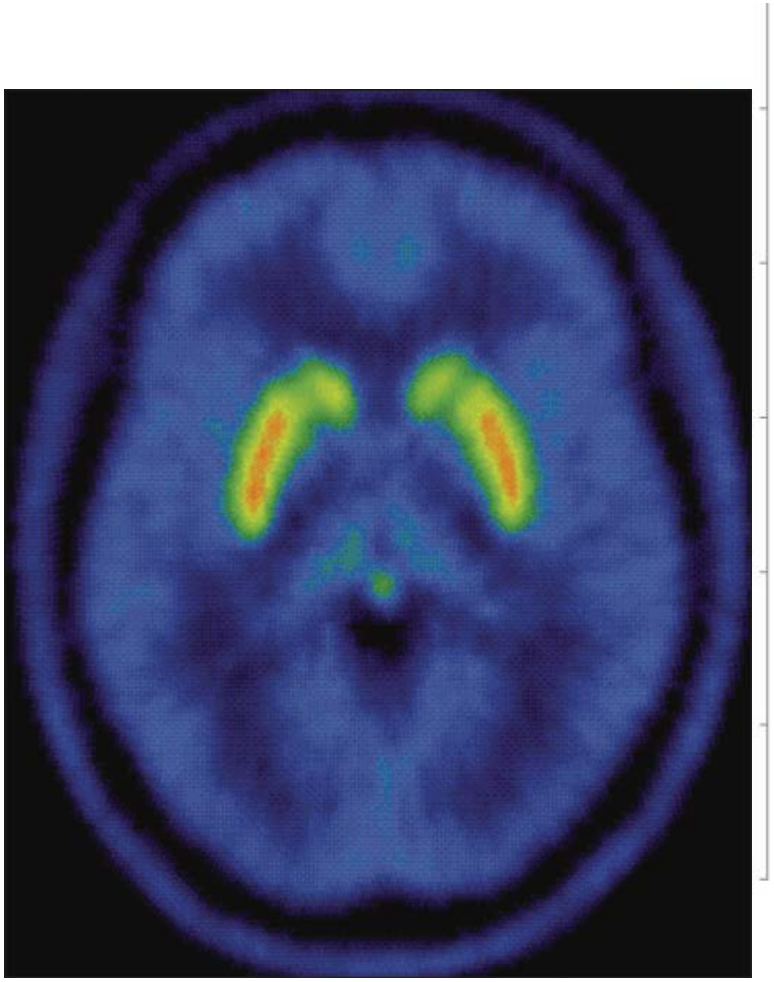
Left - Control
Right - High-Risk

MAGNETIC RESONANCE SPECTROSCOPY

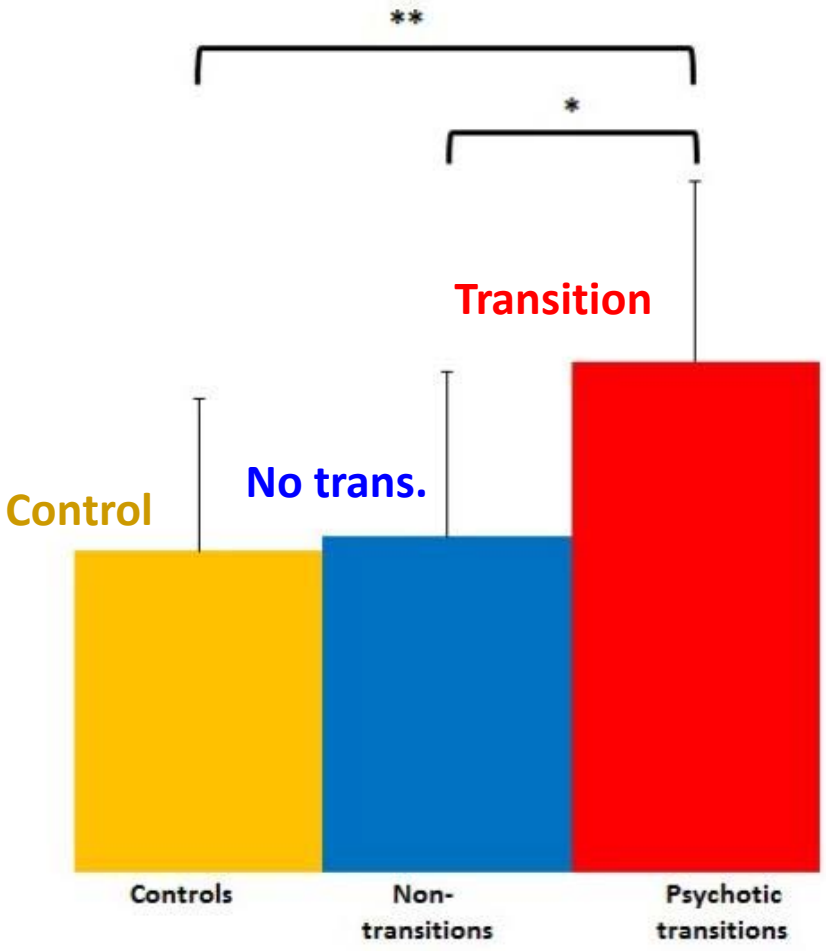
Fusar-Poli P et al, Arch Gen Psy, 2012

INCREASED STRIATAL DOPAMINE SYNTHESIS IN HIGH-RISK *VERSUS* CONTROL SUBJECTS

Visualisation of DA synthesis (^{18}F-DOPA, PET imaging)

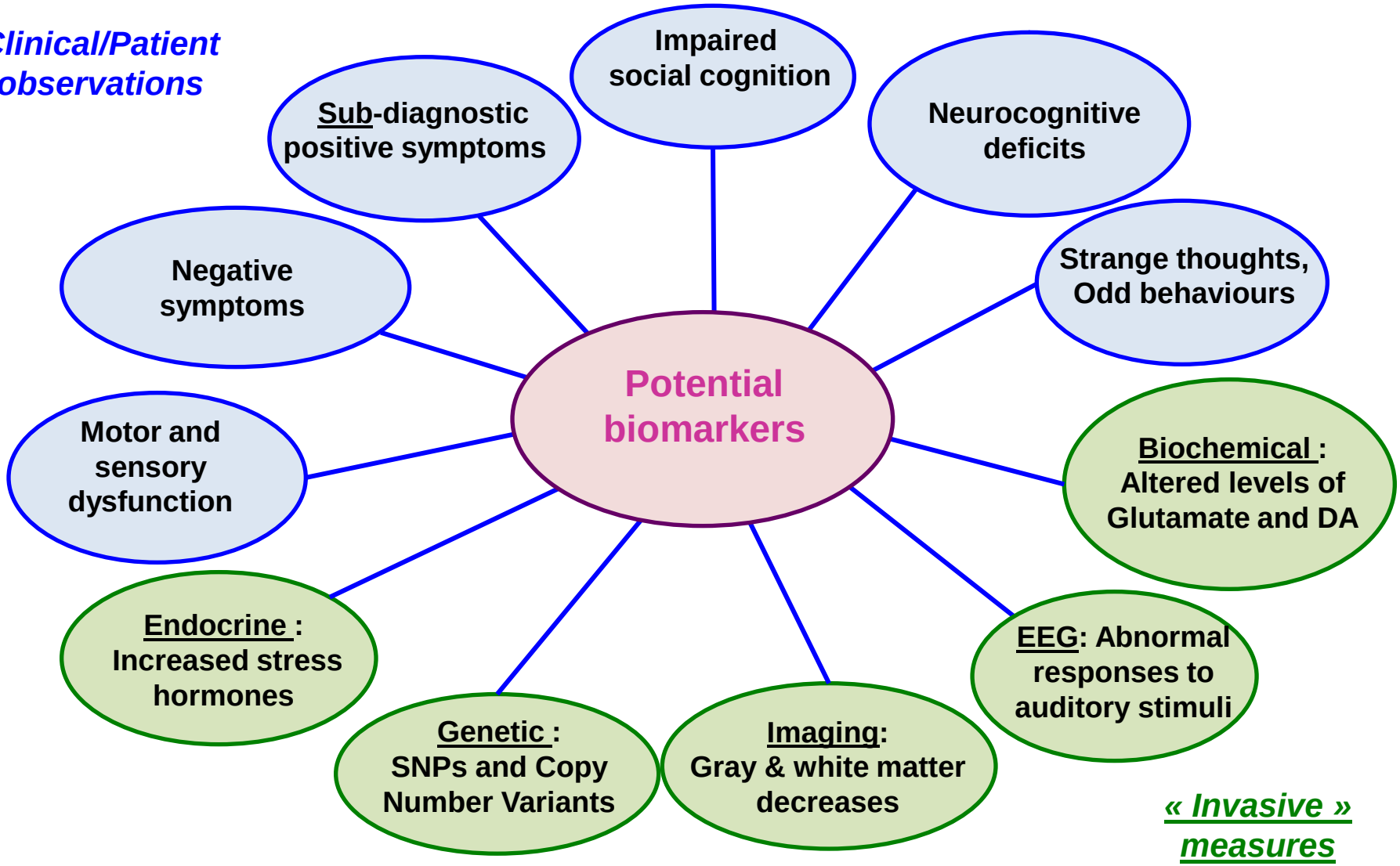


Increased DA turnover correlates with transition to Schizophrenia



Howes, O et al, Am. J. Psychiatry, 2011

DIVERSE READOUTS FOR PREDICTING RISK OF TRANSITION TO SCHIZOPHRENIA



Multi-modal strategies increase accuracy and specificity

+ Life-Style (Cannabis, stress, isolation)

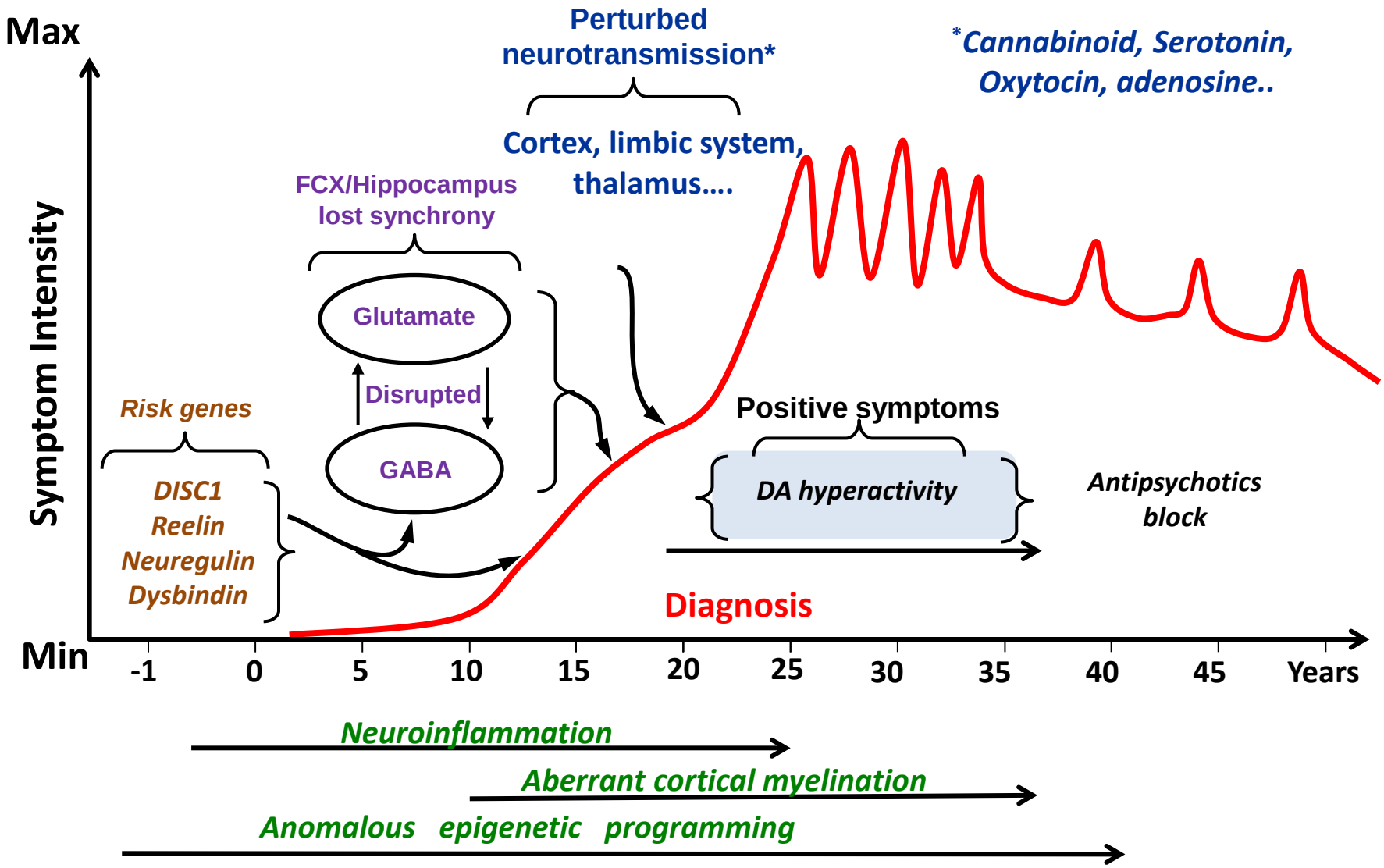
} Up to 70% accuracy

“COURSE-ALTERATION” AS A POTENTIAL PARADIGM SHIFT FOR SCHIZOPHRENIA :

HOW TO TREAT ?
THE TOUGHEST CHALLENGE OF ALL !

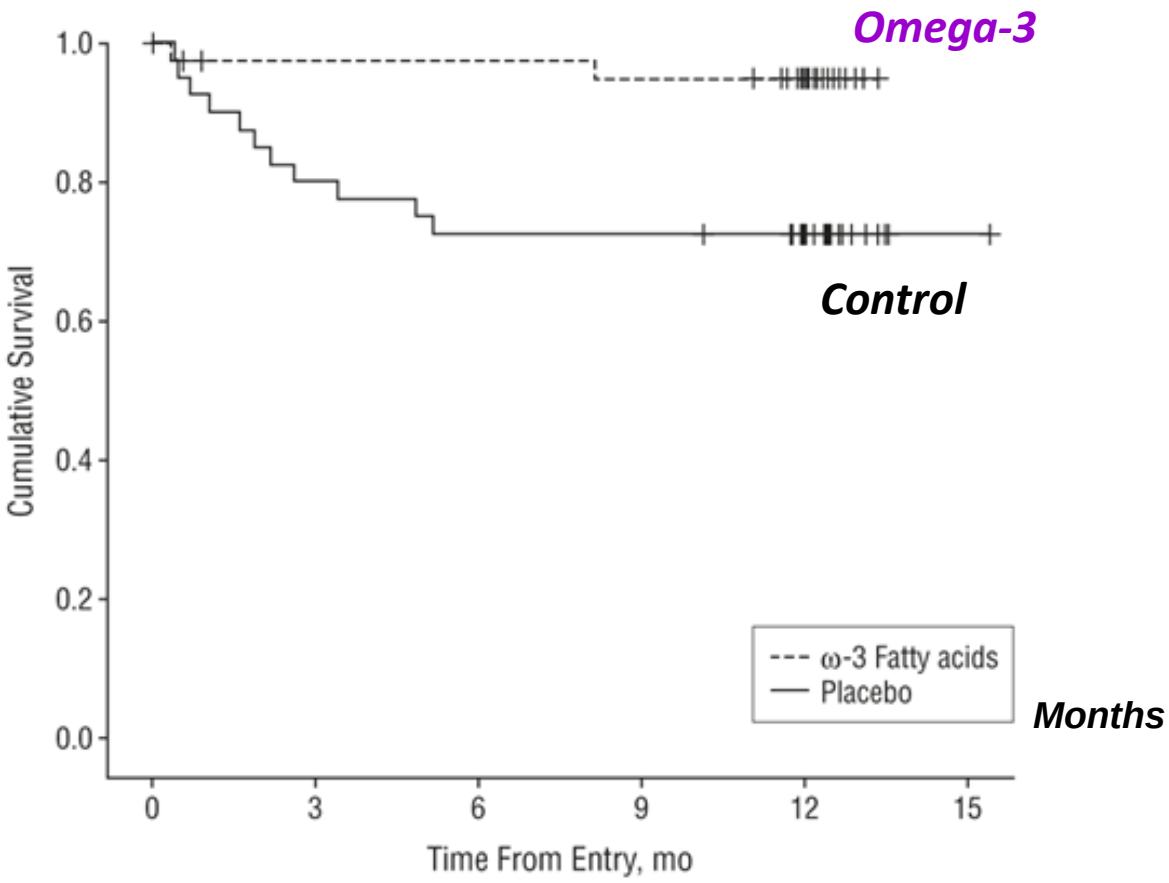
Clinical and pre-clinical studies

ANOMALIES IMPLICATED IN SCHIZOPHRENIA: MANY *POTENTIAL* TARGETS FOR COURSE-ALTERATION



LONG-CHAIN OMEGA-3 (*ω-3)* FATTY ACIDS REDUCE TRANSITION TO PSYCHOSIS UPON ADMINISTRATION TO HIGH-RISK SUBJECTS

Multi-target influence on myelination, glutamatergic transmission, inflammation….

