Preventing Treatment Resistance in Schizophrenia:
The Potential of Optimized Early Course Interventions

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InSTAR
Individualized Schizophrenia Treatment And Reintegration

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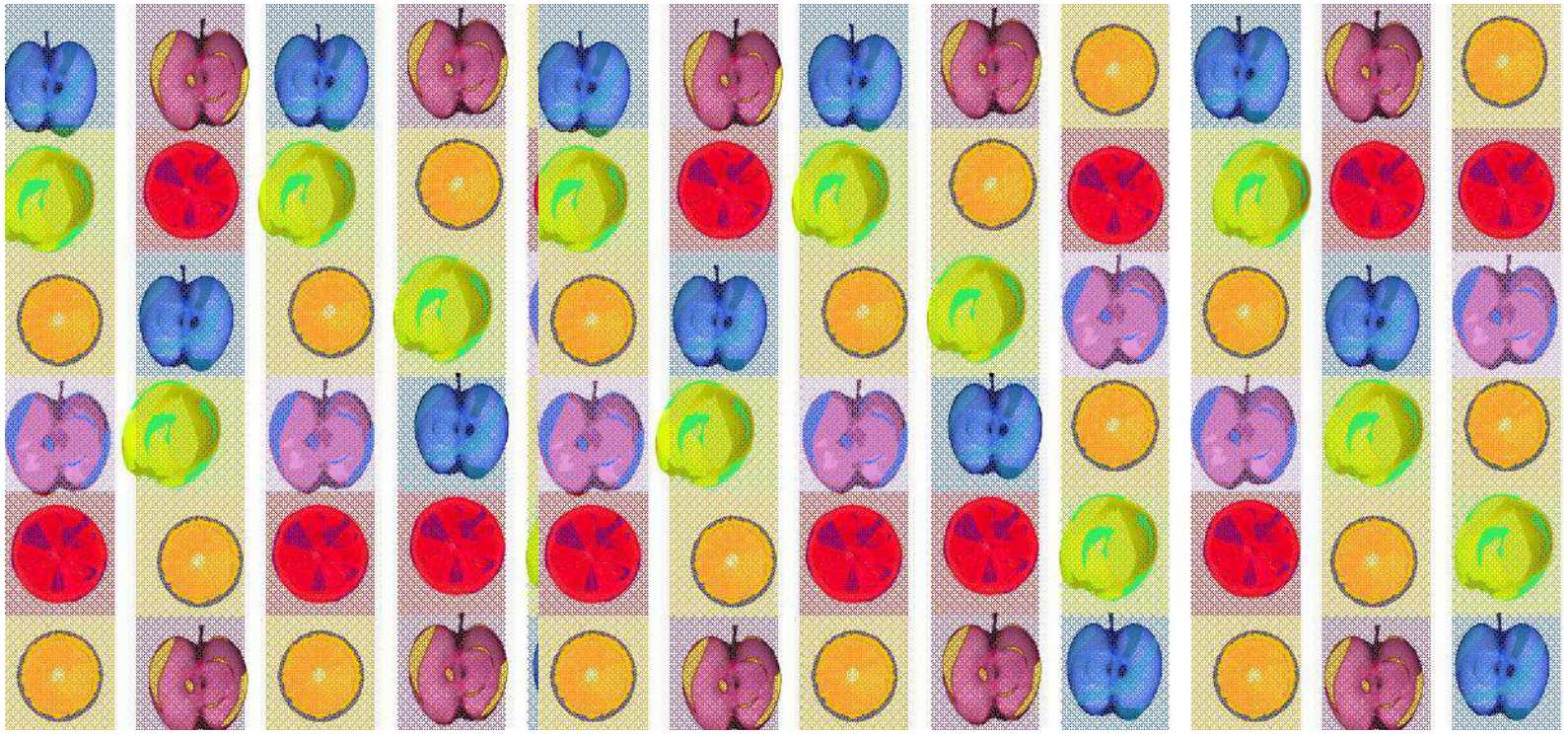
Schizophrenia – The Elusive Enigma

Understanding the molecular pathogenesis of schizophrenia has proved elusive, although there is no shortage of interesting hypotheses

“Desperate Times Call for Desperate Measures”



Many, many hypotheses…

Schizophrenia – the "Unique" Disorder

Schizophrenia – an epigenetic puzzle
[Gottesman and Shields, 1985]

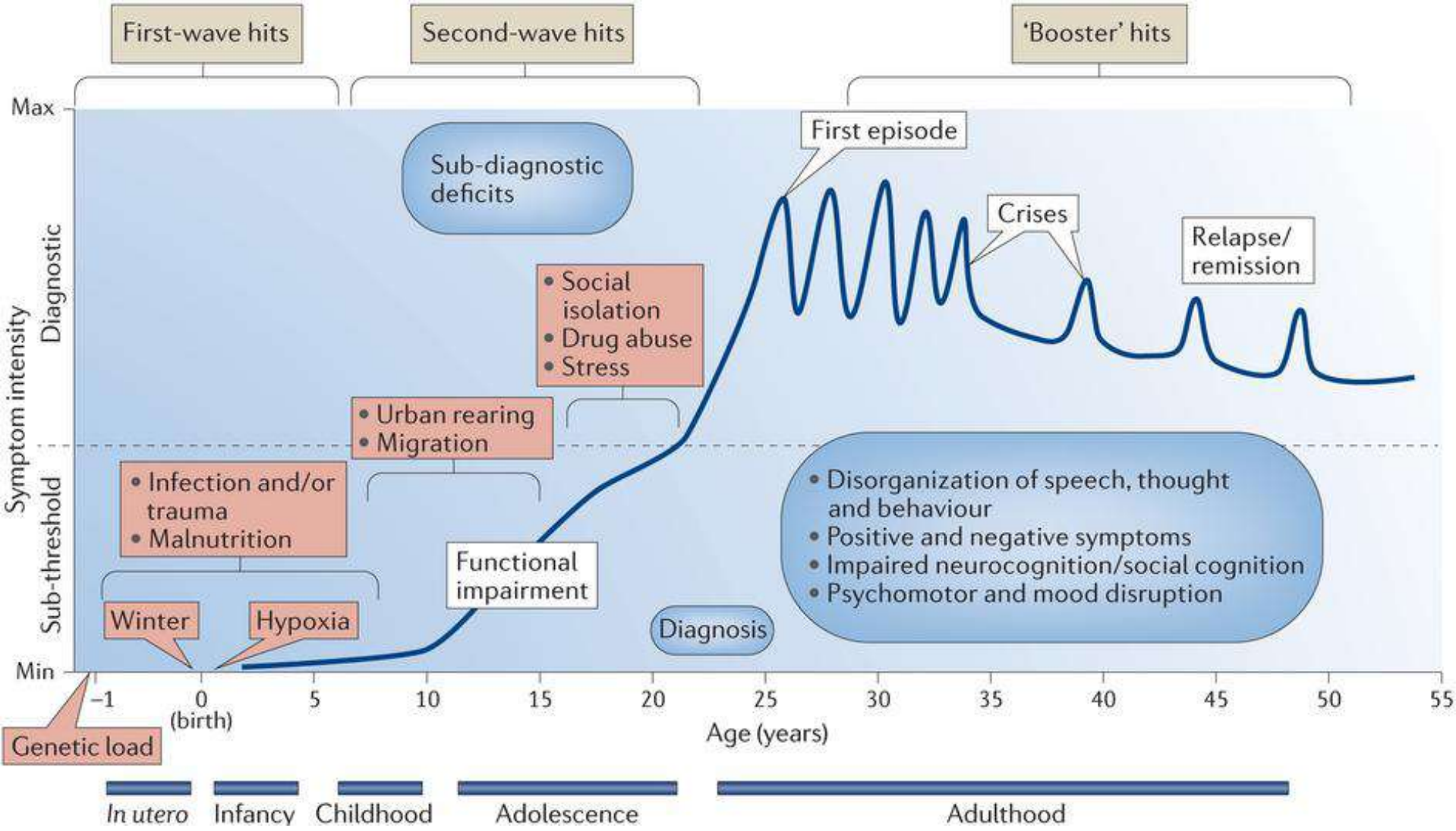
Schizophrenia is the illness that made us humans
[Horrobin 1998]

Is Schizophrenia the price that Homo Sapiens pay for language?
[Crow, 1998]

There is, in short, no such thing as schizophrenia
[Szasz, 1988]

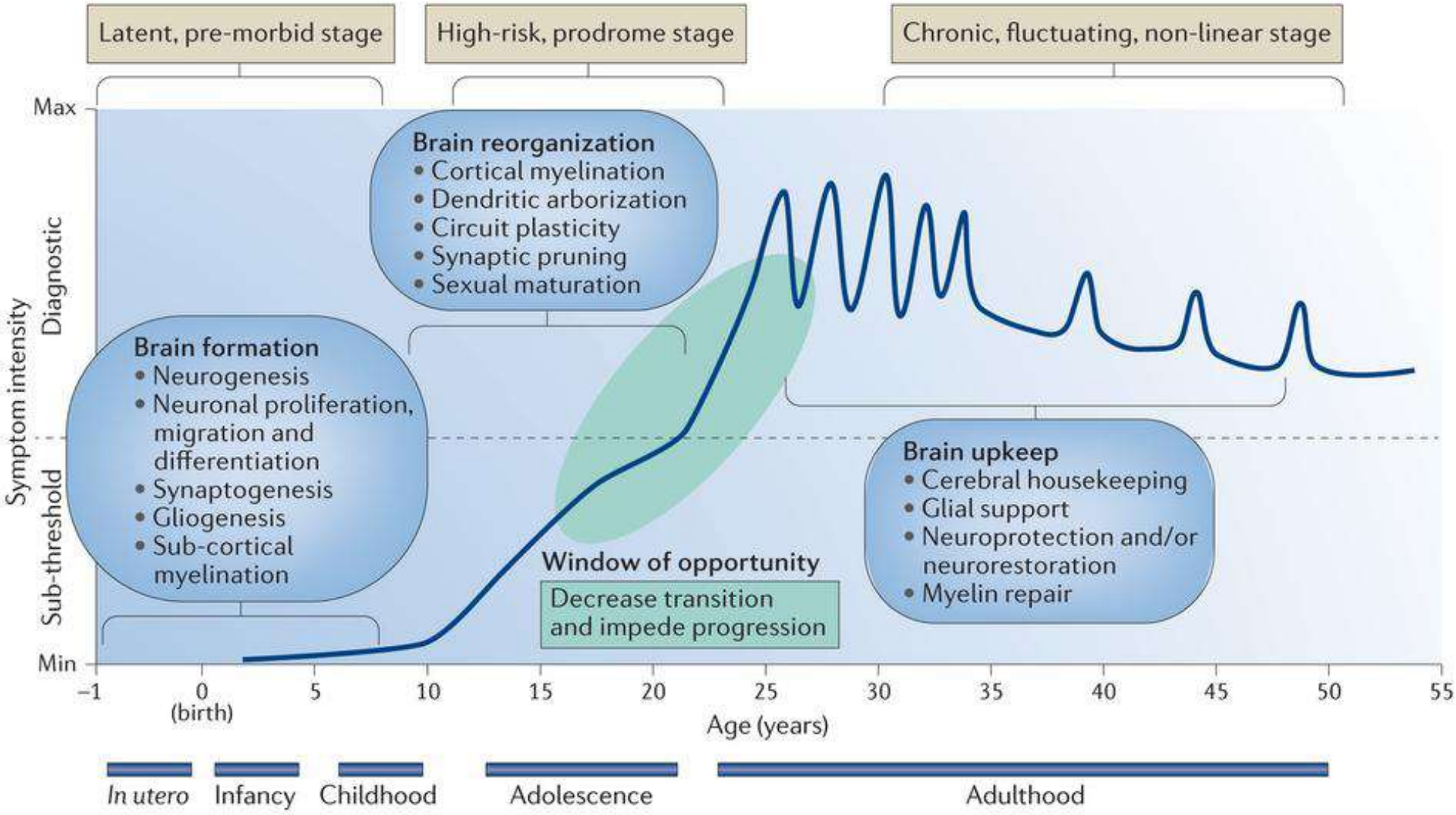
Early Course Schizophrenia: Neurobiology

Schizophrenia: Onset & Progression



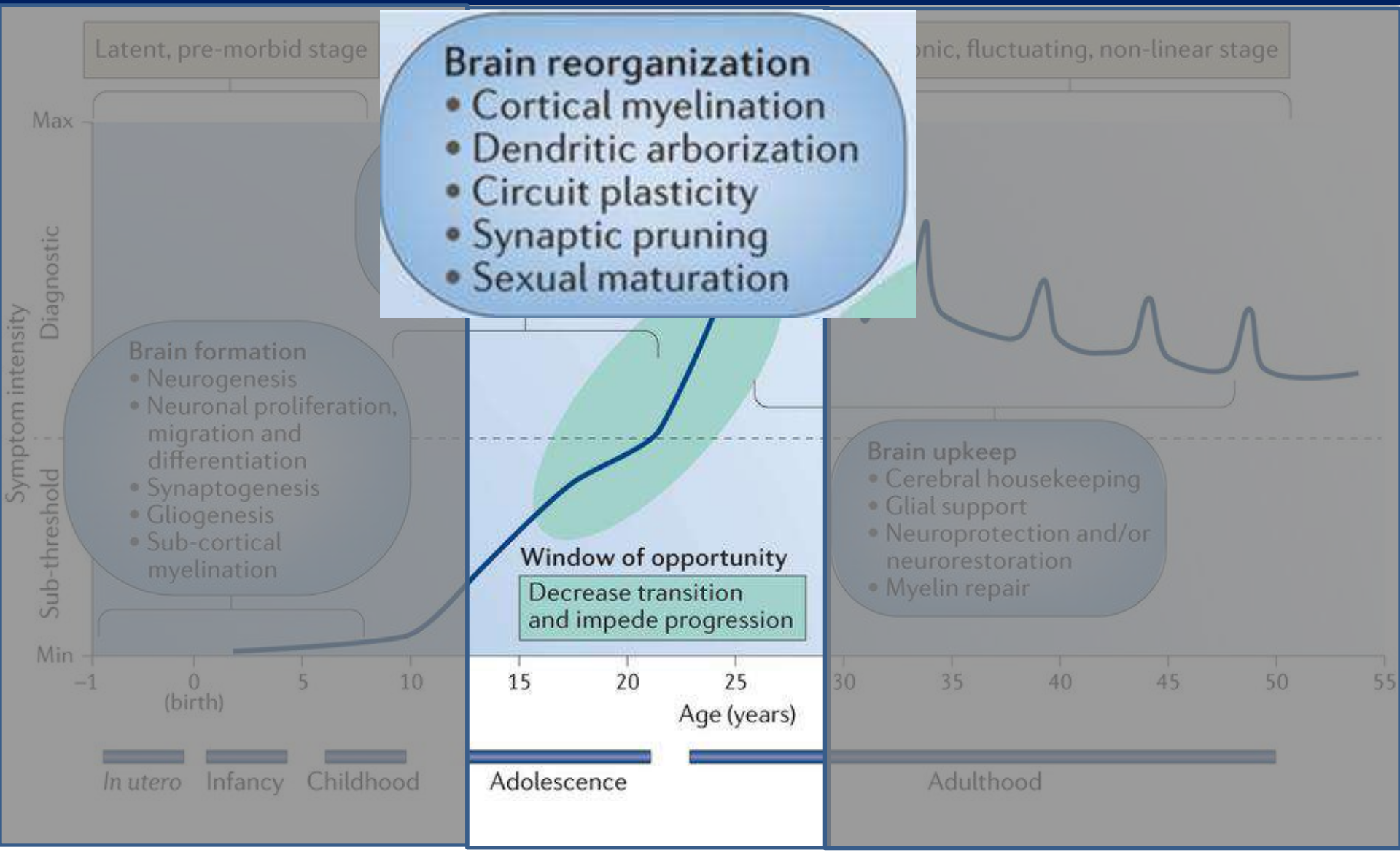
Millan et al 2016

Schizophrenia: Onset & Progression - Biology



Millan et al 2016

Early Course Schizophrenia : Window of Opportunity



Millan et al 2016

Molecular Psychiatry

EXPERT REVIEW

The neurobiology and treatment of first-episode schizophrenia

RS Kahn and IE Sommer

Brain Deficits in Early Course Schizophrenia

Available online at www.sciencedirect.com

SCIENCE DIRECT

ELSEVIER

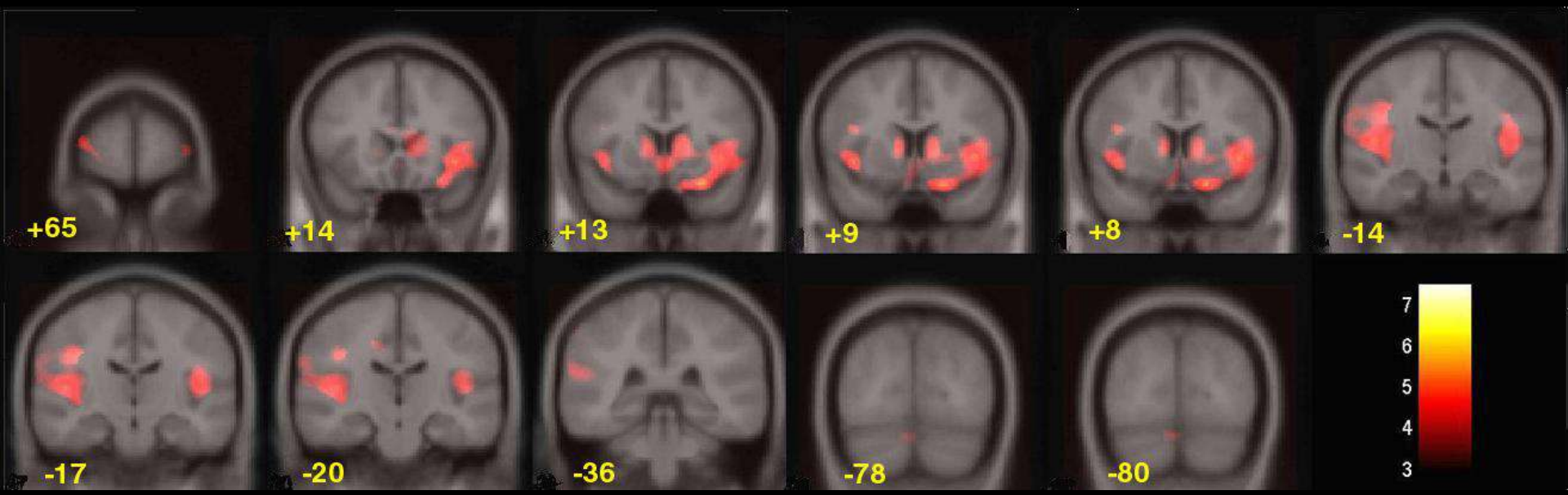
Progress in Neuro-Psychopharmacology & Biological Psychiatry 29 (2005) 587–591

Progress In Neuro-Psychopharmacology & Biological Psychiatry

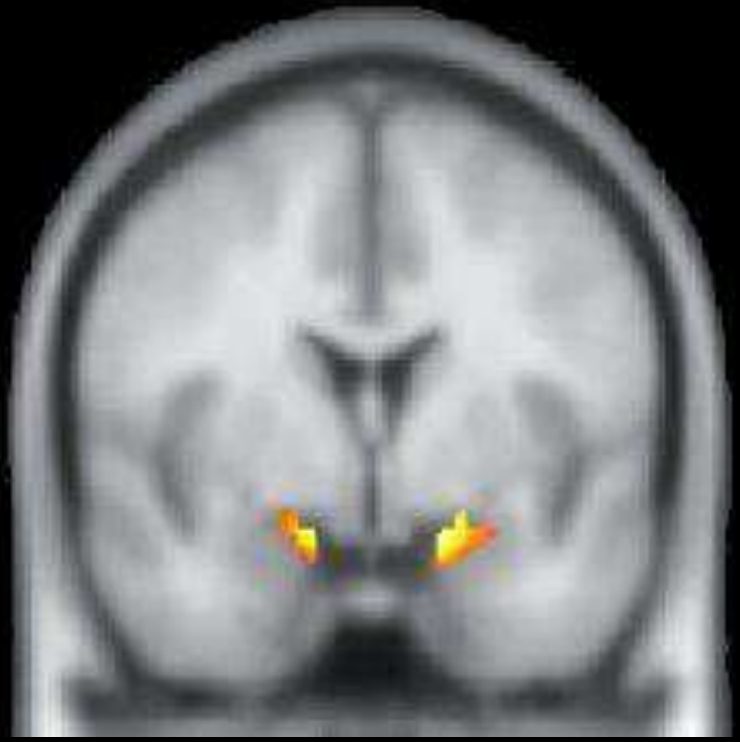
www.elsevier.com/locate/pnpbp

Optimized voxel-based morphometry of gray matter volume in first-episode, antipsychotic-naïve schizophrenia

Peruvamba N. Jayakumar[a,*], Ganesan Venkatasubramanian[b], Bangalore N. Gangadhar[b], Nimmagadda Janakiramaiah[b], Matcheri S. Keshavan[c]