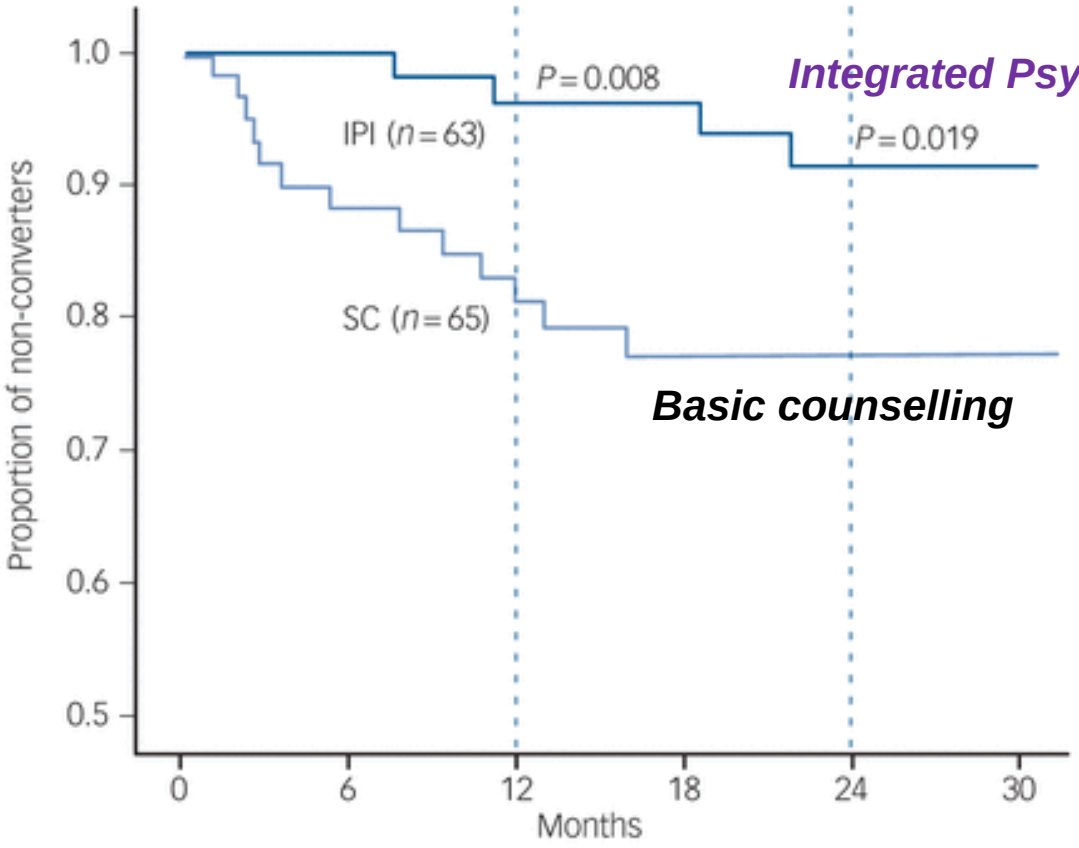


SURVIVAL CURVES:
Kaplan-Meier estimates of risk of transition from the at-risk state to psychosis in patients on ω-3 fatty acids vs placebo (P = .007 by log-rank test).

3 months: 1.2 g Omega-3 polyunsaturated fatty acids/day

Amminger, G et al., Arch Gen Psych 2010

INTEGRATED PSYCHOLOGICAL INTERVENTION REDUCES PROGRESSION TO PSYCHOSIS IN HIGH-RISK SUBJECTS *VS* "BASIC COUNSELLING".



Integrated Psychological Intervention

Basic counselling

Months

SURVIVAL CURVES:
Kaplan-Meier estimates of progression: Comparisons for difference in conversion to psychosis at 12 months (P = 0.008) and 24 months (P = 0.019).

Individual and family-based therapy for improving social skills, mental state, and cognitive status etc

Bechdolf, A et al., Br J Psy 2012

CLINICAL STUDIES OF COURSE-ALTERING THERAPY FOR REDUCING TRANSITION TO SCHIZOPHRENIA: OVERVIEW

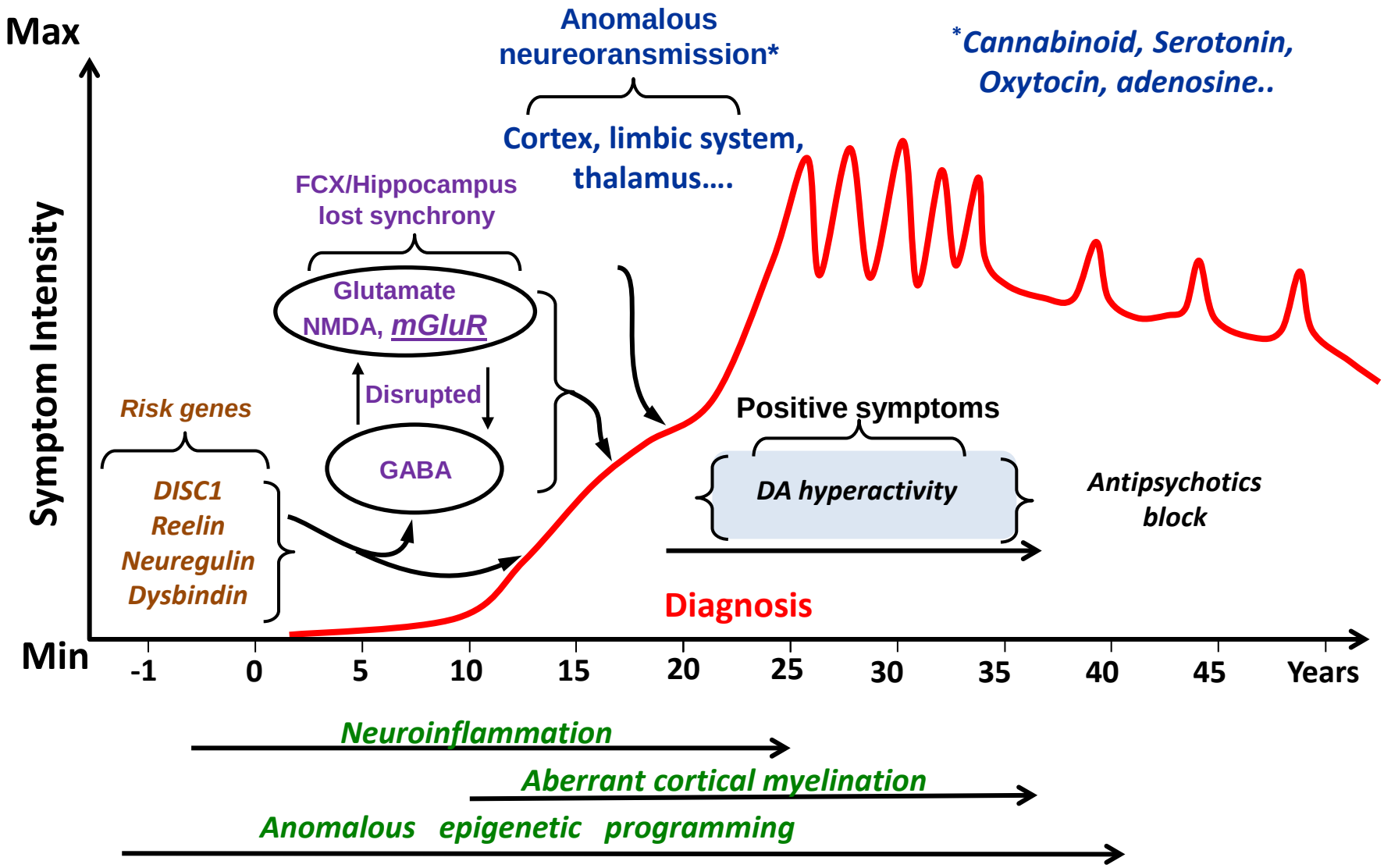
- **Meta-analysis of nine studies for delaying conversion in high-risk subjects: significant overall effectiveness (Fusar-Poli P. et al, Am J Psychiatry, 2013).**

- **For individual drugs:**
  - **Risperidone and olanzapine - data not significant and risk of side-effects.**
  - **Omega-3 data - delayed transition exceeded treatment period.**
  - **Cognitive-behavioural/psychological interventions - effective in several studies.**

- **Collectively: Preventative "course-altering" treatments for schizophrenia:**
  - **Can be clinically-evaluated.**
  - **Can delay onset.**
  - **Can reduce pre-transition, sub-diagnostic symptoms.**

- **Need for further studies!! Both clinical and experimental.**

ANOMALIES IMPLICATED IN SCHIZOPHRENIA: MANY *POTENTIAL* TARGETS FOR COURSE-ALTERATION



RODENT MODELS FOR STUDYING COURSE-ALTERATION IN SCHIZOPHRENIA: PRE-SYMPTOMATIC INTERVENTIONS

- **Many models *for* schizophrenia - genetic and developmental, conception to adolescence.**
- **Many possible readouts (behavioural, structural, biochemical……..).**

Focus today on:

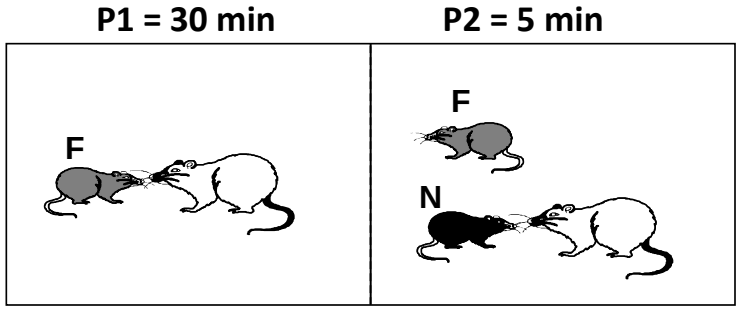
- One model: neonatal exposure to Phencyclidine ("Angel-dust") - disrupts brain development

- One readout: disrupted social discrimination, a measure of social cognition.

- One treatment mechanism - activation of mGluR5 receptors*.

***mGluR5 receptors promote synaptic plasticity and are impacted by events leading to schizophrenia.**

A MEASURE OF SOCIAL COGNITION IN RODENTS: SOCIAL NOVELTY DISCRIMINATION TEST



Novelty discrimination index (NDI) = N/F

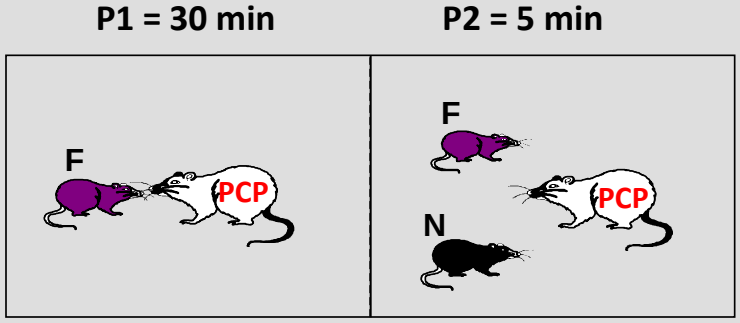
Interaction duration (sec)

P2N > P2F

F: Familiar
N: Novel
} **Juvenile**

Neonatal exposure to Phencyclidine (PCP) (10 mg/kg, s.c., days 7, 9 and 11)