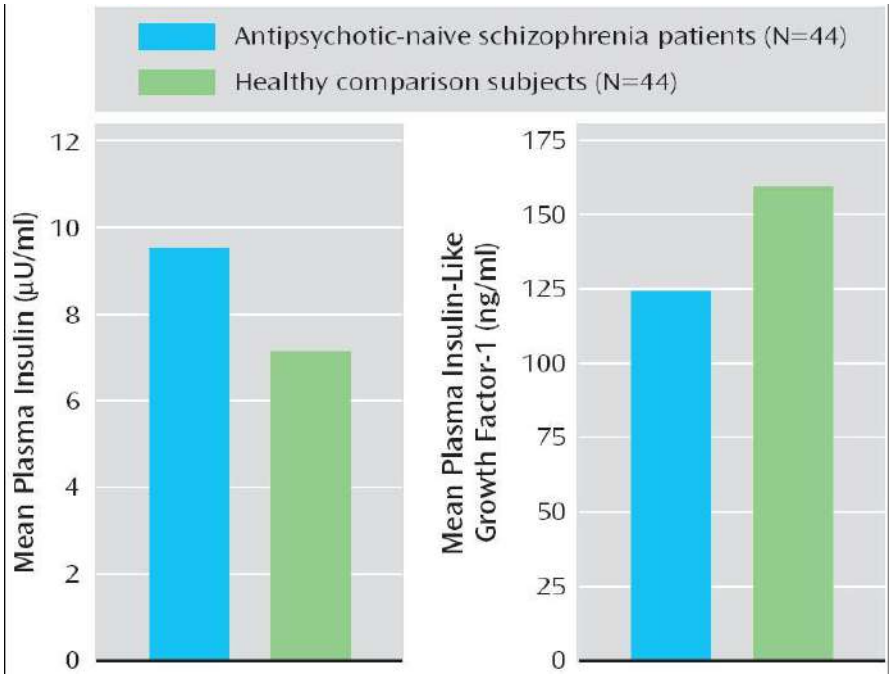
Hippocampal Deficits in Antipsychotic-naïve Schizophrenia



Jayakumar, Venkatasubramanian, Gangadhar et al 2005

The American Journal of Psychiatry

IGF-1 & Schizophrenia: A Critical Hippocampal Neuroplasticity Modulator



The total positive symptoms score as well as the hallucinations score had a significant inverse relationship with IGF-1 levels.

Venkatasubramanian et al 2007

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NEUROBIOLOGY RESEARCH CENTRE
NIMHANS, INDIA

OPEN ACCESS Freely available online

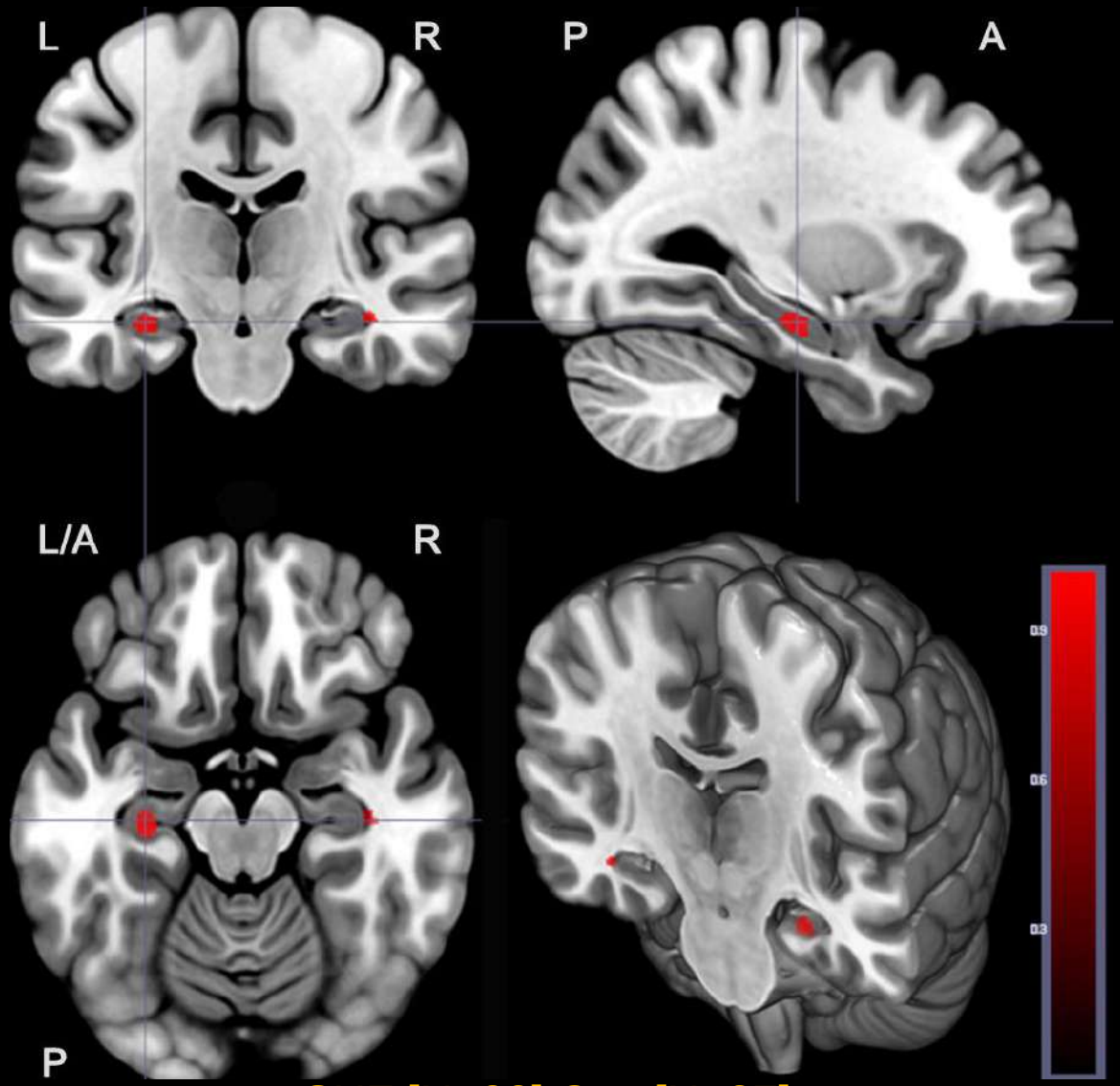
PLOS | ONE

Relationship between Interleukin-6 Gene Polymorphism and Hippocampal Volume in Antipsychotic-Naïve Schizophrenia: Evidence for Differential Susceptibility?

Sunil Vasu Kalmady[1,2], Ganesan Venkatasubramanian[1,2]*, Venkataram Shivakumar[1,2], S. Gautham[2], Aditi Subramaniam[1,2], Dania Alphonse Jose[1,2], Arindam Maitra[3], Vasanthapuram Ravi[4], Bangalore N. Gangadhar[1]

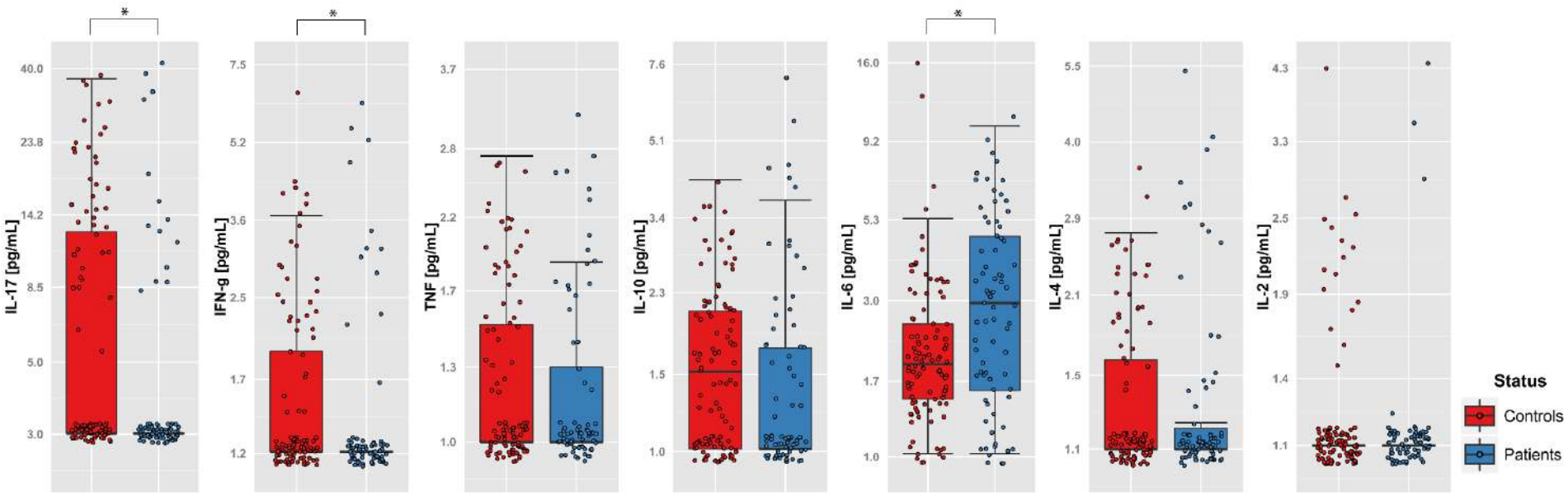
VBM: Diagnosis by IL6-genotype interaction

Hippocampus



SHZ [N=28] Con [N=37]

Plasma Cytokine Abnormalities in Untreated Schizophrenia

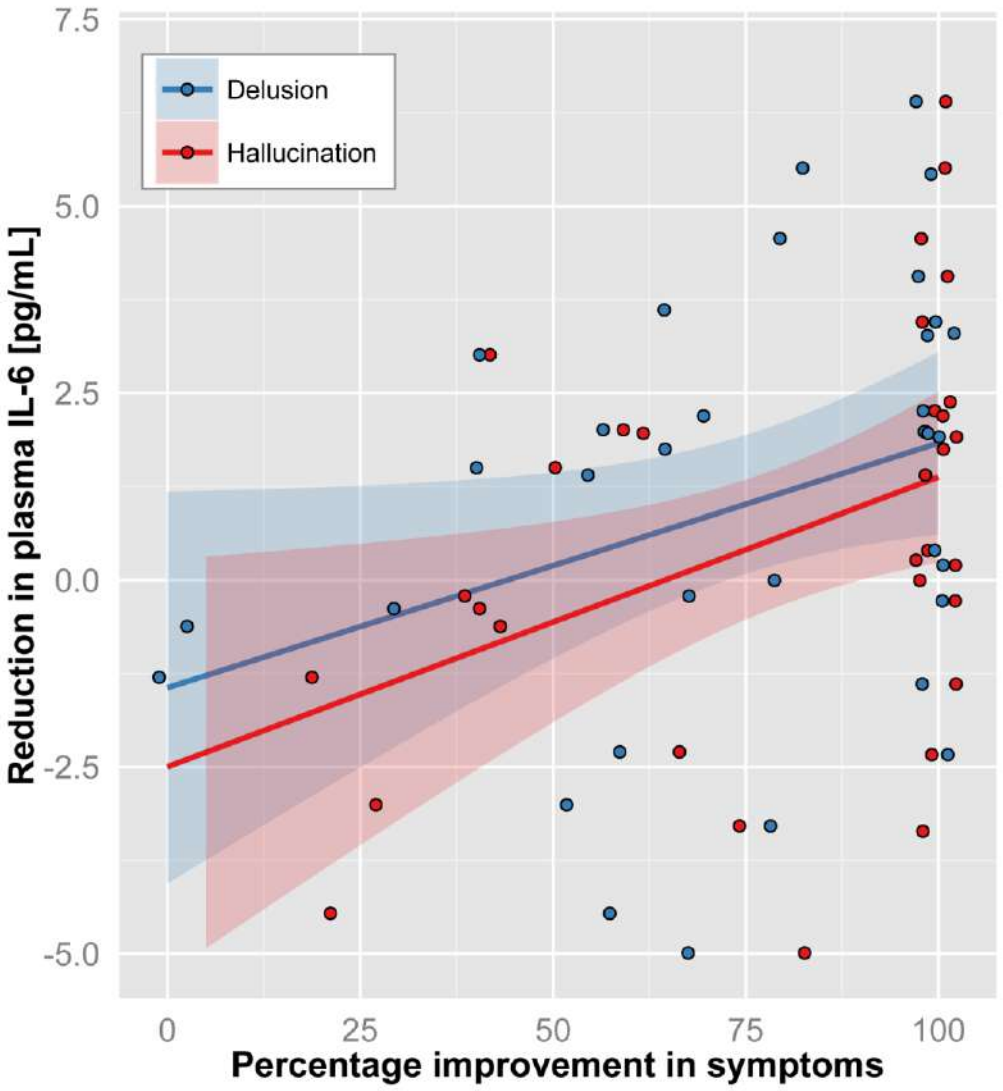


antipsychotic-naïve/free schizophrenia patients (N=75) compared with healthy controls (N=102)

patients had significantly greater plasma levels of IL-6 &
lower levels of IL-17a as well as IFN-g in comparison to healthy controls

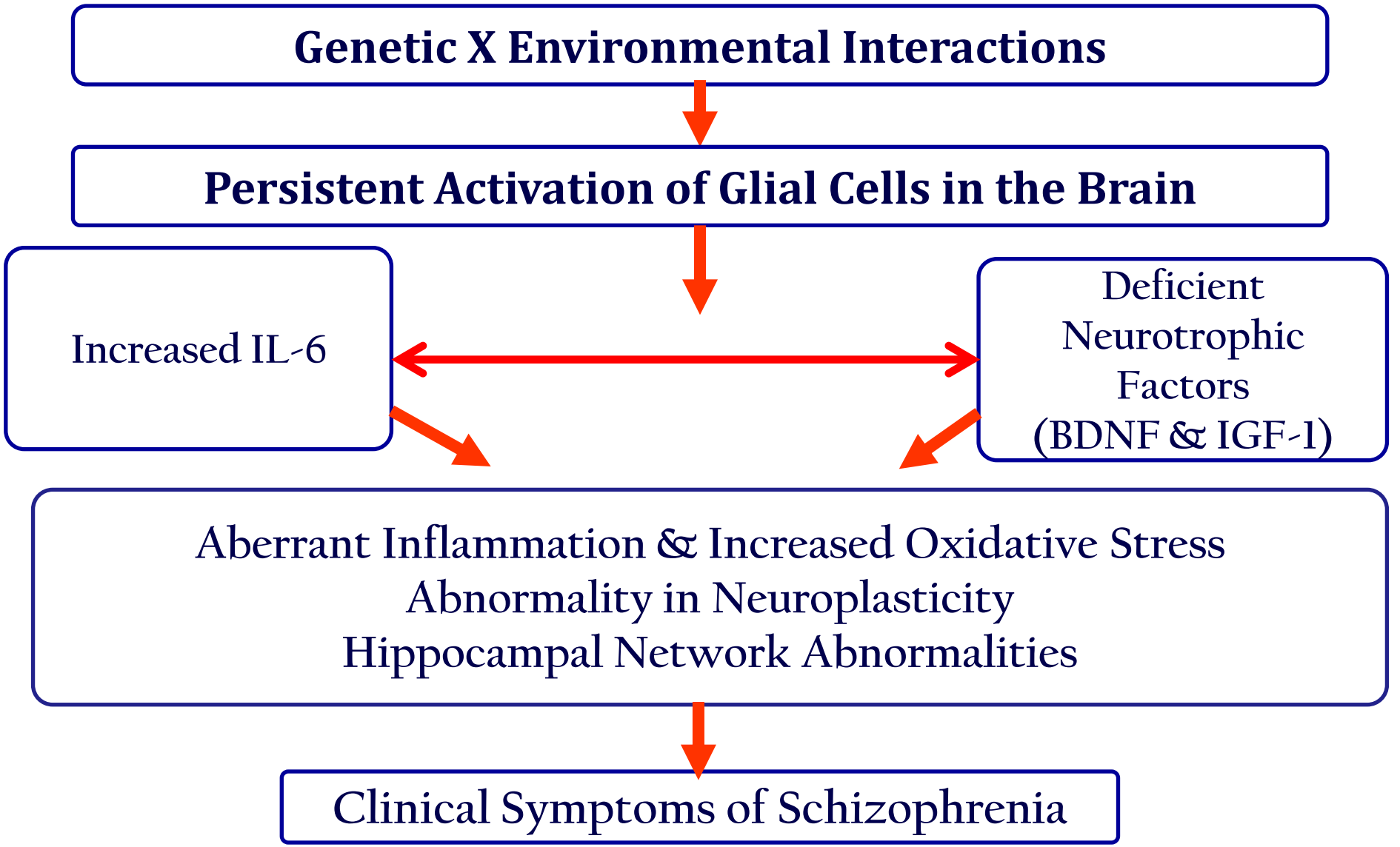
Kalmady, Venkatasubramanian et al (manuscript under review)

Schizophrenia: Reduction in Cytokine Levels & Clinical Improvement



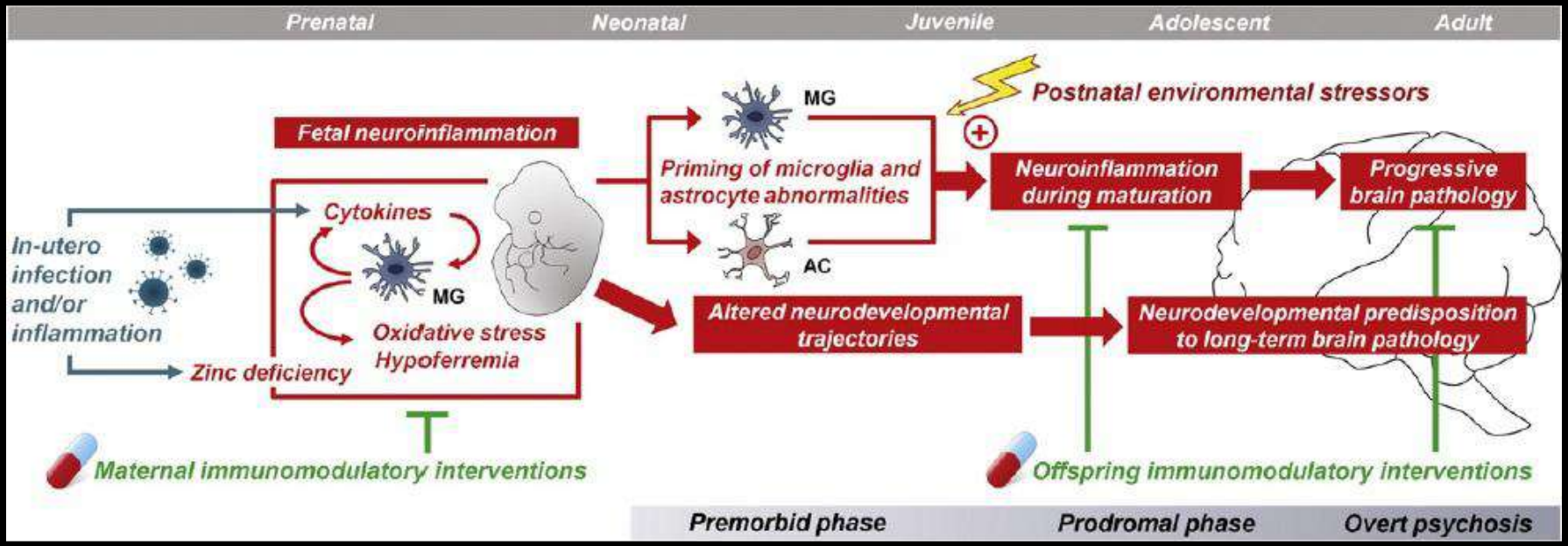
Kalmady, Venkatasubramanian et al (manuscript under review)

SCHIZOPHRENIA: NEUROIMMUNOMETABOLIC ABERRATIONS



Venkatasubramanian et al 2007; Venkatasubramanian, 2008

Schizophrenia: Potential for Immunomodulatory Interventions



1- Potvin et al. 2008; 2- Watanabe et al. 2010; 3 - Meyer et al, 2011

Systematic review and meta-analysis of the efficacy and safety of minocycline in schizophrenia

CNS Spectrums

Minocycline appears to be an effective adjunctive treatment option in schizophrenia, improving multiple relevant disease dimensions.

Moreover, minocycline has an acceptable safety and tolerability profile.

However, more methodologically sound and larger RCTs remain necessary to confirm and extend these results

Solmi et al 2017

THE ROLE OF ANTI-INFLAMMATORY AGENTS

Molecular Psychiatry

EXPERT REVIEW

The neurobiology and treatment of first-episode schizophrenia

RS Kahn and IE Sommer

- The use of anti-inflammatory agents to improve symptoms of schizophrenia is still in its infancy.