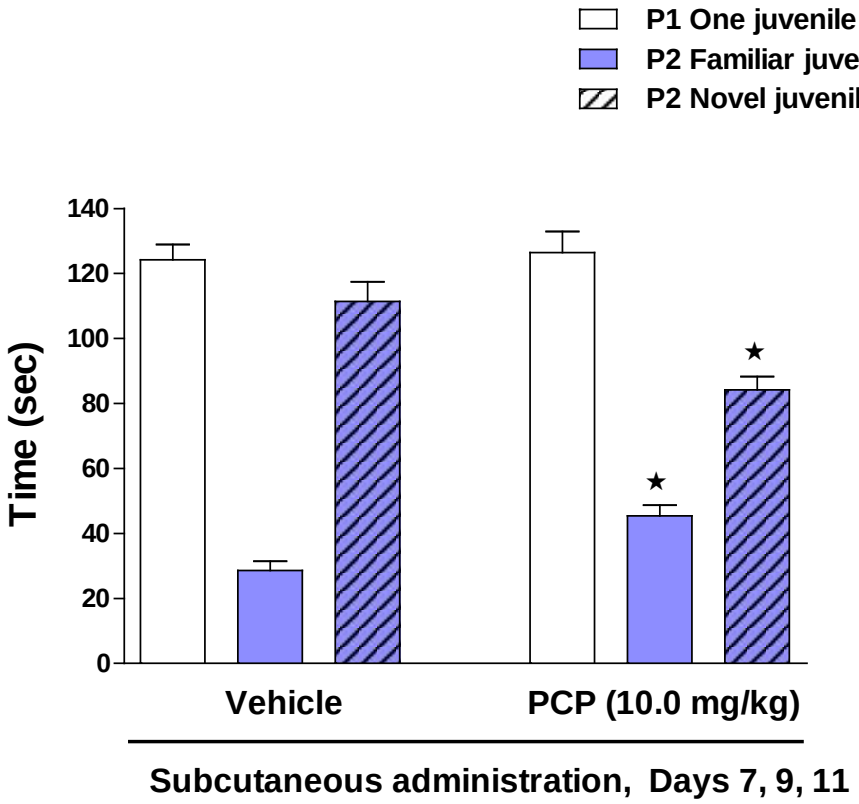
TEST

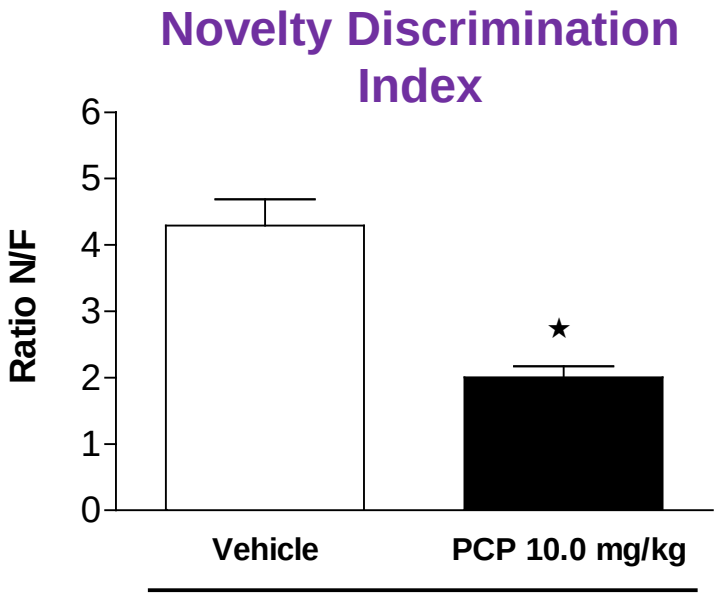


DIMINISHED DISCRIMINATION

P2N >= P2F
NDI (N/F) DECREASED

NEONATAL PCP MODEL OF SCHIZOPHRENIA: DISRUPTION BY SOCIAL NOVELTY DISCRIMINATION IN ADULTS

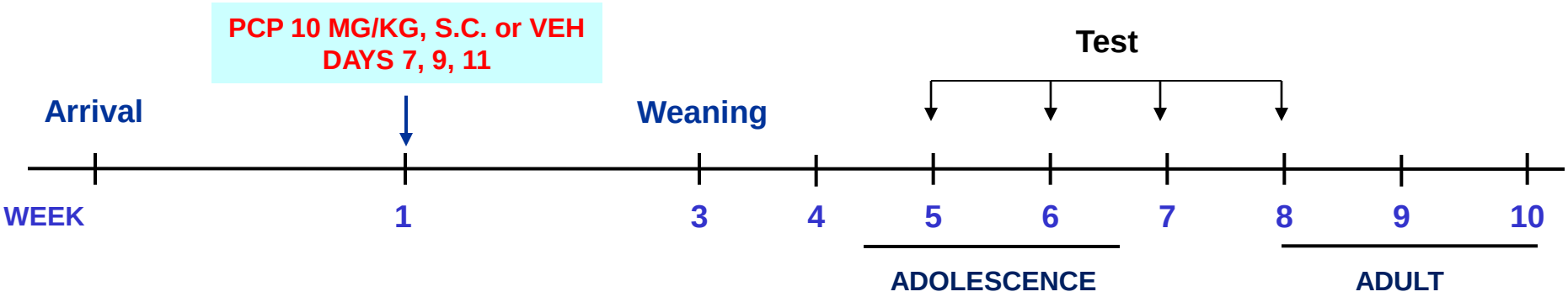




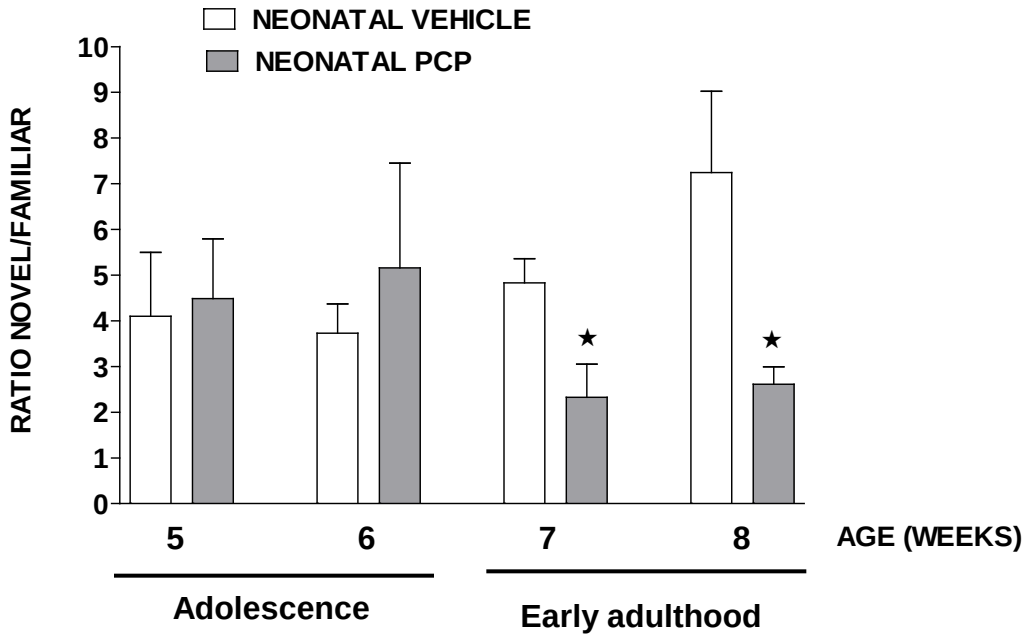
Neonatal PCP induces a deficit in «Social Cognition» in adult rats.

Clifton, N et al, Psychopharmacology, 2013

DEFICIT IN SOCIAL NOVELTY DISCRIMINATION INDUCED BY NEONATAL PCP: YOUNG ADULT ONSET



Time-course of deficit



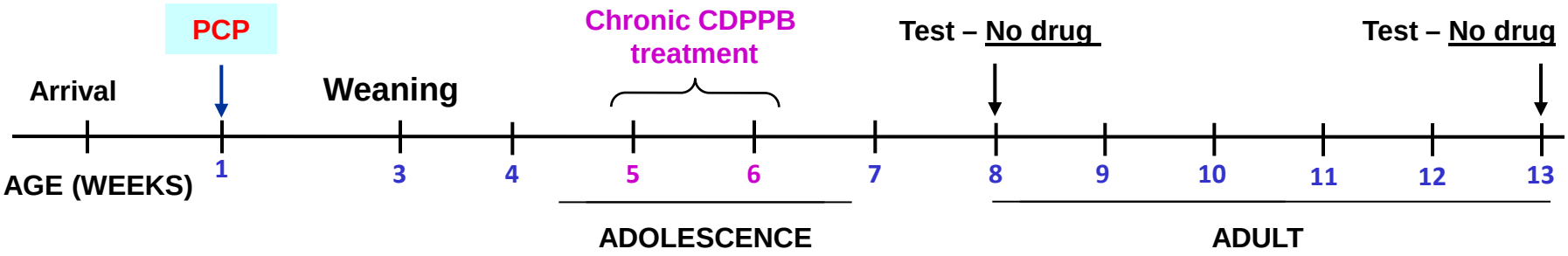
Emergence of social cognitive deficits in young adults (resembling patients)

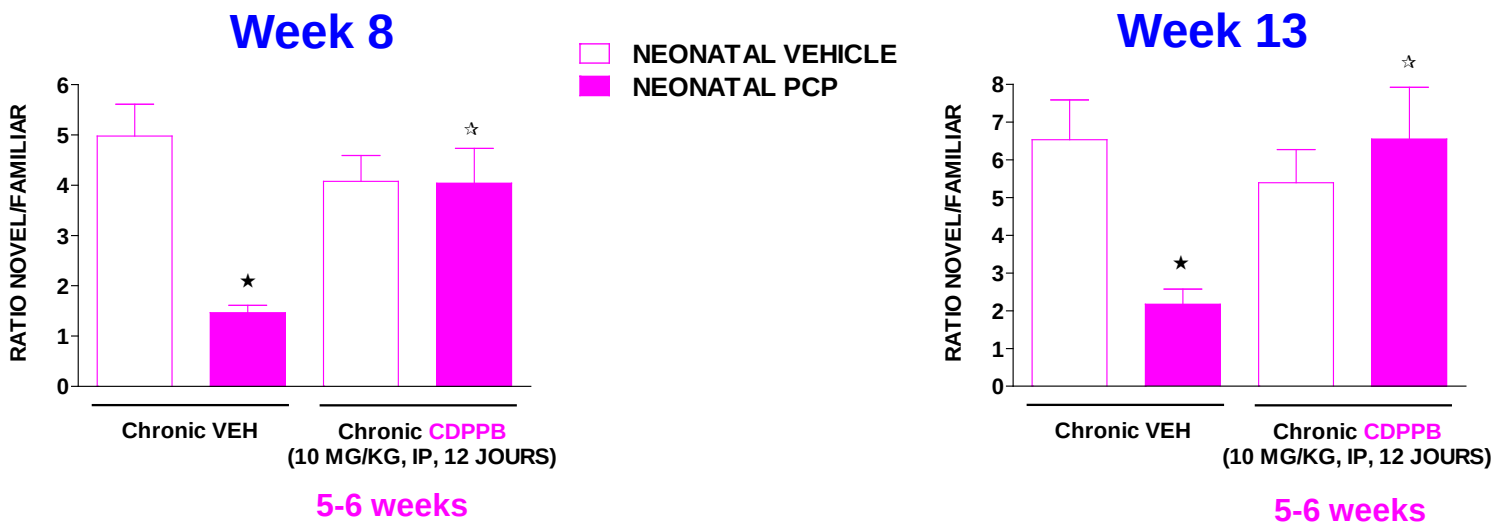
Can disruption be *prevented* ?

mGluR5 receptor activation

PREVENTION BY mGluR5 RECEPTOR ACTIVATOR OF SOCIAL COGNITION DEFICIT INDUCED BY NEONATAL PCP

Chronic **administration during adolescence**
Measurement in adults *after* stopping drug





Sustained *preventative* action of adolescent mGluR5 stimulation - blocks emergence of social cognition deficit.

EXPERIMENTAL STUDIES IN RODENTS OF COURSE-ALTERING THERAPY FOR SCHIZOPHRENIA: SUMMARY

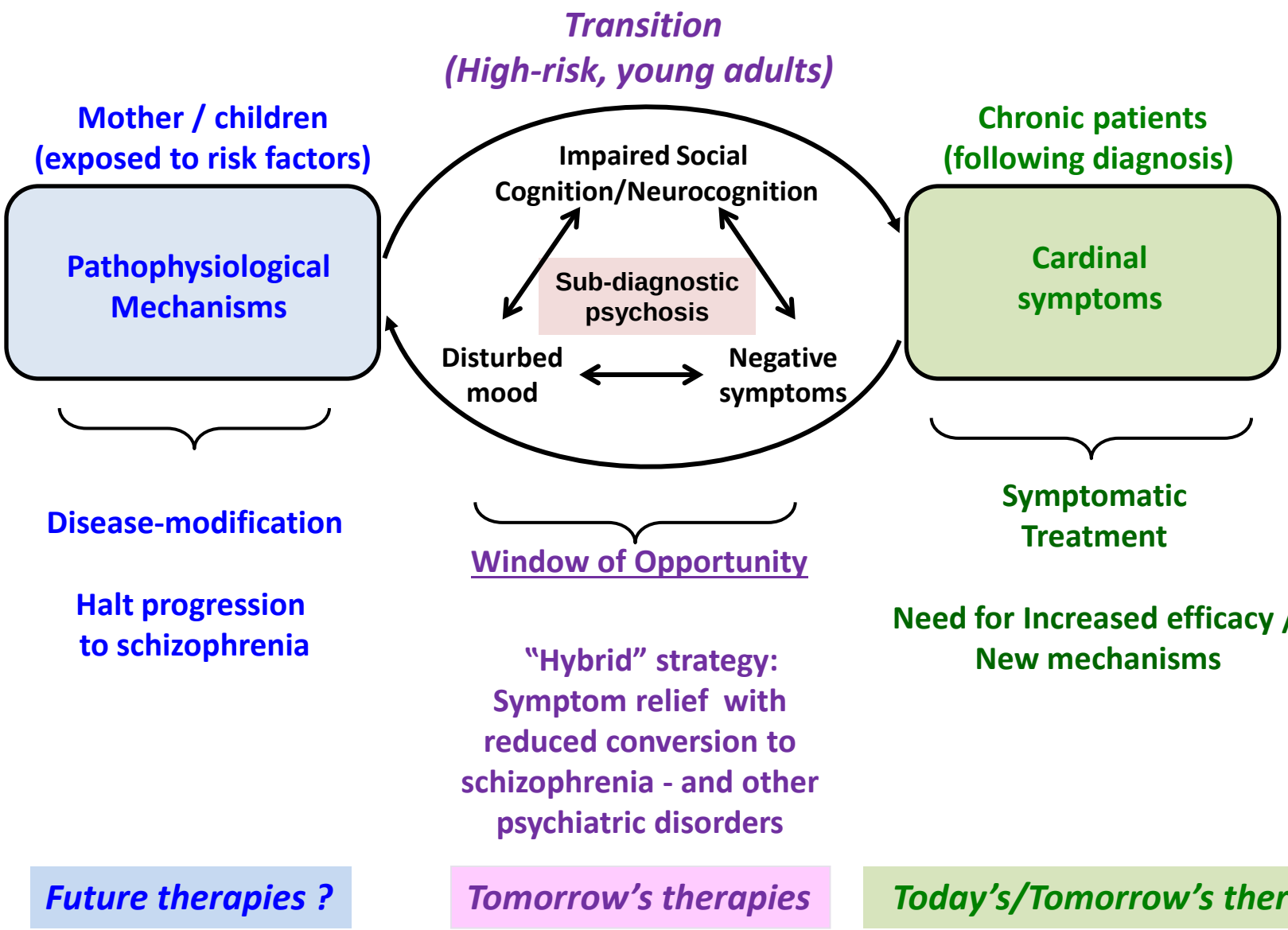
- **Sustained mGluR5 receptor activation during adolescence *before* symptoms *prevents* onset of impaired social cognition in a developmental model for schizophrenia.**

- **Treatment *not* effective if given to adults *after* appearance of symptoms.**

- **More than 20 studies of diverse agents (epigenetic modulators, anti-inflammatory agents, antidepressants..): prevention of adult onset of symptoms.**

These experimental data support clinical work suggesting early "course-altering" treatment can delay or prevent transition to schizophrenia.

COURSE-ALTERATION FOR PREVENTION OF SCHIZOPHRENIA: STRATEGIC OVERVIEW AND COMPARISON TO SYMPTOMATIC CONTROL

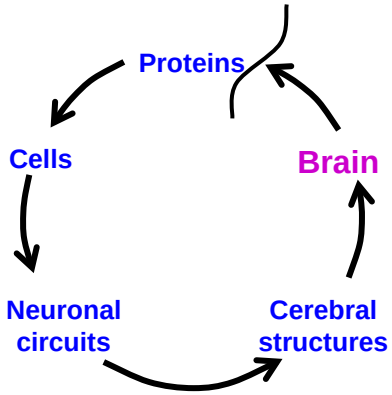


ALTERING THE COURSE OF SCHIZOPHRENIA:
PARALLELS TO OTHER DOMAINS:

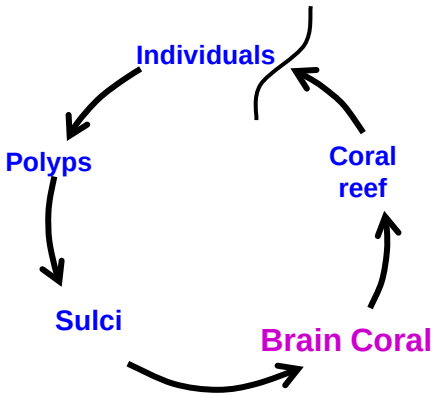
ECOSYSTEM DEGRADATION IS A THREAT TO HUMAN MENTAL HEALTH

Early course-altering strategies to protect threatened ecosystems.

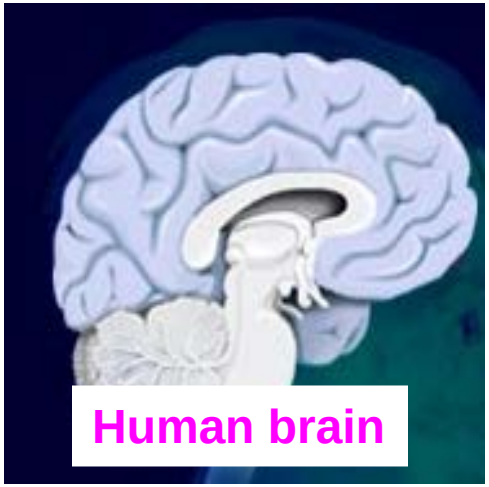
HUMAN BRAIN AND (BRAIN) CORALS: PARALLELS ON MULTIPLE SPATIAL (AND TEMPORAL) SCALES



Common principles of organisation and operation



Social communities



Common threats:

Multiple impacts provoke irreversible disease/network-shifts

Common course-alterating strategies:

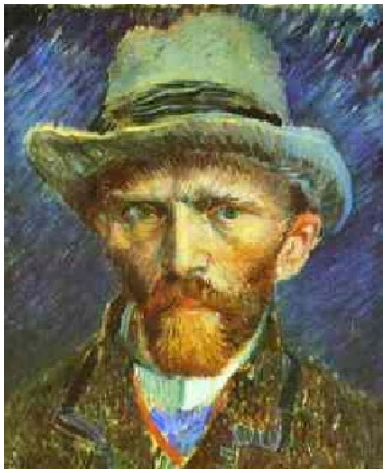
Prevention/early intervention

Marine ecosystems

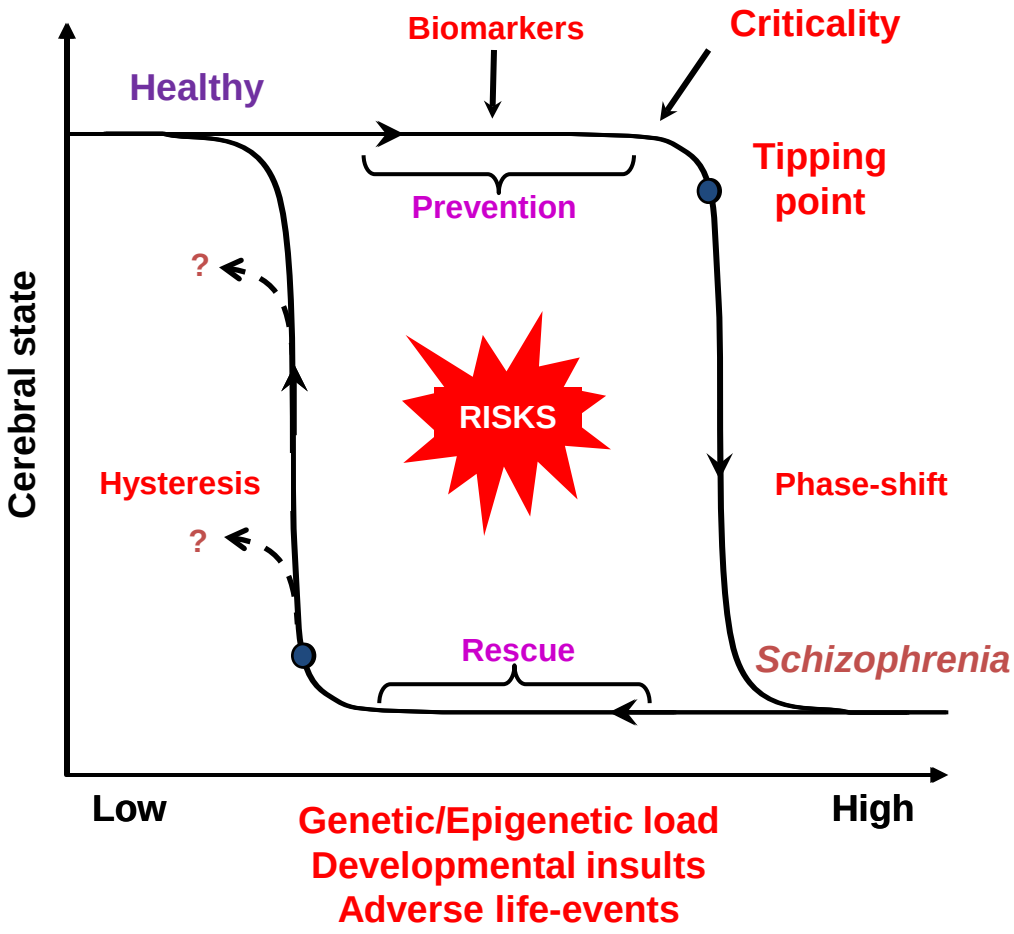
Millan, M.J., in press

MULTIPLE RISK FACTORS PROVOKE TRANSITION TO SCHIZOPHRENIA: NEED FOR COURSE-ALTERING STRATEGIES

Healthy



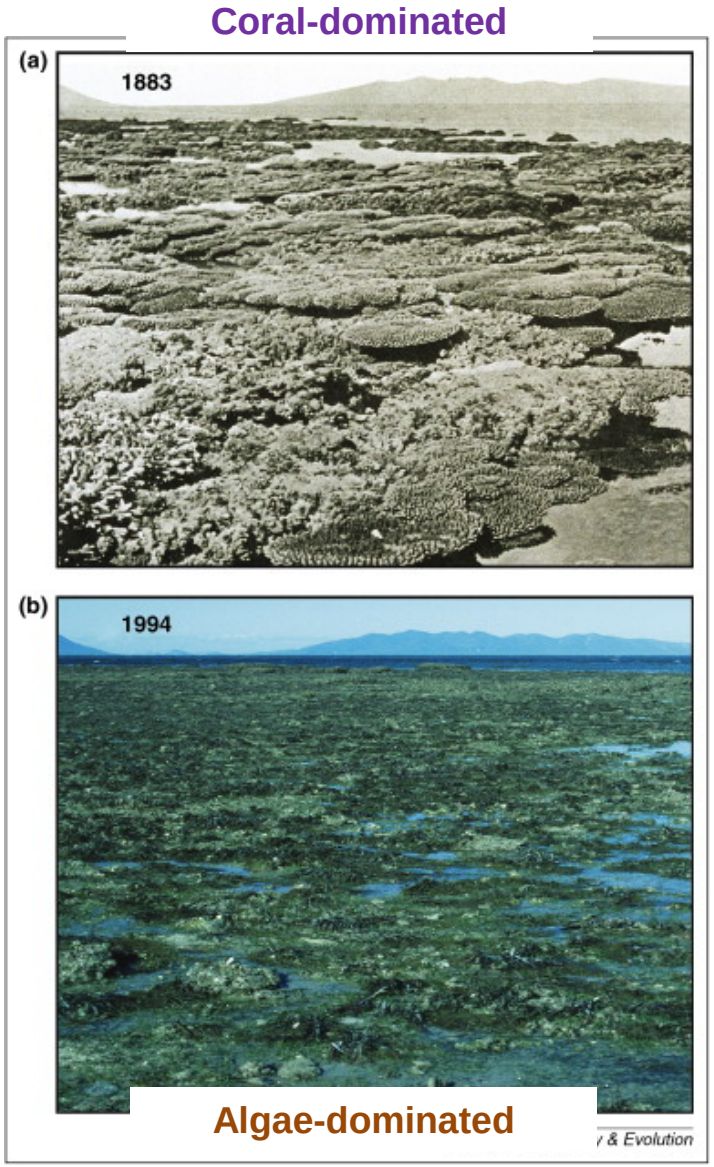
Sick

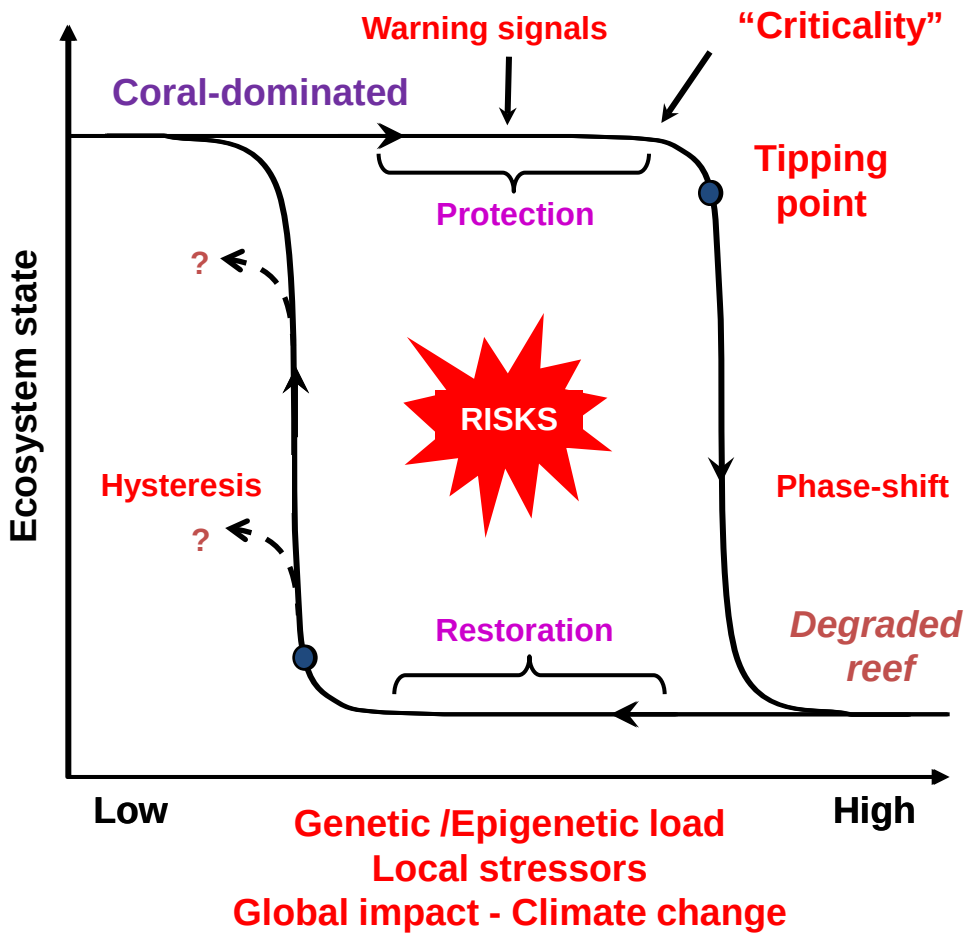


Multiple Risk Factors: Inherited, conception, childhood, adolescence…….

Millan, M.J., in press

MULTIPLE (NATURAL AND ANTHROPOLOGICAL) FACTORS DEGRADE ECOSYSTEMS: NEED FOR COURSE-ALTERING STRATEGIES





Multiple stressors: Hurricanes, nutrient outflow, sea-surface warming, over-fishing….

(Barrier Reef, Australia, T.P. Hughes, 2010)

Millan, M.J., in press

MANY THANKS TO:

- **You for this kind invitation !!!!!!!!**
- **Cambridge University - Gonville & Caius College, Dept of Zoology**
- **Max-Plank Institute for Psychiatry, Munich*.**
- **Institute de Recherches Servier, Paris*.**

Many gifted, dedicated and highly-skilled internal and external co-workers too numerous to mention !!

ALTERING THE COURSE OF SCHIZOPHRENIA: CHALLENGES AND OPPORTUNITIES

CORE MESSAGES OF PRESENTATION

- ***Course-alteration for Schizophrenia*:**
  - **Chronic, debilitating, costly: need for better symptomatic medication.**
  - **New concept of course-alteration : prevention and interruption of progression.**
  - **Window of Opportunity: stopping conversion in young people at high-risk.**

- ***Clinical data:***
  - **Improved procedures for identifying subjects at risk of developing schizophrenia.**
  - **Transition *can* be delayed in high-risk young - Omega-3 and psychotherapies.**
  - **Control of sub-diagnostic symptoms may itself reduce conversion ("hybrid" strategy).**

- ***Experimental data:***
  - **Treatment of adolescent rodents *blocks* adult appearance of schizophrenia-like symptoms.**
  - **Diverse interventions effective - pharmacological and behavioural.**

- ***Perspectives and Conclusions***

  - Course-alteration for schizophrenia: major challenge but rapid progress and long-term optimism !

  - We live in service-providing *ecosystems*: protection critical to reduce risk of mental health disorders.

What is the ECNP?

- Independent, non-governmental, scientific association
- For the science and treatment of disorders of the brain
- Brings together European scientists and facilitates information-sharing
- Spurs new discoveries in basic, applied and translational neuroscience

Our mission:

To advance the science of the brain, to promote brain health, and to improve the treatment of brain disorders

Output at a glance

- **More than 20 scientific meetings held every year**
  - All aspects of brain function and dysfunction.
  - Brings together 5,000 researchers and psychiatrists for exchange

- **A major journal, European Neuropsychopharmacology**

- **More than 300 Young Researchers trained every year**
  - Paid for by ECNP

Largest non-institutional supporter of applied and translational neuroscience research and education in Europe

Advancing young researchers and psychiatrists

- **Three Schools**
  - 5 Week-long programmes of training for 5x50 (250) young psychiatrists (Oxford, Venice)
  - General (2); Child and Adolescent (2); Old Age
- **Two Workshops**
  - Annual 3-day interactive Neuropsychopharmacology workshop for 100 young scientists/psychiatrists (Nice, France, Spring). *MJ Millan, Chair.*
  - Three-day interactive workshop on Clinical Research Methods for 25 junior psychiatrists.

All participants supported by ECNP for travel, registration and accommodation

ECNP

28th ECNP Congress

29 August-1 September 2015, Amsterdam

- Europe's largest meeting for applied and translational neuroscience.
- 6 plenary lectures, 80 long talks, 16 Young Scientist short talks, hundreds of posters, 7 educational update sessions.
- **Junior scientists/psychiatrists**
  Free registration if abstract accepted for publication, and 50 Travel Awards of € 500 for best Abstracts.

For the science and treatment of disorders of the brain

Register at **www.ecnp-congress.eu**

We welcome you

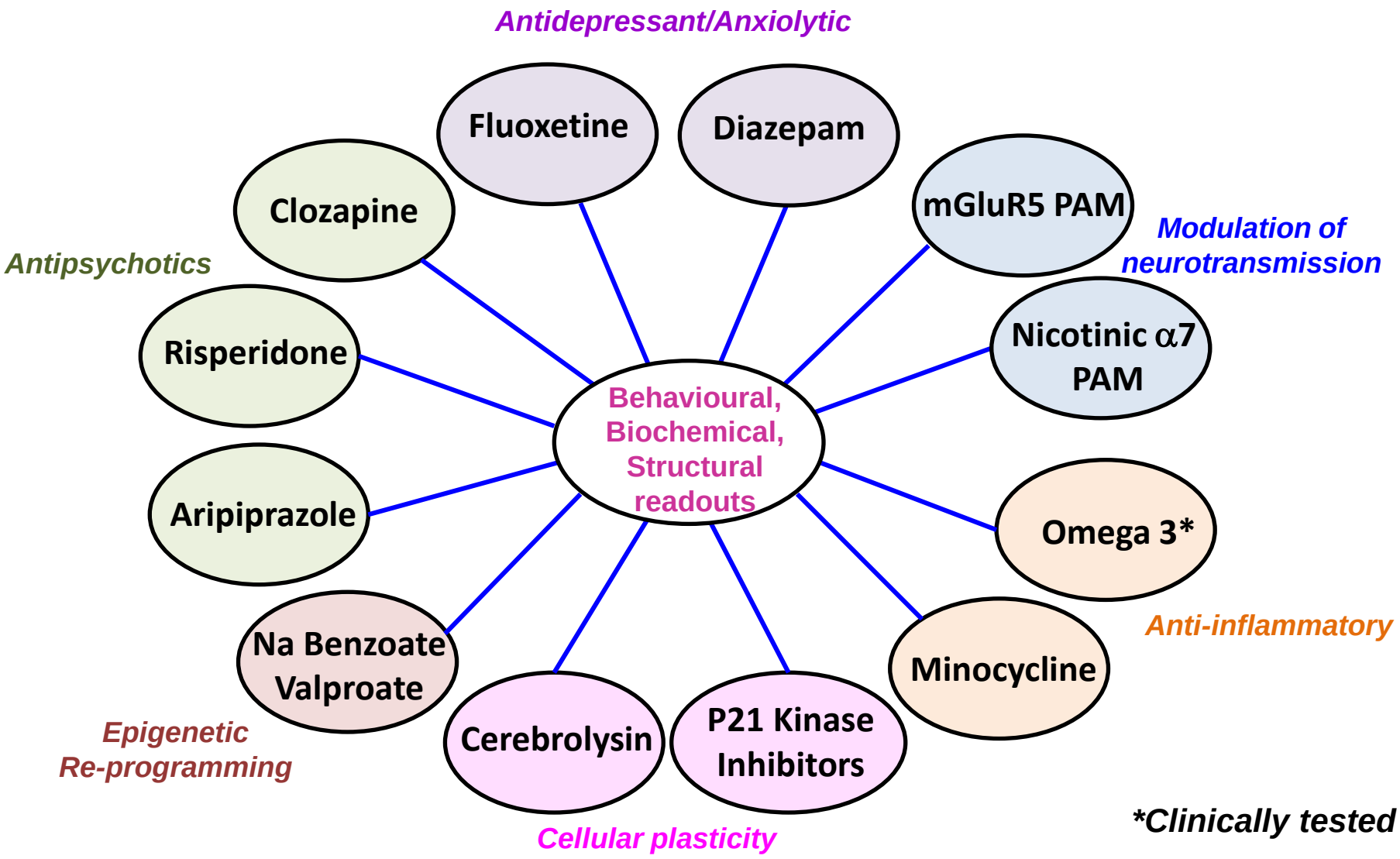
Young Psychiatrists and Scientists to join us !!