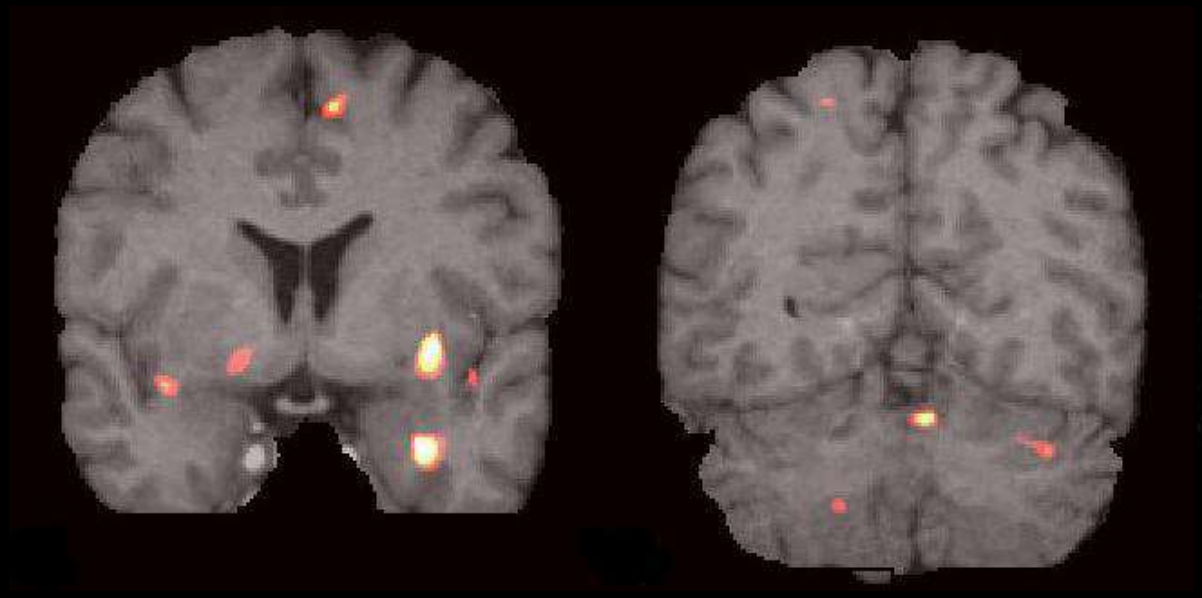
- N-Acetyl Cysteine may be of particular interest, as this component targets not only a diverse array of factors including glutamatergic neurotransmission, the antioxidant glutathione, neurotrophins, apoptosis, mitochondrial function, but also the inflammatory pathways.

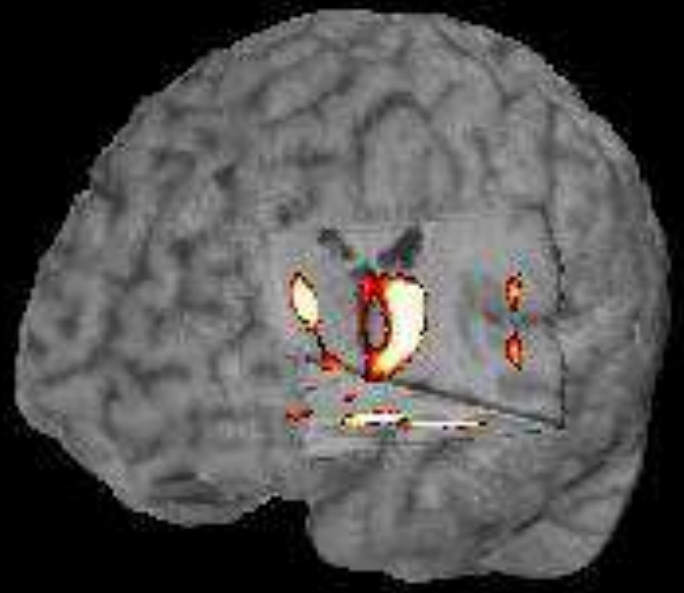
- N-Acetyl Cysteine displays a benign side-effect profile and may even have some anti-addictive properties, which would make this component a valuable substance for prevention of brain volume loss, cognitive deterioration and subsequent transition to psychosis in individuals at (genetic) risk for schizophrenia

- Efficacy of N-Acetyl Cysteine as an add-on agent has partial support from a meta-analysis

Early Course Schizophrenia: Neuroprogression

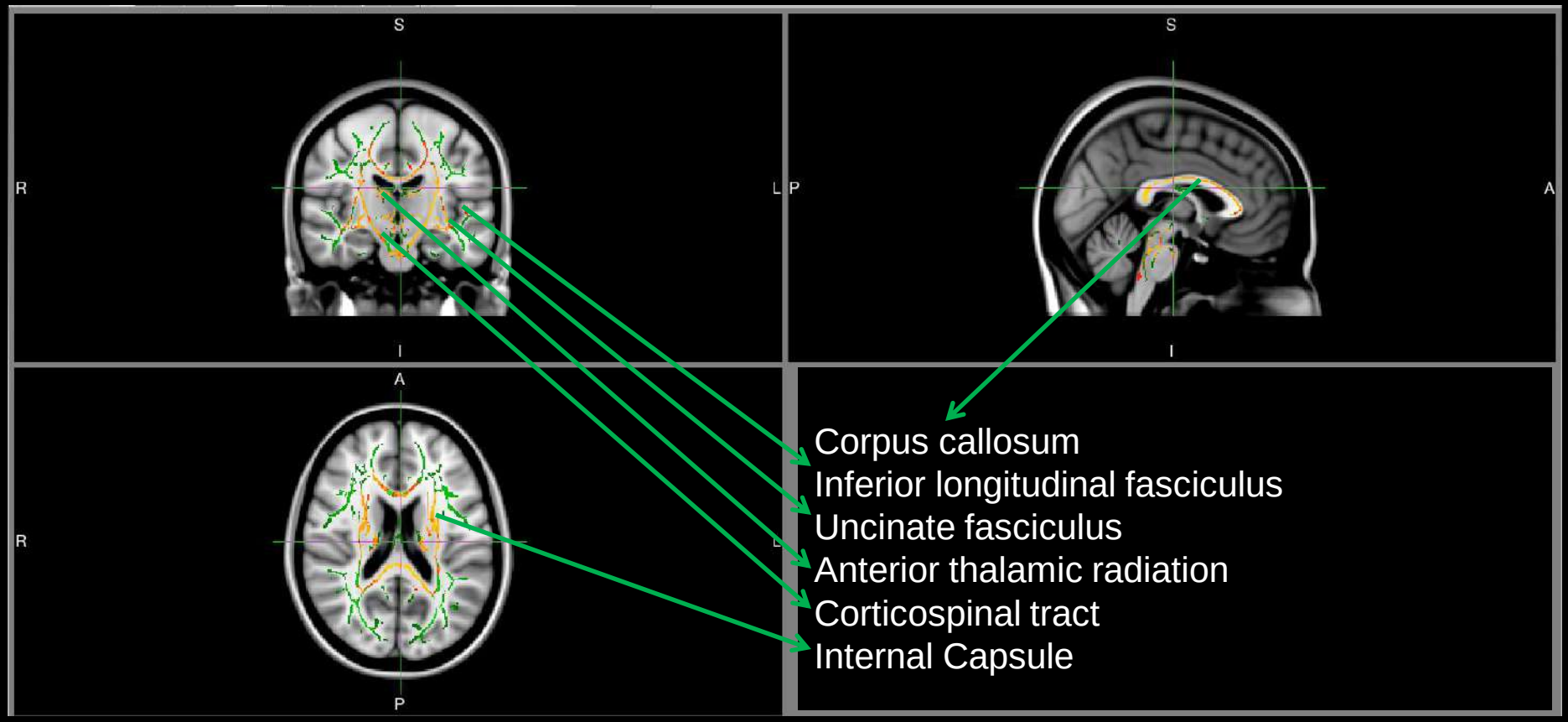
Significant gray matter volume loss in schizophrenia patients at 1- year





Venkatasubramanian et al 2004

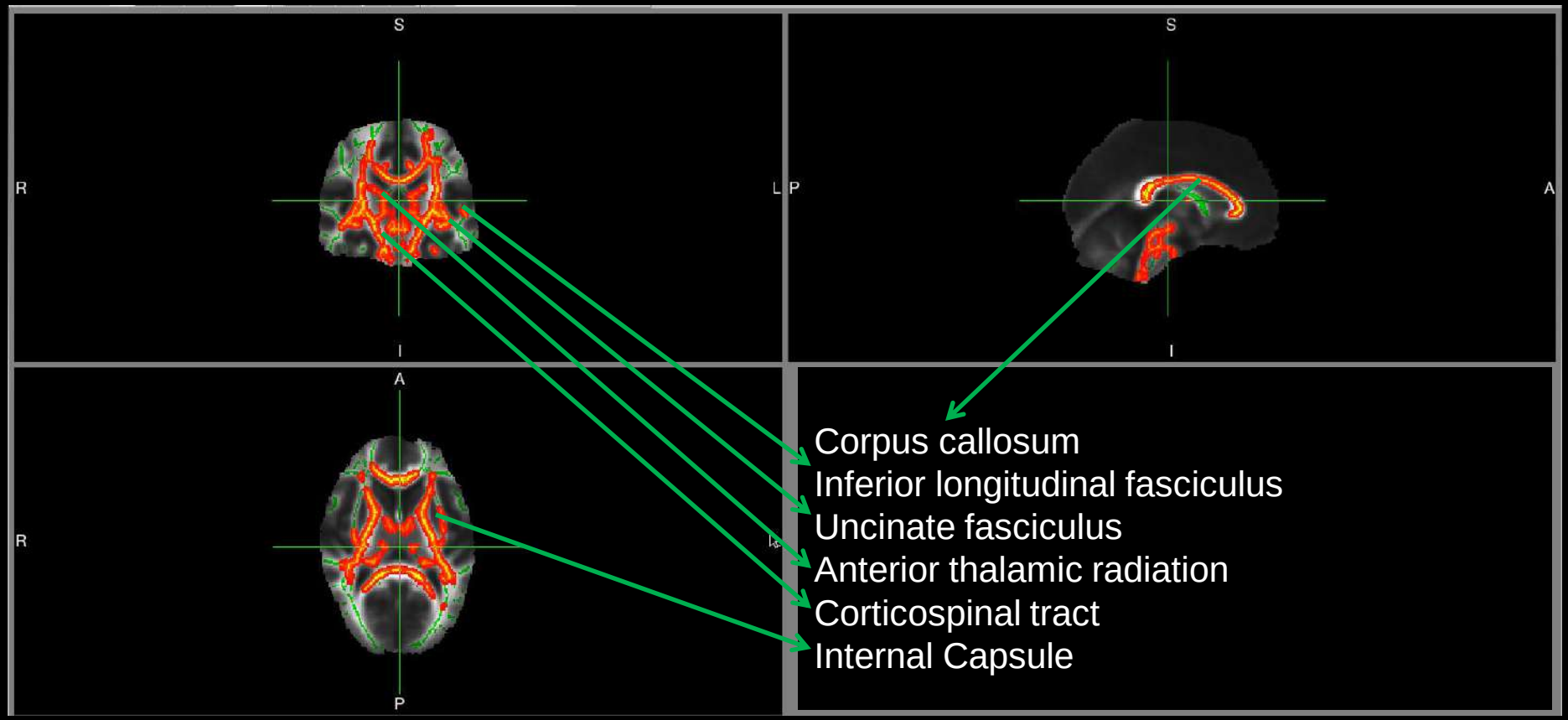
White Matter Abnormalities in first-episode untreated schizophrenia patients



White matter tracts with yellow or red fill indicate areas of significant greater fractional anisotropy in schizophrenia (N=28) vs healthy controls (N=28). Areas in green indicate areas of no significant difference.