Our mission:

To advance the science of the brain, to promote brain health, and to improve the treatment of brain disorders

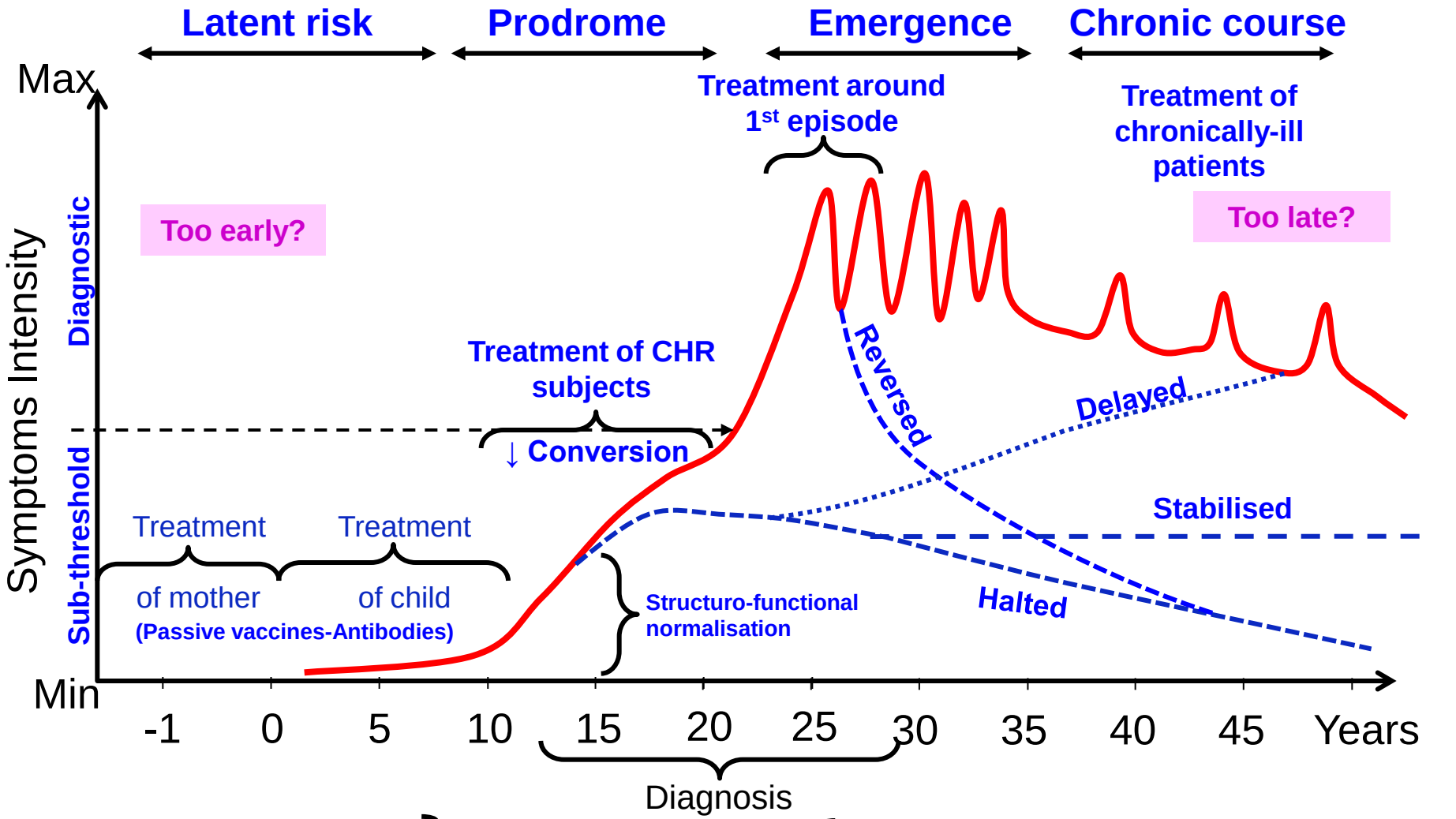
RESERVE

DIVERSE MECHANISMS PREVENT ONSET OF SCHIZOPHRENIA-LIKE SYMPTOMS IN ADULT RODENTS UPON ADOLESCENT ADMINISTRATION

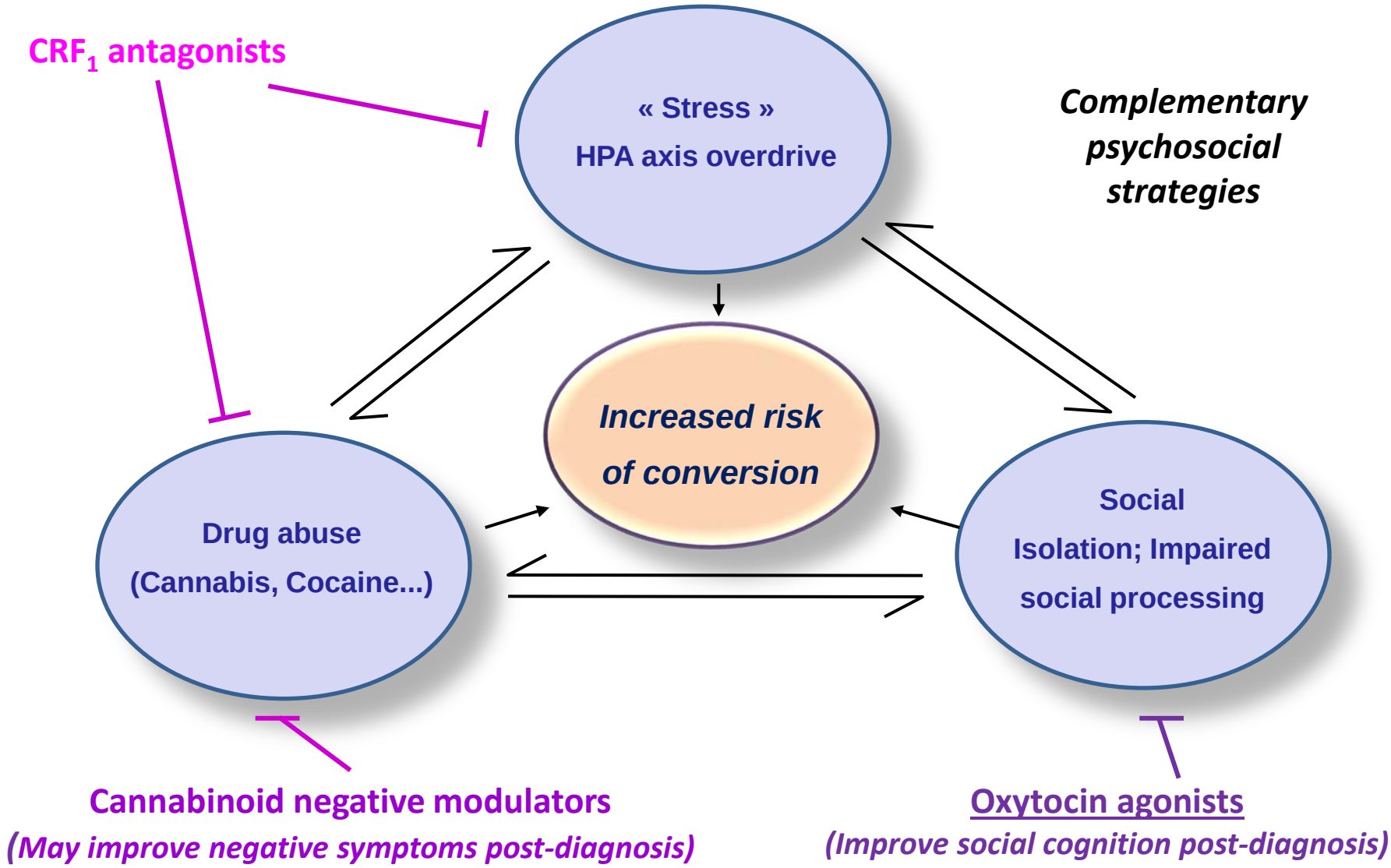


Also environmental enrichment and cognitive training

CHRONOLOGY OF SCHIZOPHRENIA: DISEASE MODIFICATION, WHEN TO TREAT AND THEORETICAL CONSEQUENCES

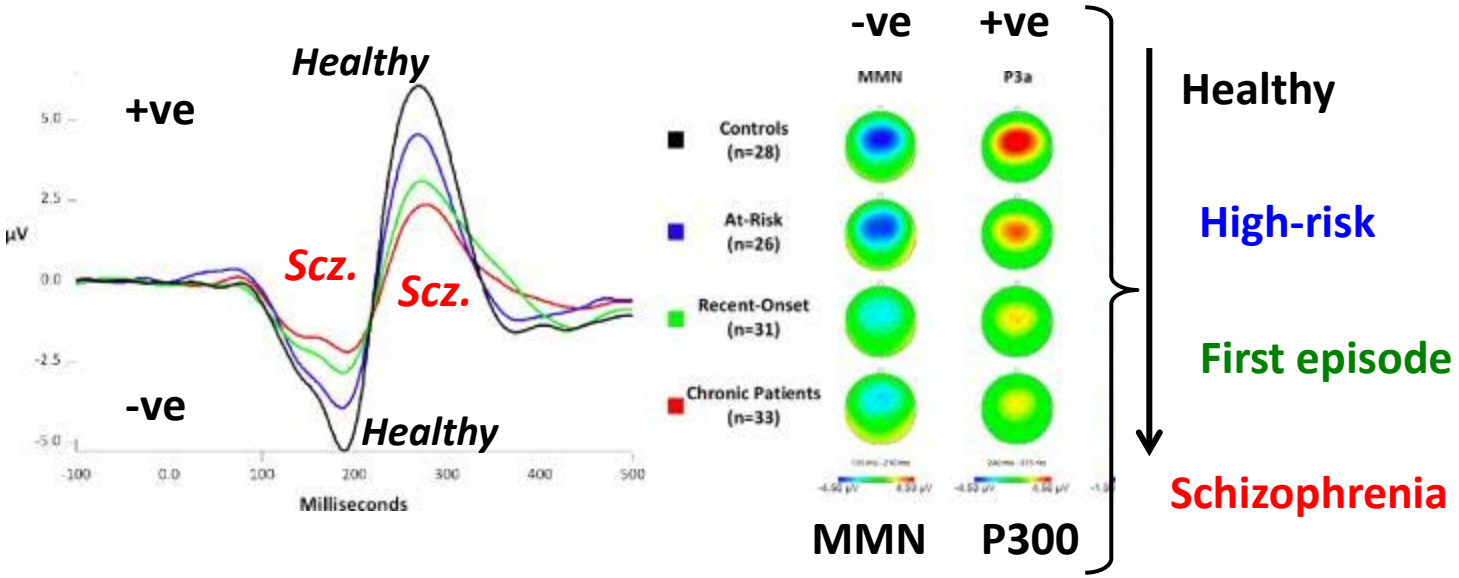


FACTORS IN ADOLESCENTS/YOUNG ADULTS INCREASING RISK FOR SCHIZOPHRENIA: PRIMARY PREVENTION TO THERAPY?



EEG BIOMARKER OF HIGH-RISK: REDUCED RESPONSE TO AN "ABERRANT" INPUT IN A TRAIN OF SIMILAR AUDITORY STIMULI

EEG readout to a «deviant« stimulus

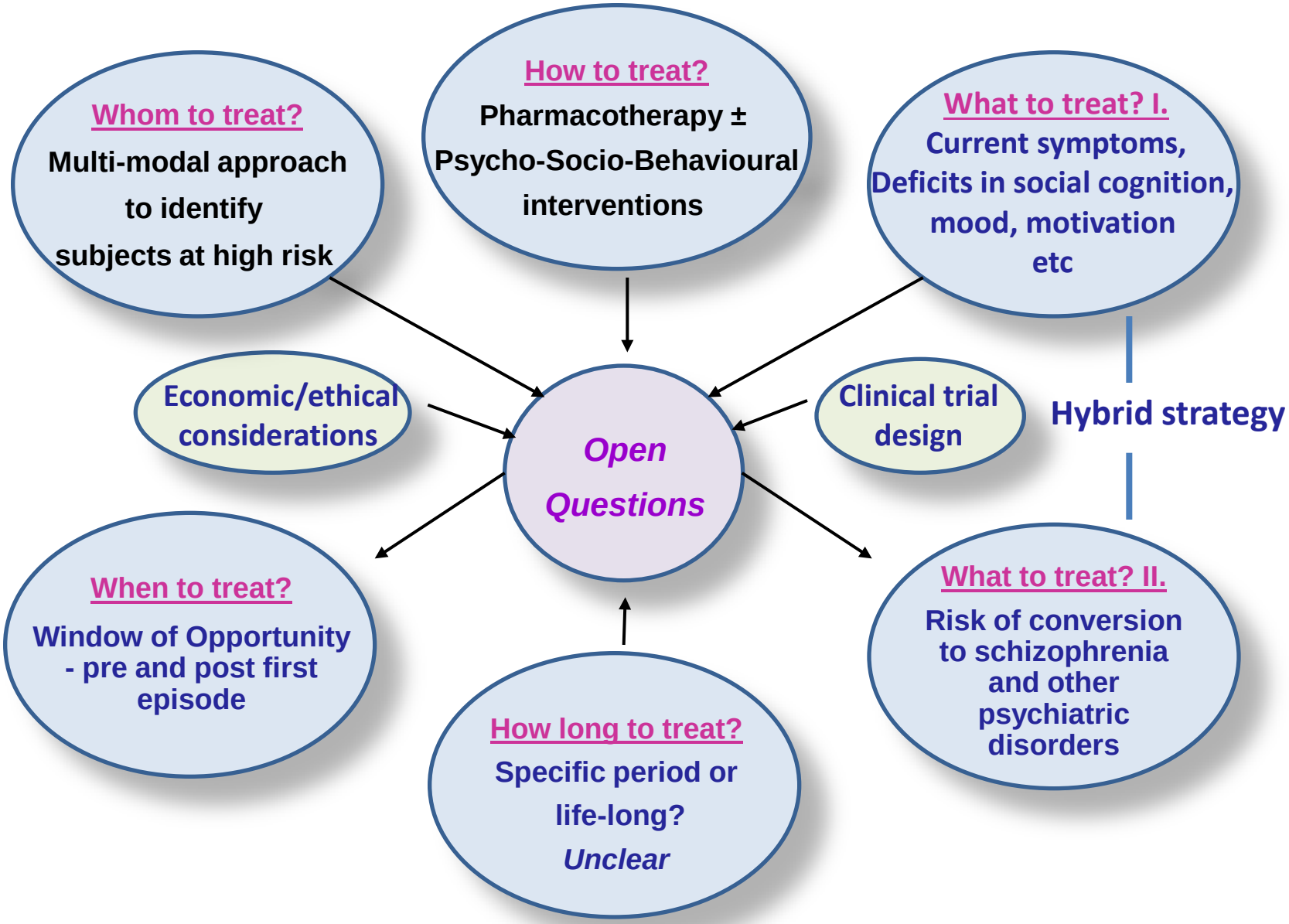


Deflection

- **Negative = MMN (Miss-Match Negativity) at 200 msec**
- **Positive = P300 at 300 msec**

Jahshon C et al., Psychological Medicine, 2012

ALTERING THE COURSE OF SCHIZOPHRENIA: MAJOR QUESTIONS AWAITING CLARIFICATION



SOCIAL COGNITION*:
CORE FEATURES AND RELEVANCE TO SCHIZOPHRENIA

Social cognition is profoundly disrupted in schizophrenia and more closely linked to real-world dysfunction than deficits in classical neurocognition

***Processes used to:**

- **Monitor and interpret social signals from others**
- **Decipher their mind-set, emotional state and intentions**
- **Understand social situations and rules of interaction**
- **Adopt appropriate social behaviour.**

SOCIAL COGNITION: CONSTRASTING DIMENSIONS IN HUMANS *VS* OTHER SPECIES?

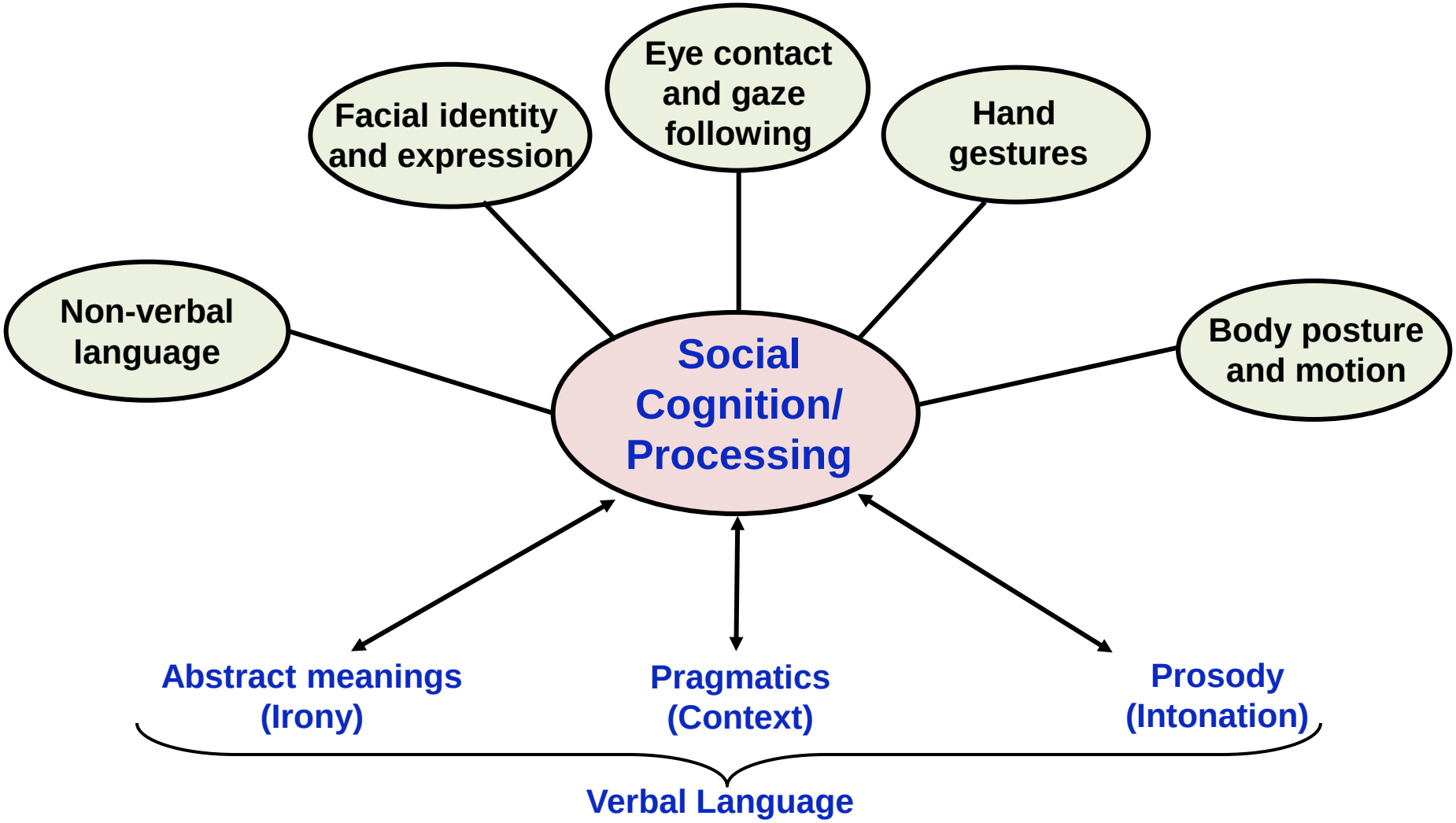
Past Recollection ***Future Prospection***	**Gaze, Face, Gesture, Body motion**	**Semantics, Prosody, Pragmatics**	**TOM (Self/Other), Introspection**
			At least certain dimensions
Episodic Memory	**Visual > Tactile/ Olfactory**	**Verbal (Written!)**	**Flexible Mental Representation**
Rudimentary - Past	**Olfactory/Tactile > Visual**	**Vocal (USV)**	**Notions of Intention**
<u>Non</u>-Autonoeitic (<u>No</u> Self-Projection)	**Recognition (Partner, Kin, Stranger…)**	**Communication (Sexual, Agonistic…)**	**(Instinct/Associative Learning?)**

Humans (Great Apes, Higher Birds, Dolphins, Elephants*)

Rodents (Rats, Mice, Prairie Voles…)

“Mind the gap”

SOCIAL COGNITION: MULTIPLE SOURCES OF INFORMATION FOR GUIDING SOCIAL BEHAVIOUR - PROFOUND DISRUPTION IN SCHIZOPHRENIA

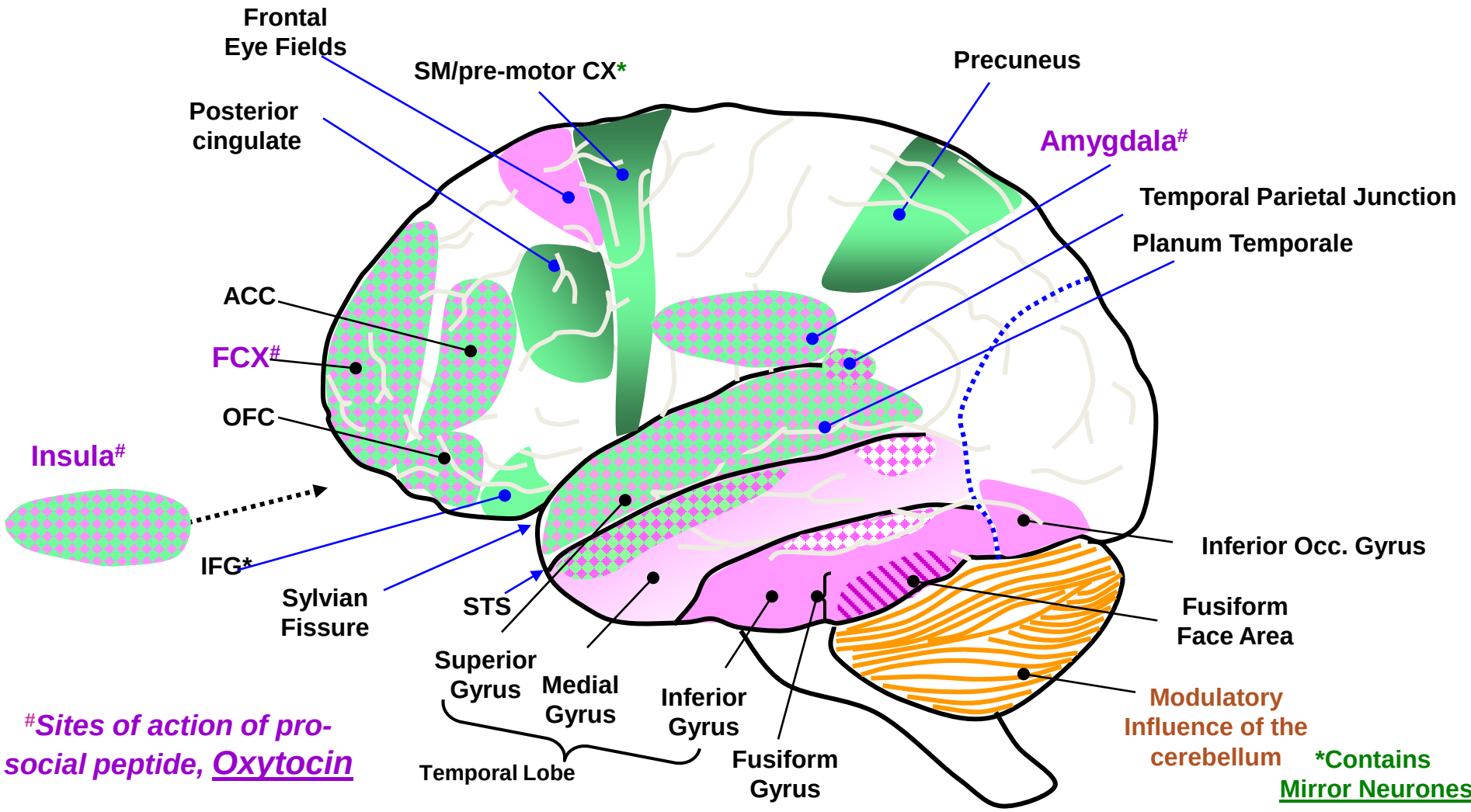


Interpretation of social cues to assess emotional/mental states and intentions of others

Social Cognition

Appropriate social behaviour

SOCIAL COGNITION: DISTRIBUTED CEREBRAL CIRCUITS DISTINCT TO THOSE RECRUITED BY CONVENTIONAL COGNITIVE DOMAINS



Millan MJ et al, Nature Rev Drug Disc, 2012

OXYTOCIN: BROAD-BASED «PRO-SOCIAL» EFFECTS RELEVANT TO SCHIZOPHRENIA

Volunteers, Autistic Subjects and Schizophenics

Actions* in rodents (only certain elements) and humans

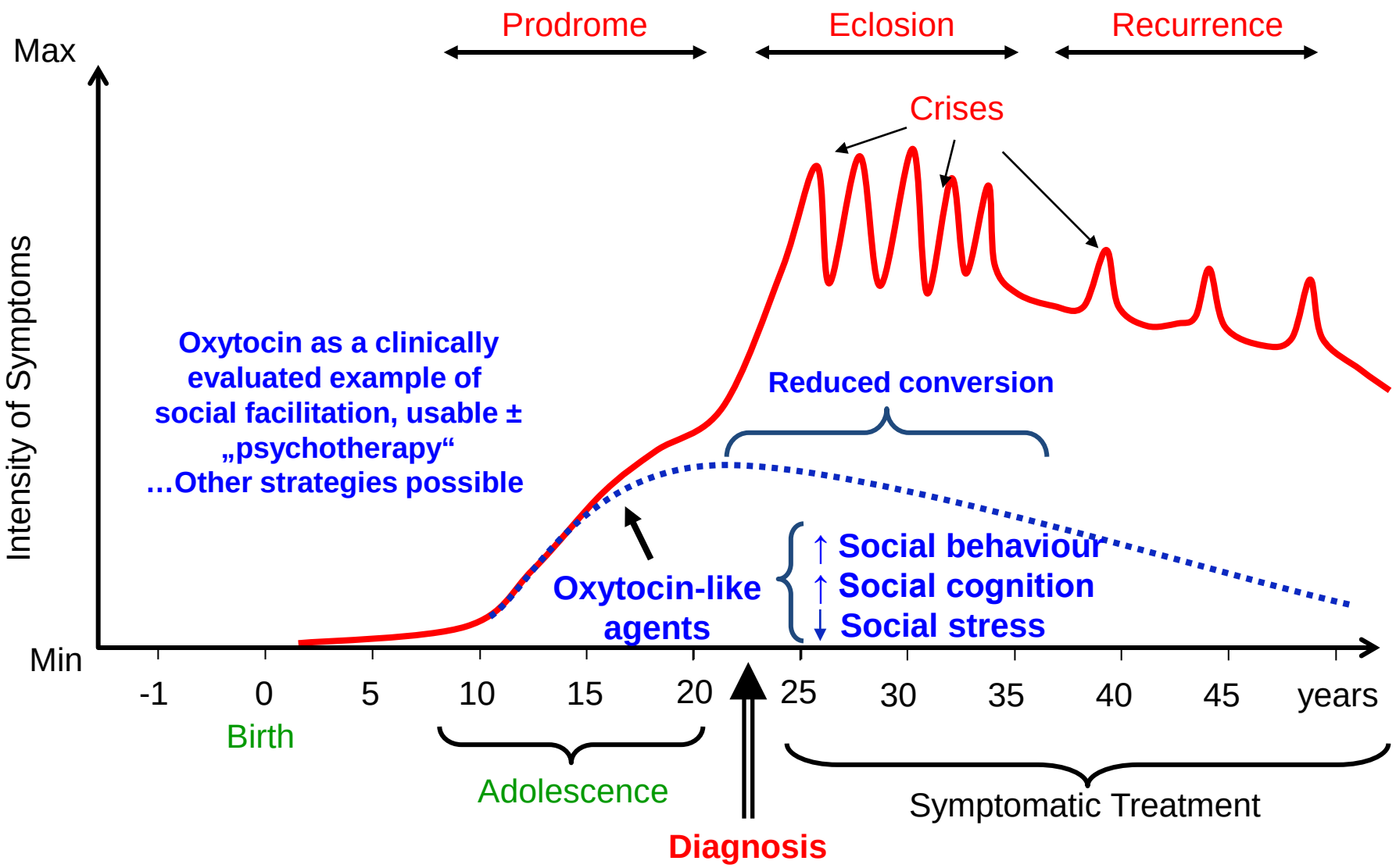
- ↑ Social recognition
- ↑ Eye-gaze following
- ↑ Theory of mind
- ↑ Trust and empathy
- ↑ Positive attribution bias
- ↑ Social approach/preference
- ↓ Social anxiety

Frontal cortex, medial amygdala, lateral septum, insula, medial pre-optic hypothalamus

Oxytocin, key and translatable validator for experimental models of social cognition and schizophrenia

****Note: some data suggest a more complex, non-unitary role, at least long-term***

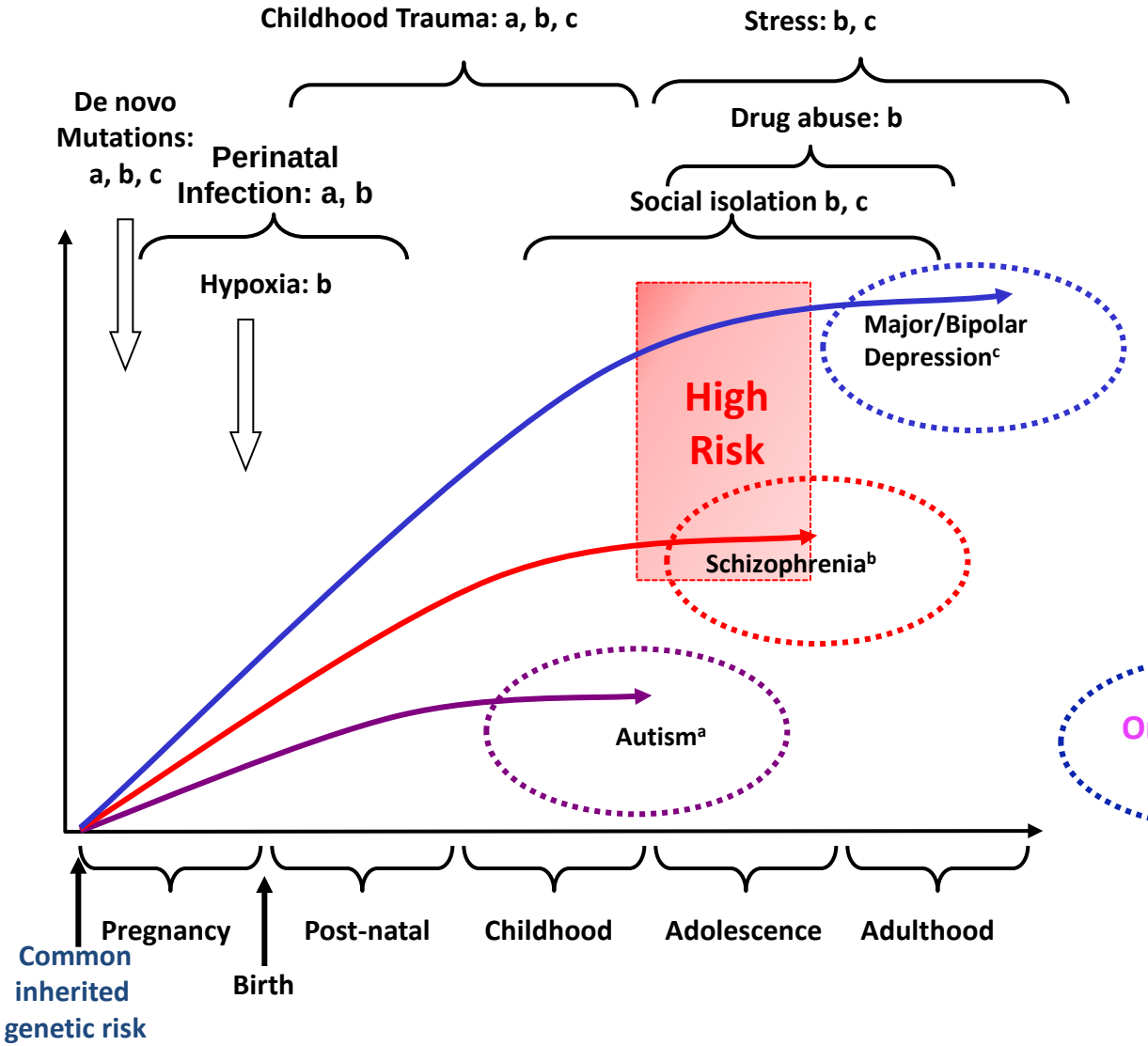
CORRECTING SOCIAL COGNITION DEFICITS AS A « HYBRID » STRATEGY TO ALTER THE COURSE OF SCHIZOPRHENIA ?