(TBSS using FSL; $p<0.01$ after multiple comparison correction using threshold-free cluster enhancement with 5000 permutations)

White Matter Abnormalities in first-episode untreated schizophrenia patients



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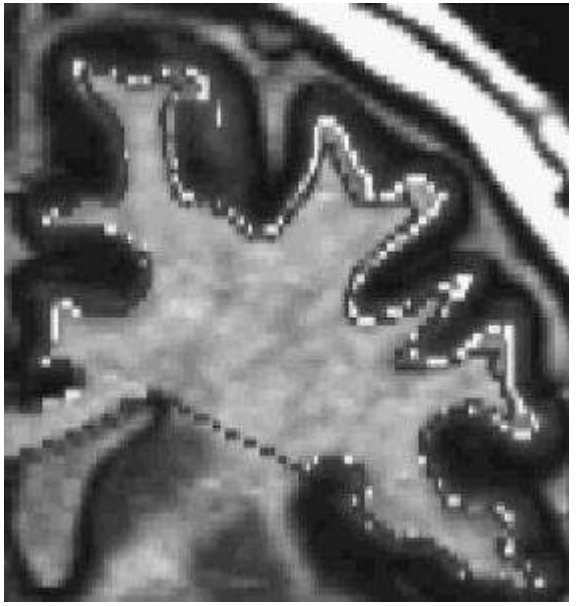
Contents lists available at SciVerse ScienceDirect

Schizophrenia Research

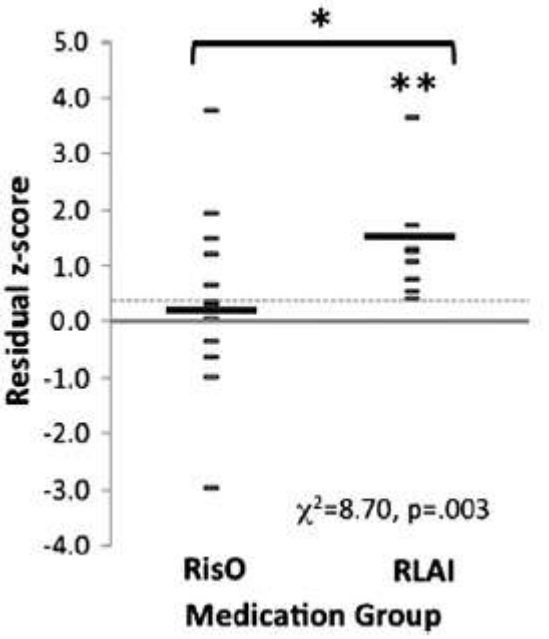
journal homepage: www.elsevier.com/locate/schres

Impact on intracortical myelination trajectory of long acting injection versus oral risperidone in first-episode schizophrenia

Bartzokis et al 2012



Measurement of Intracortical Myelination Volume using Inversion Recovery MRI



Following 6 months of treatment, frontal ICM volume increased significantly (p=.005) in depot group (N=9) and non-significantly (p=0.39) in the oral group (N=13) compared with that of the healthy controls

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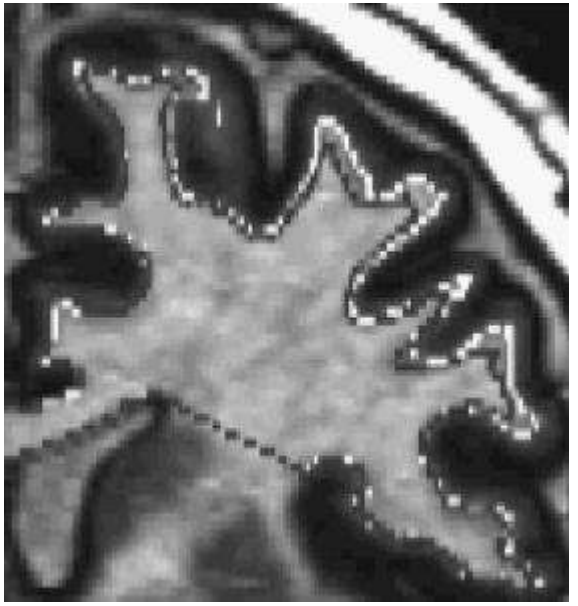

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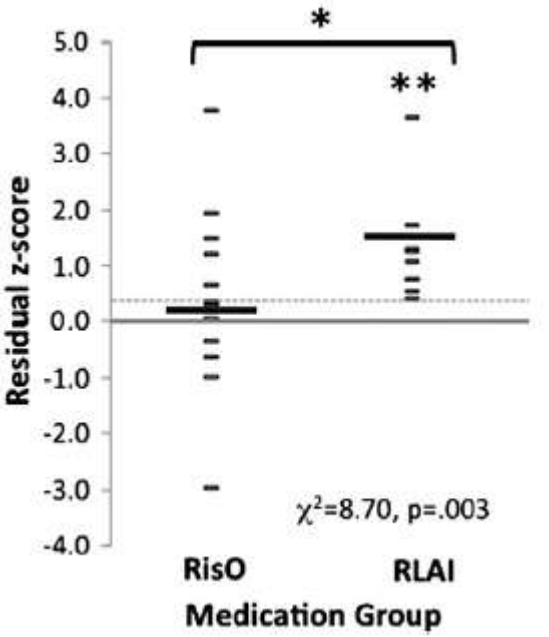


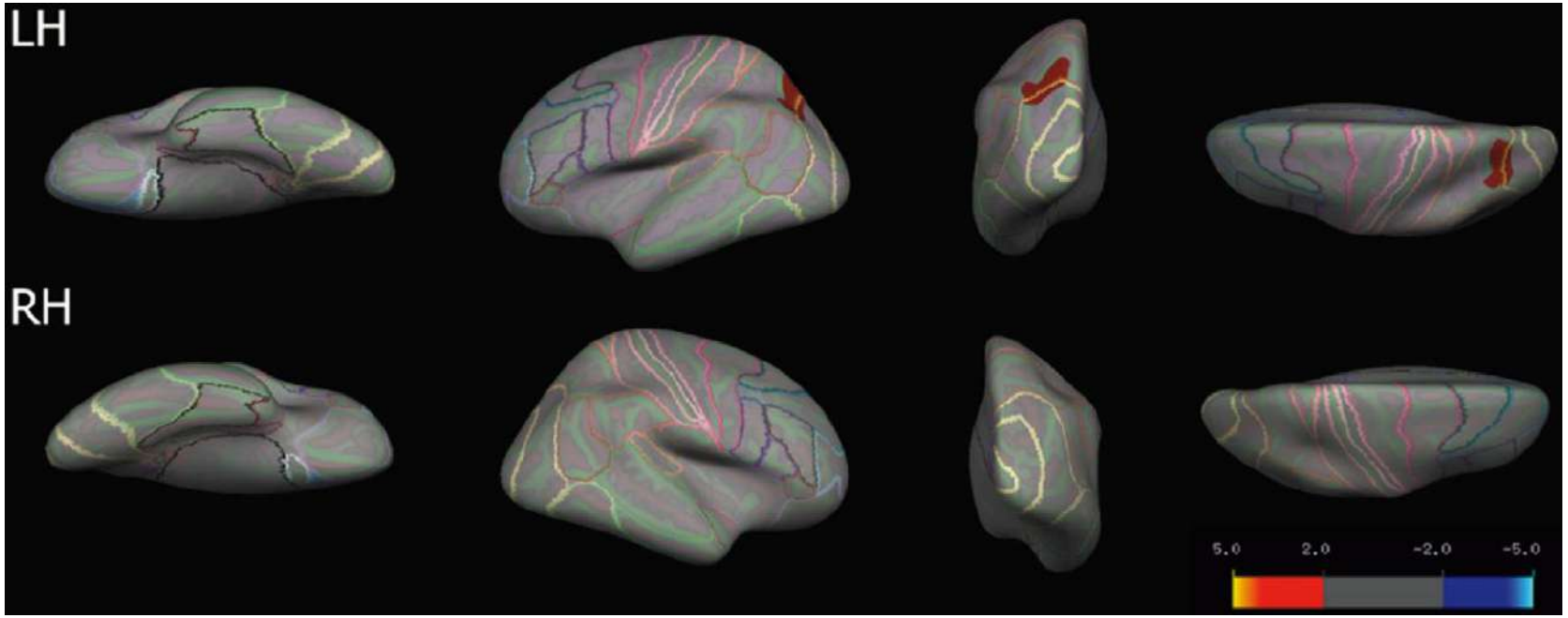
Pro-myelination effects might lead to better symptom remission – minimize relapse??
(Boter et al 2009)

Omega-3 fatty acid supplementation may prevent loss of gray matter thickness in the left parieto-occipital cortex in first episode schizophrenia: A secondary outcome analysis of the OFFER randomized controlled study

- Study examined changes in cortical thickness related to the use of n-3 polyunsaturated fatty acids (PUFA) as add-on therapy in patients with first episode schizophrenia.
- A double-blind randomized controlled study was conducted using a 26-week intervention [N=18] composed of concentrated fish oil containing 2.2 g/d of eicosapentaenoic (EPA – 1320 mg) and docosahexaenoic acid (DHA – 880 mg) or placebo (olive oil) [N=11].
- Participants underwent MRI scanning twice to assess changes in cortical thickness: at the beginning and at the end of intervention.

Pawełczyk et al 2018

Omega-3 fatty acid supplementation may prevent loss of gray matter thickness in the left parieto-occipital cortex in first episode schizophrenia: A secondary outcome analysis of the OFFER randomized controlled study



Significant differences in cortical thickness loss were observed between the groups in left parieto-occipital regions of Brodmann areas 7 and 19.

[Omega-3 fatty acid supplemented group had lesser gray matter loss]

Pawełczyk et al 2018

Early Course Schizophrenia: Deficient Neuroplasticity

frontiers in PSYCHIATRY

ORIGINAL RESEARCH ARTICLE
published: 02 July 2013
doi: 10.3389/fpsyt.2013.00064

Relationship between brain-derived neurotrophic factor and Schneiderian first rank symptoms in antipsychotic-naïve schizophrenia

Sunil Vasu Kalmady[1,2], Ganesan Venkatasubramanian[1,2], Venkataram Shivakumar[1,2], Dania Jose[1,2], Vasanthapuram Ravi[3] and Bangalore N. Gangadhar[1]*

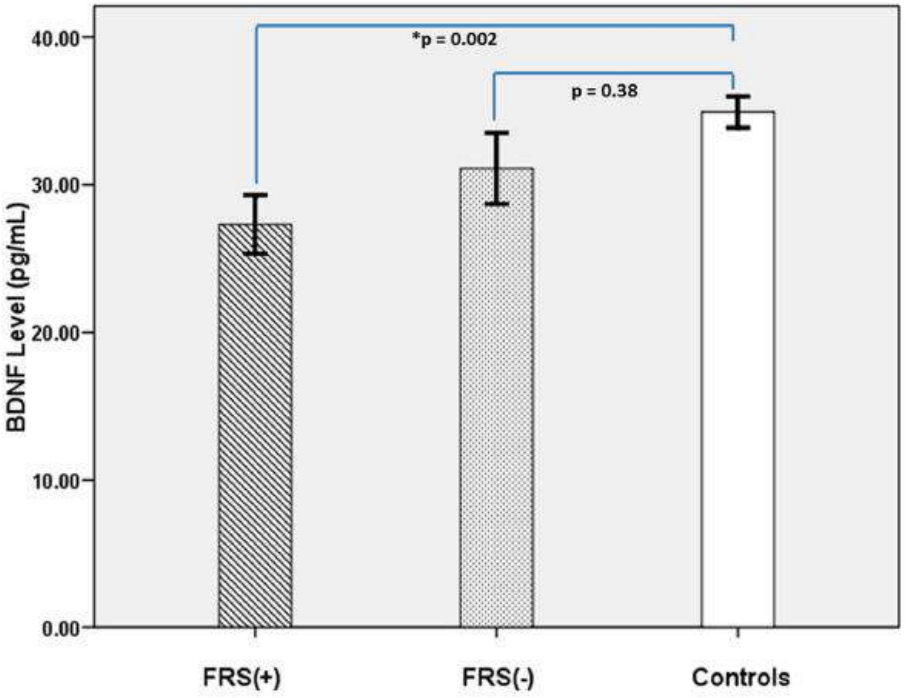
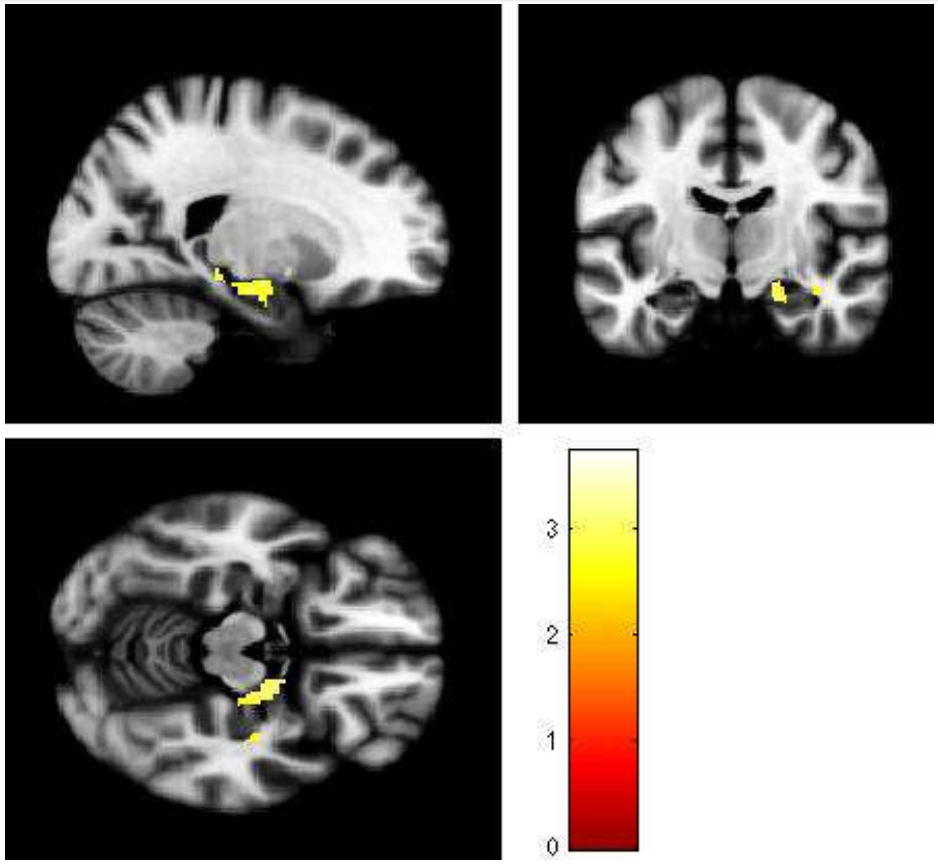
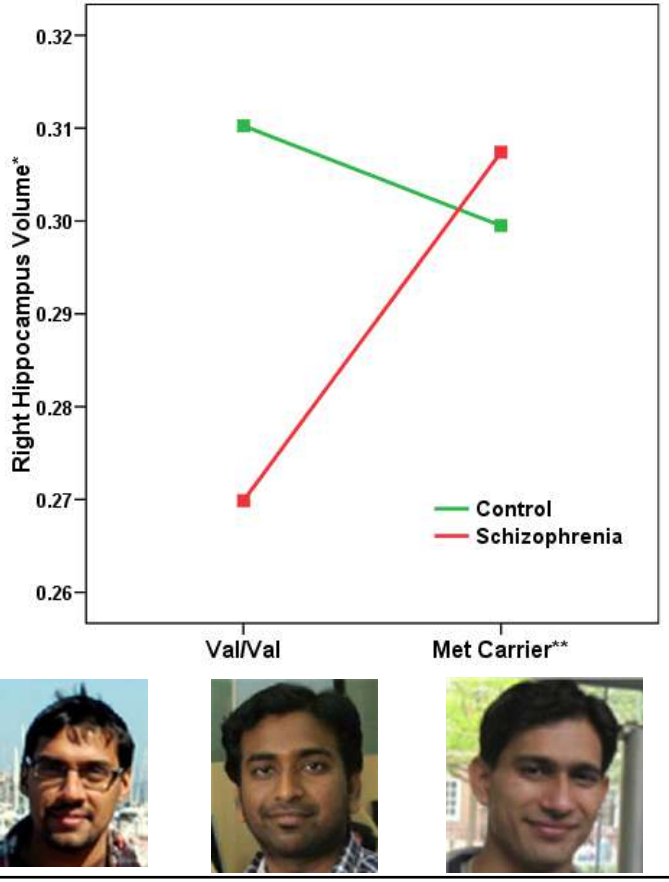


FIGURE 1 | It shows comparative profile of serum BDNF levels in FRS(+) patients ($N = 36$), FRS(−) ($N = 23$), and healthy controls ($N = 60$).

BDNF Gene Polymorphism & Hippocampus Volume in Schizophrenia Patients vs Healthy Controls

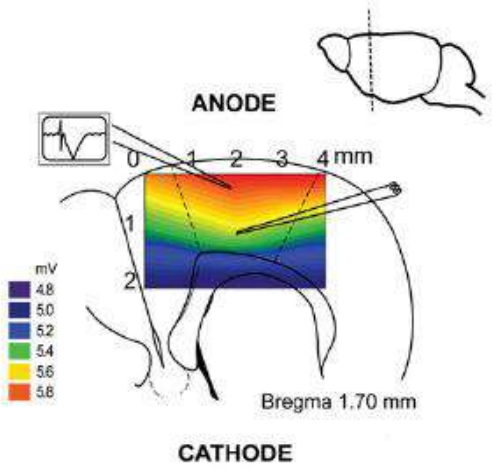


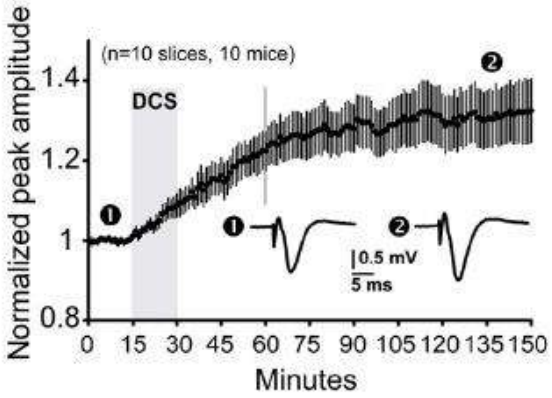


ROI based VBM analyses of hippocampal grey matter volume showed a significant BDNF genotype-by-diagnosis interaction ($F = 12.8$; $p = 0.0004$). Val-homozygous patients (N=48) significantly smaller right hippocampus volume than Val-homozygous healthy controls (N=96) as well as Met-carrier patients (N=38).