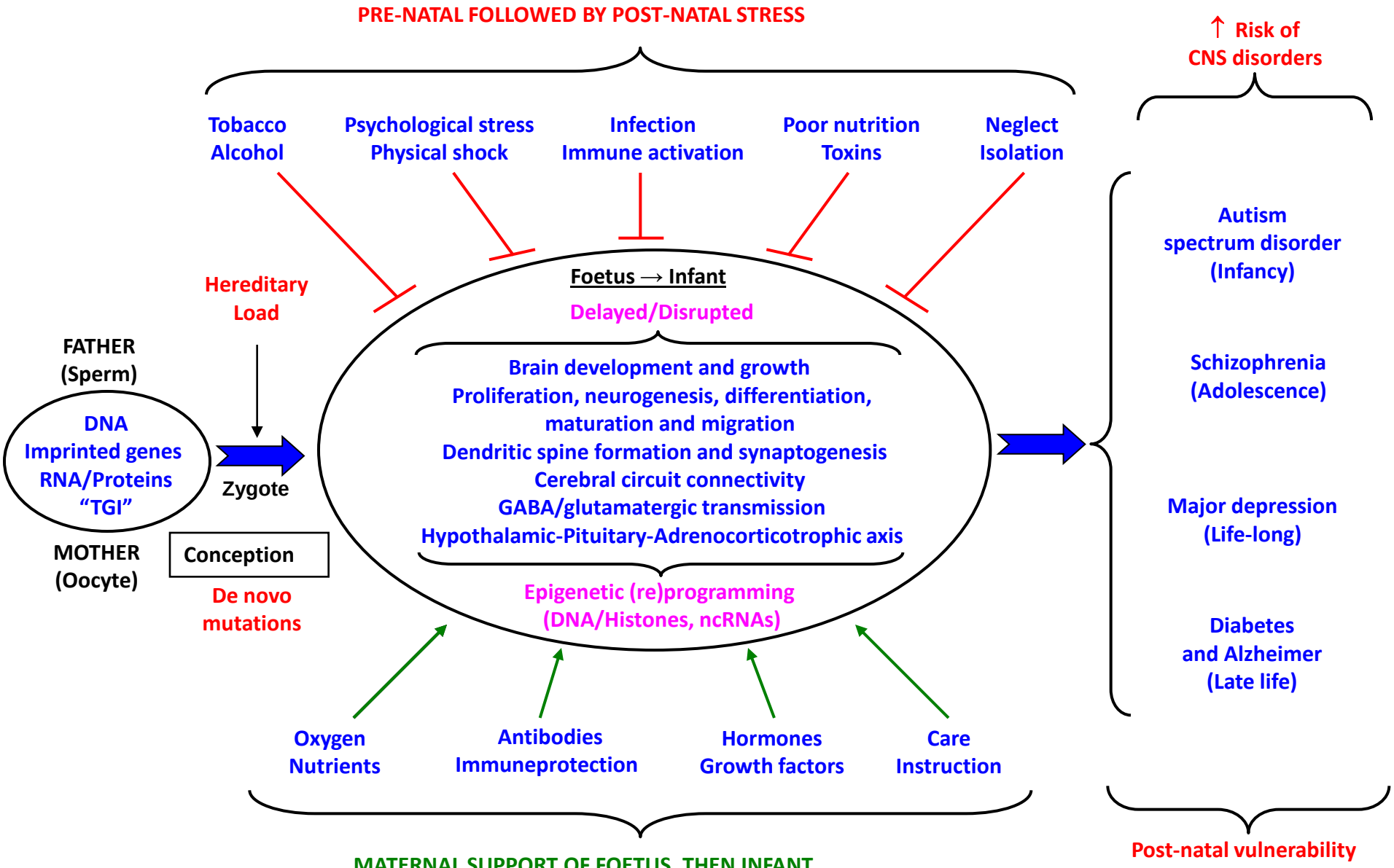


EVEN WITH SAME RISK GENES, ONE MAY DEVELOP CONTRASTING PSYCHIATRIC DISORDERS

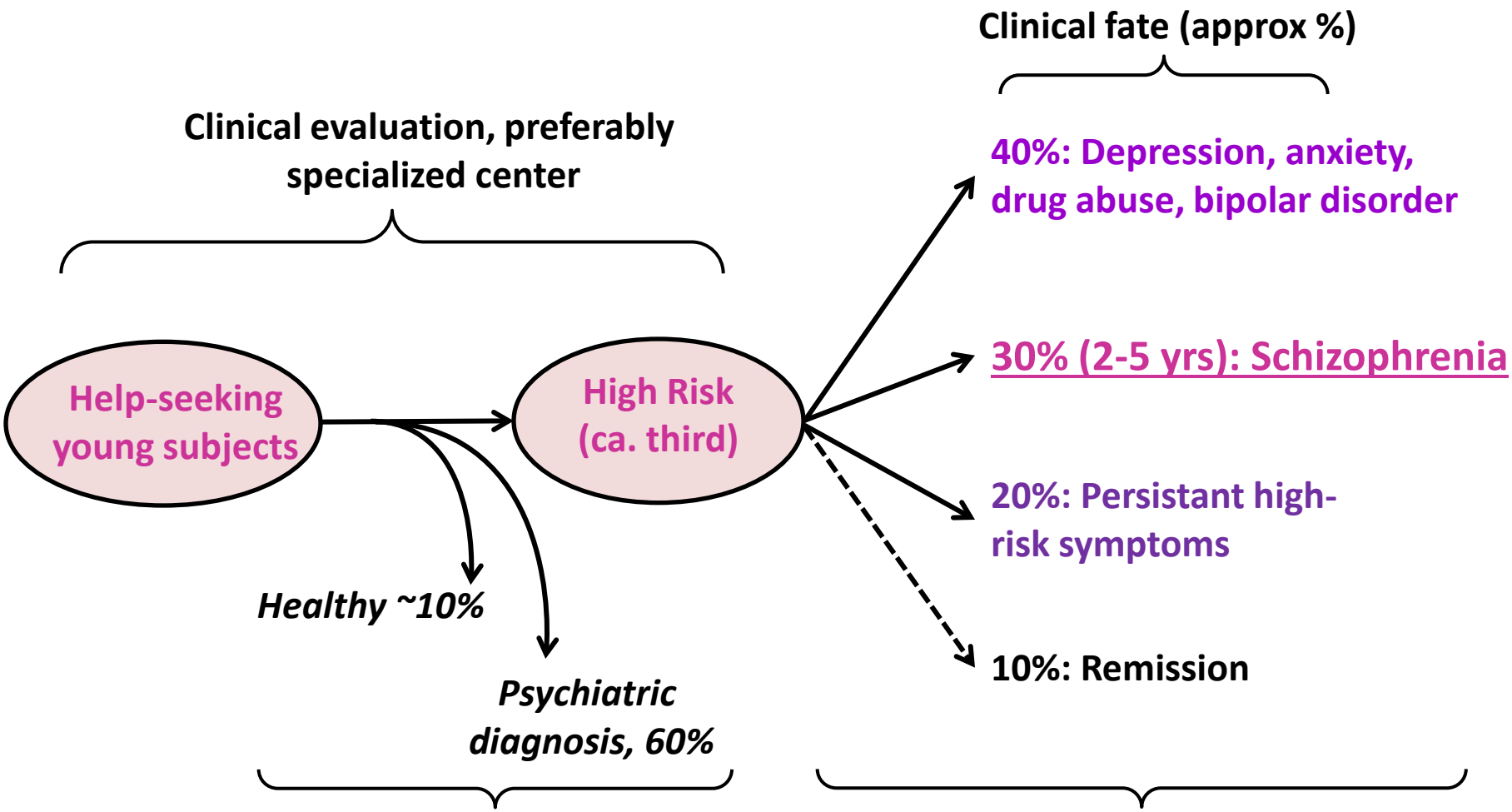
Similar genetic profiles from conception on..

Environment and epigenetics drive to contrasting fates



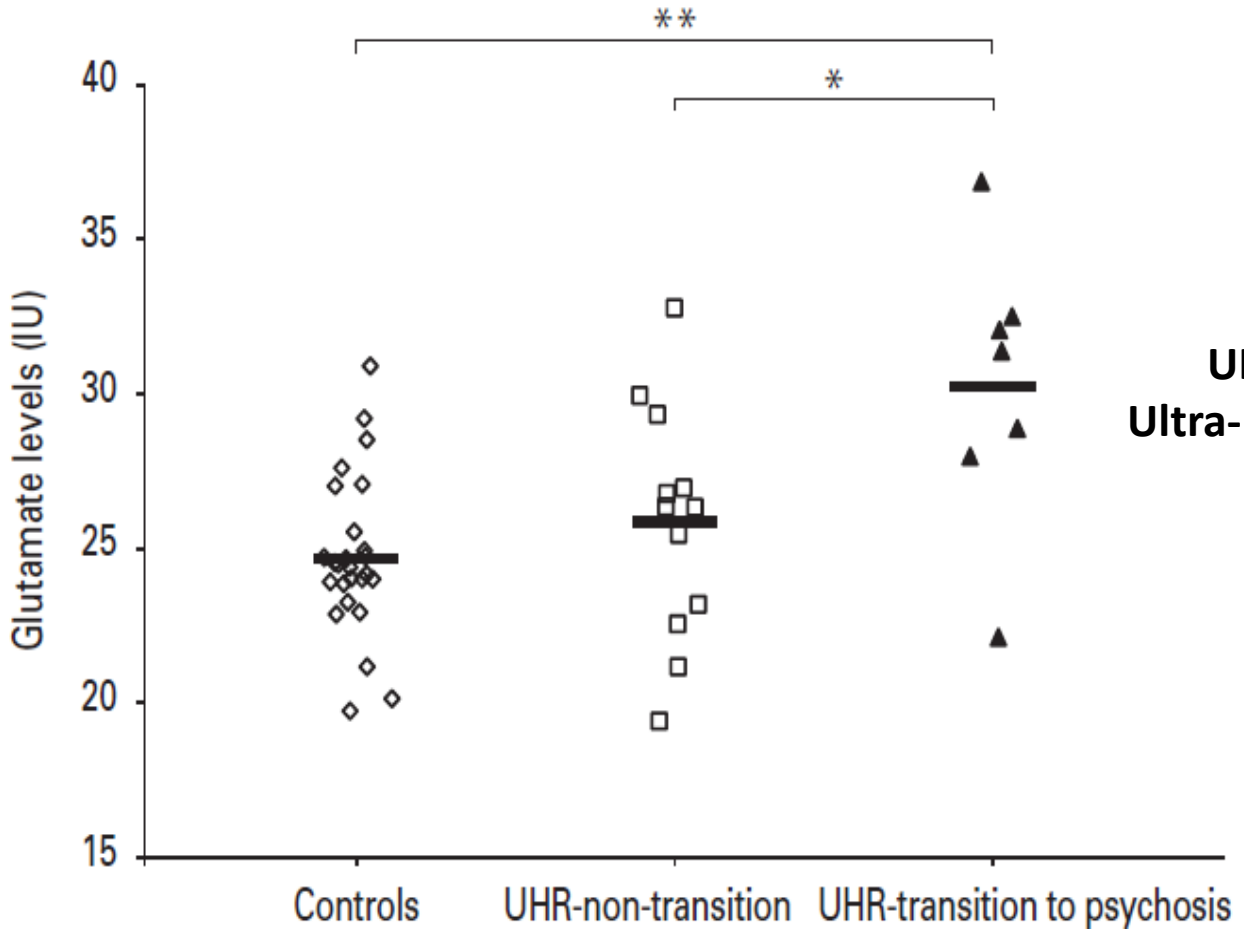

PRE-NATAL FOLLOWED BY POST-NATAL STRESS
↑ Risk of CNS disorders
Tobacco
Alcohol
Psychological stress
Physical shock
Infection
Immune activation
Poor nutrition
Toxins
Neglect
Isolation
Hereditary Load
FATHER (Sperm)
DNA
Imprinted genes
RNA/Proteins
"TGI"
Zygote
MOTHER (Oocyte)
Conception
De novo mutations
Foetus → Infant
Delayed/Disrupted
Brain development and growth
Proliferation, neurogenesis, differentiation, maturation and migration
Dendritic spine formation and synaptogenesis
Cerebral circuit connectivity
GABA/glutamatergic transmission
Hypothalamic-Pituitary-Adrenocorticotrophic axis
Epigenetic (re)programming
(DNA/Histones, ncRNAs)
Autism spectrum disorder (Infancy)
Schizophrenia (Adolescence)
Major depression (Life-long)
Diabetes and Alzheimer (Late life)
Oxygen
Nutrients
Antibodies
Immuneprotection
Hormones
Growth factors
Care
Instruction
MATERNAL SUPPORT OF FOETUS, THEN INFANT
Post-natal vulnerability

CONTRASTING FATES OF SUB-DIAGNOSTIC « HIGH-RISK » SUBJECTS



Fusar-Poli P. et al, Am J Psychiatry 2013

INCREASED GLUTAMATE IN STRIATUM PREDICTS CONVERSION TO PSYCHOSIS: MAGNETIC RESONANCE SPECTROSCOPY

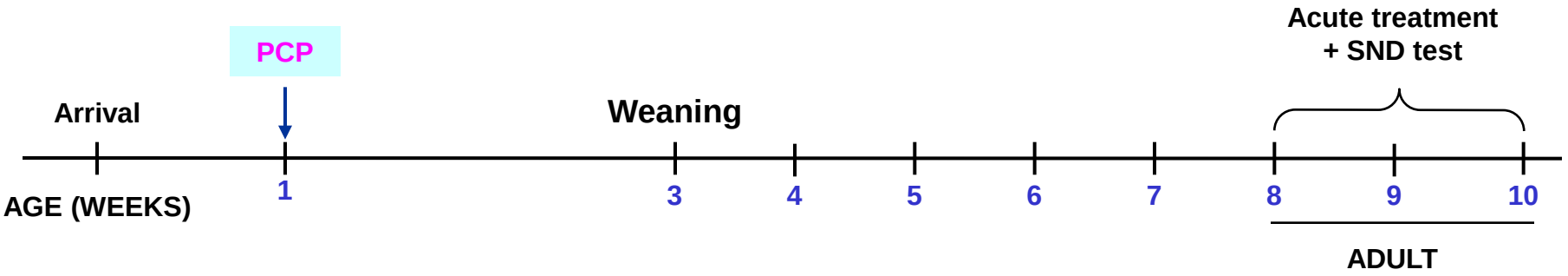


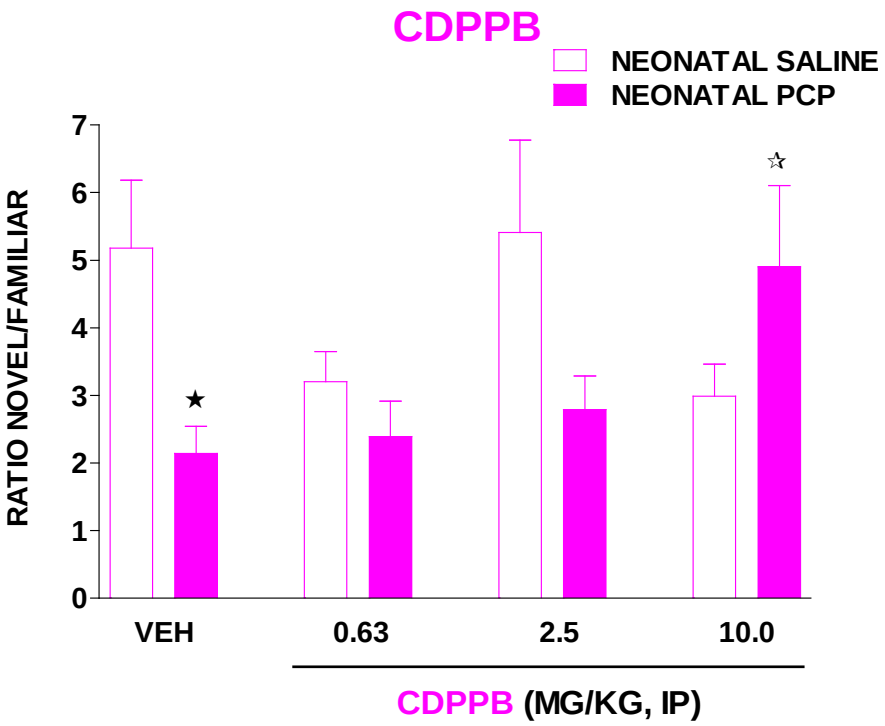
UHR:
Ultra-High Risk

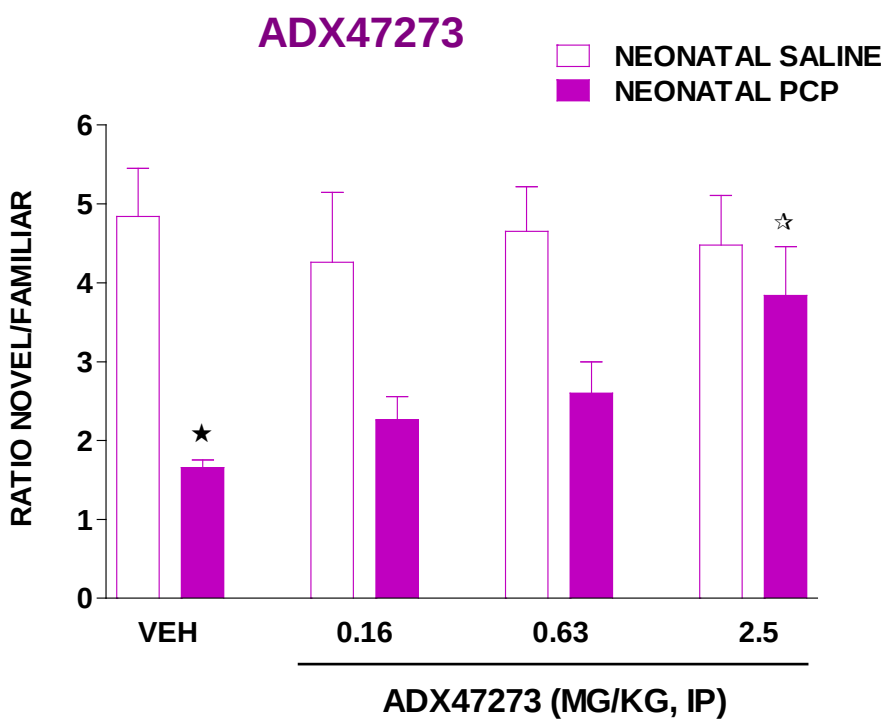
de la Fuente-Sandoval, et al., 2013

RESCUE BY mGluR5 IN ADULT RATS OF UPON A SOCIAL COGNITION DEFICIT INDUCED BY NEONATAL PCP

Acute administration at *early* <u>*adult stage*</u>



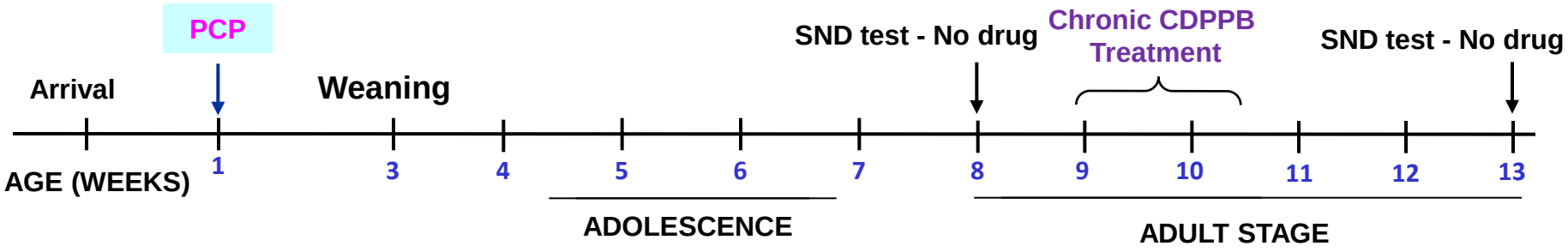


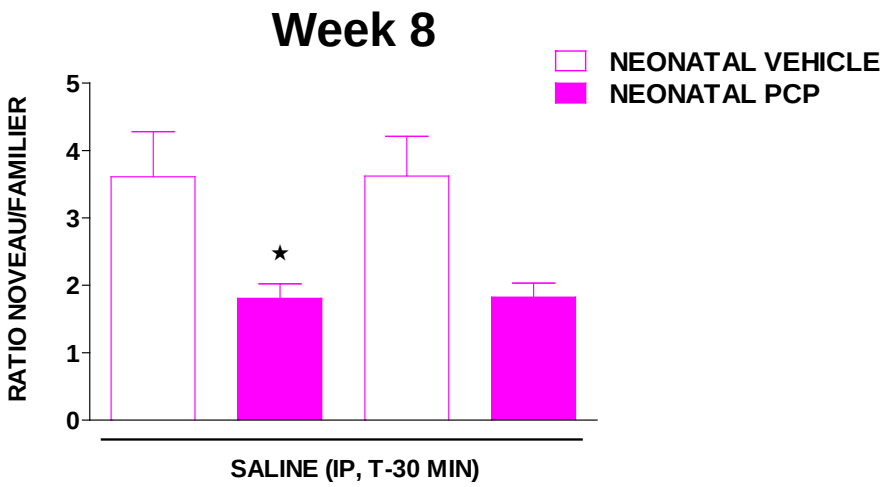


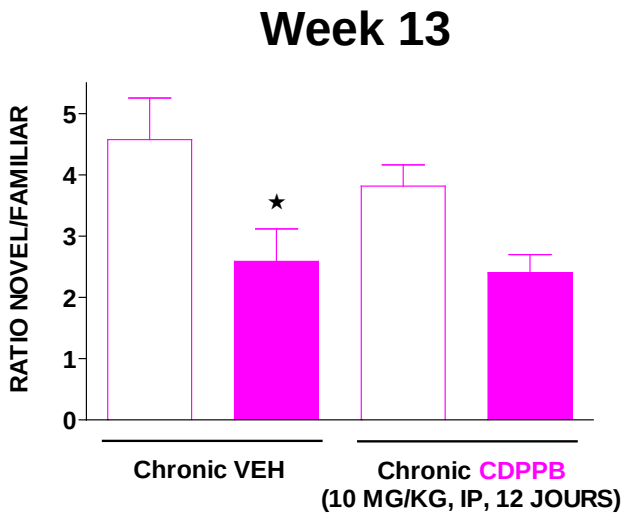
$mGluR_5$ PAMs *<u>rescue</u>* established deficits in adults.

INFLUENCE OF mGluR5 PAMs UPON DEFICIT OF NOVELTY DISCRIMINATION INDUCED BY NEONATAL ADMINISTRATION OF PCP

Chronic administration to adult rats
Measurement in adult rats







No influence of mGluR5 PAMs when chronically administered at adult stage

NEONATAL ADMINISTRATION OF PCP CHARACTERISATION IN ADULTS

BEHAVIOUR

- **Hyperactivity and hypersensitivity to locomotor effects of amphetamine and NMDA antagonists.**
- **Social interaction deficit.***
- **Cognitive deficits* : social cognition (Soc Disc), sensory-motor gating (PPI), executive function (reversal learning) and working memory (T-maze, radial maze).**

MORPHOLOGY AND NEUROCHEMISTRY

- **↓ Volume of hippocampus .***
- **↑ Apoptose – neuronal death.**
- **↓ GABA interneurones in frontal cortex and hippocampus .***
- **↓ NMDA, D_2 and $GABA_A$ receptor expression.***
- **Changes in DISC1 expression**

*** Like schizophrenia**

EXPERIMENTAL MODELS FOR STUDYING NEGATIVE SYMPTOMS AND THEIR CONTROL

Models (can be combined) | **General read-outs (preferably multiple)** | **NS Sub-domains (may overlap)**

[a] *Acute, sub-chronic, long-term and withdrawal*

Pharmacological[a]:

- NMDA antag.
- Cannabinoid (CB1) modn
- Haloperidol (secondary)

Genetic[b]:

- D_3R Overexp.
- Oxytocin R KO
- CNVs (22q11.2)

Developmental:

- Peri-natal Inflammation
- Neonatal PCP
- Adolescent isolation

[b] *Single gene - examples, Copy Number Variants (CNV)*

Behavioural:

- Self-stim / Sucrose consumption/preference (hedonic state)
- Locomotion (approach/exploration etc)
- Operant lever pressing
- Place conditioning
- Nest-building

Mechanistic (cells to circuits):

- Biochemistry
- Neurochemistry (dialysis)
- Electrophysiology
- Structural/functional imaging

[a] *PCP-disrupted*

Asociality[a]:

- Soc. preference
- Soc. interaction
- Soc. place pref

Blunted affect:

- USV
- Touch/grooming

Amotivation/ Anhedonia[b]:

- PR: Working for
- reward (effort)
- Adolescent play

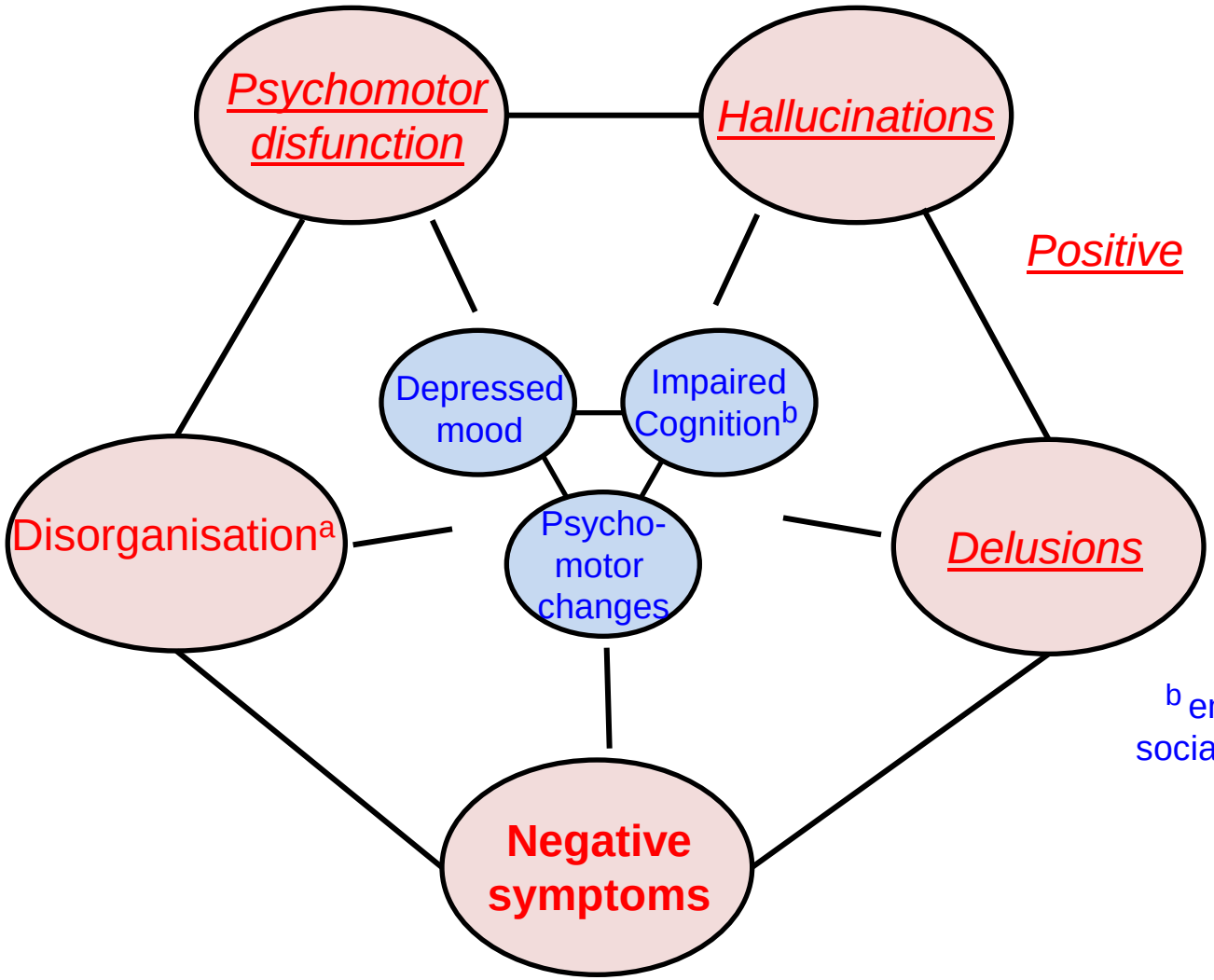
[b] *Anticipatory*

Selected for GPR88 studies.
PR = Progressive Ratio.

MAJOR NEURODEVELOPMENTAL MODELS OF SCHIZOPHRENIA

Time	Protocol	Pathological Impact
G17	*Conception*	
	Exposure to methylazoxymethanol *in utero*	Disruption of genesis and migration of neurons
	Maternal viral infection	Maternal immune activation; Fetal brain damage
D0	*Birth*	
D7	Neonatal lesion of ventral hippocampus	Disruption of hippocampal-cortical circuits.
D9	Neonatal Phencyclidine (s.c.)	Blockade of NMDA receptor control of brain development
D11		
D21	Post-weaning isolation	Social isolation
	Adolescence	
D28	Cannabis, cocaine, PCP ("angel dust") administration	Drug abuse during adolescence
	Adulthood	
D60 And over	*Impairments in social cognition and social interaction; Hypersensitivity to psychotomimetics; Sensory-motor gating and neurocognitive deficits; Morphological and biochemical (GABA-Glu etc) anomalies*	

DSM-5 AND NEGATIVE SYMPTOMS: STILL A CARDINAL (« DEFINING ») SYMPTOM !

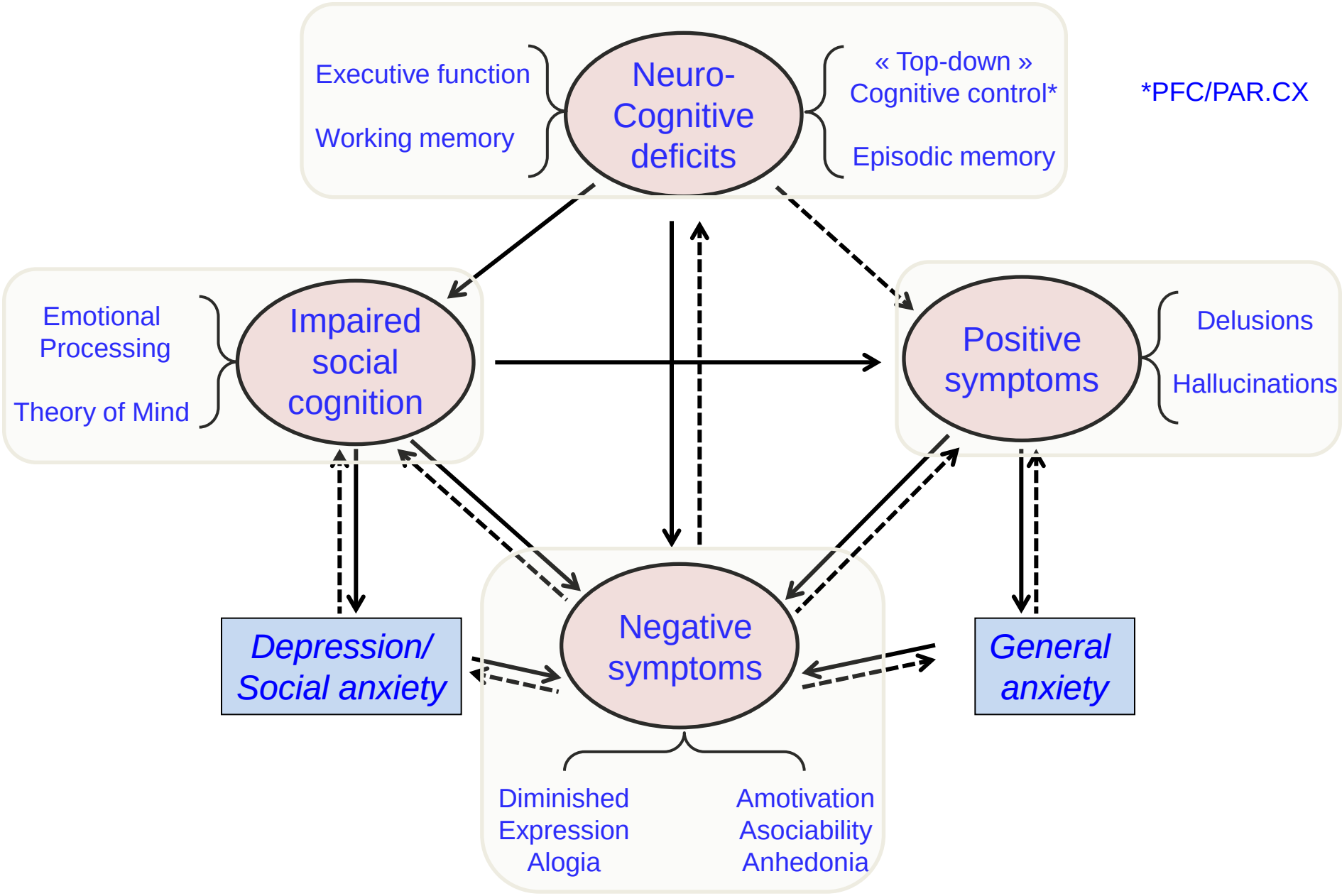


[a] in particular of speech

[b] embraces social cognition

« *Defining* » *symptoms* → DSM-5 diagnosis of schizophrenia ← « *Other relevant* » *symptoms*

LINKED


Executive function
Working memory
Neuro-Cognitive deficits
« Top-down » Cognitive control*
Episodic memory
*PFC/PAR.CX
Emotional Processing
Theory of Mind
Impaired social cognition
Positive symptoms
Delusions
Hallucinations
Depression/ Social anxiety
Negative symptoms
General anxiety
Diminished Expression
Alogia
Amotivation
Asociability
Anhedonia