Direct Current Stimulation Promotes BDNF-Dependent Synaptic Plasticity: Potential Implications for Motor Learning

Neuron
Report





Direct Current Stimulation results in long-lasting synaptic potentiation

This is dependent on BDNF secretion

Val/Val Genotype show significantly greater synaptic potentiation than Met/Met Genotype

Fritsch et al, NEURON, 2010

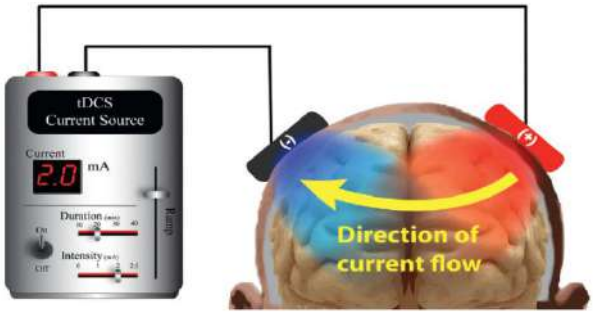
WISER Program @ NIMHANS

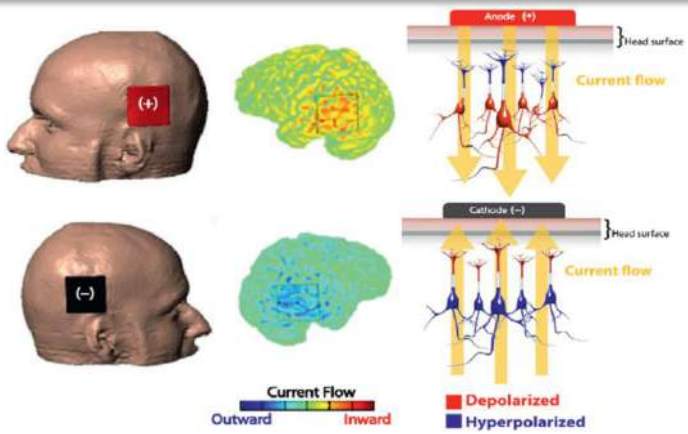
WISER Neuromodulation Program

Weak **I**ntensity **S**timulation for **E**nhancement and **R**e-integration

http://www.instar-program.org/wiser-program.html

Transcranial Direct Current Stimulation (tDCS)



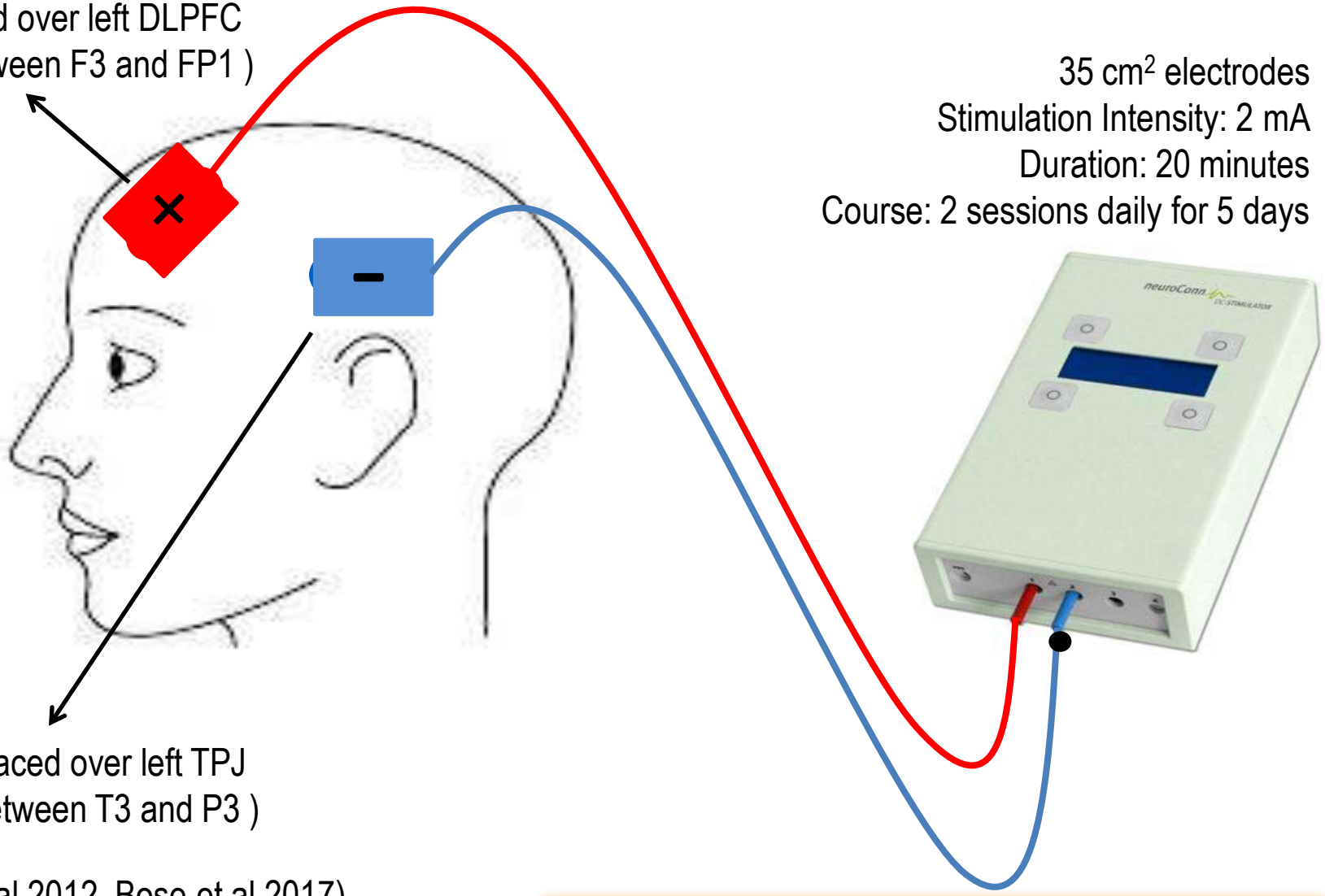


tDCS is a non-invasive, safe technique that involves application of low intensity, direct current (1-2 mA) using electrodes placed on the scalp resulting in polarity specific neuromodulation & adaptive neuroplasticity changes.

(Nitsche & Paulus, 2000)

tDCS: Application Schema in Schizophrenia

Anode placed over left DLPFC
(midway between F3 and FP1)



35 cm^2 electrodes
Stimulation Intensity: 2 mA
Duration: 20 minutes
Course: 2 sessions daily for 5 days

Cathode placed over left TPJ
(midway between T3 and P3)

(Brunelin et al 2012, Bose et al 2017)

WISER Program @ NIMHANS

WISER Program for Schizophrenia @ NIMHANS

- tDCS: Standard Operating Procedures (SoP)[1]
- Successful implementation of add-on tDCS for treating Schizophrenia[2]
- Improvement of Insight in Schizophrenia[2]
- Monotherapy in schizophrenia[3] / Negative symptoms in schizophrenia[4]
- Successful application in early course schizophrenia[5]
- Successful application in a pregnant woman with schizophrenia[6]
- Novel Application: Targeted Intermittent Booster tDCS for Schizophrenia[7]
- 3000+ sessions over the past years without any critical adverse event[8]

1-Fregni..Venkatasubramanian et al 2014; 2-Bose..Venkatasubramanian et al 2014; 3-Rakesh..Venkatasubramanian et al 2013; 4-Narayanaswamy..Venkatasubramanian et al 2014; 5-Shivakumar..Venkatasubramanian et al 2014; 6-Shenoy..Venkatasubramanian et al 2015; 7-Shivakumar..Venkatasubramanian et al 2014; 8 -Chhabra..Venkatasubramanian et al (in preparation);

Contents lists available at ScienceDirect

Schizophrenia Research

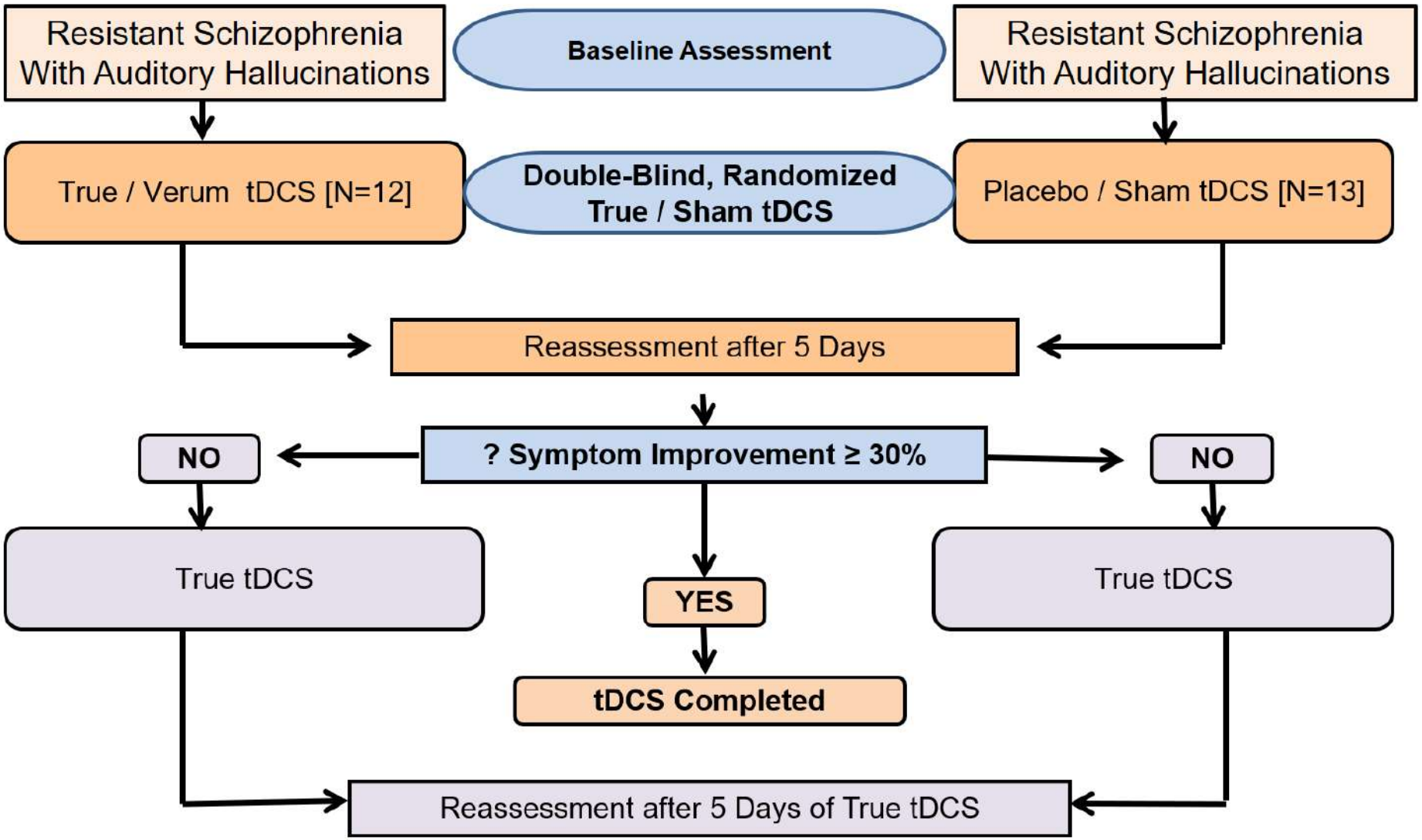
journal homepage: www.elsevier.com/locate/schres

Efficacy of fronto-temporal transcranial direct current stimulation for refractory auditory verbal hallucinations in schizophrenia: A randomized, double-blind, sham-controlled study☆

Anushree Bose, Venkataram Shivakumar, Sri Mahavir Agarwal, Sunil V. Kalmady, Sonia Shenoy, Vanteemar S. Sreeraj, Janardhanan C. Narayanaswamy, Ganesan Venkatasubramanian *

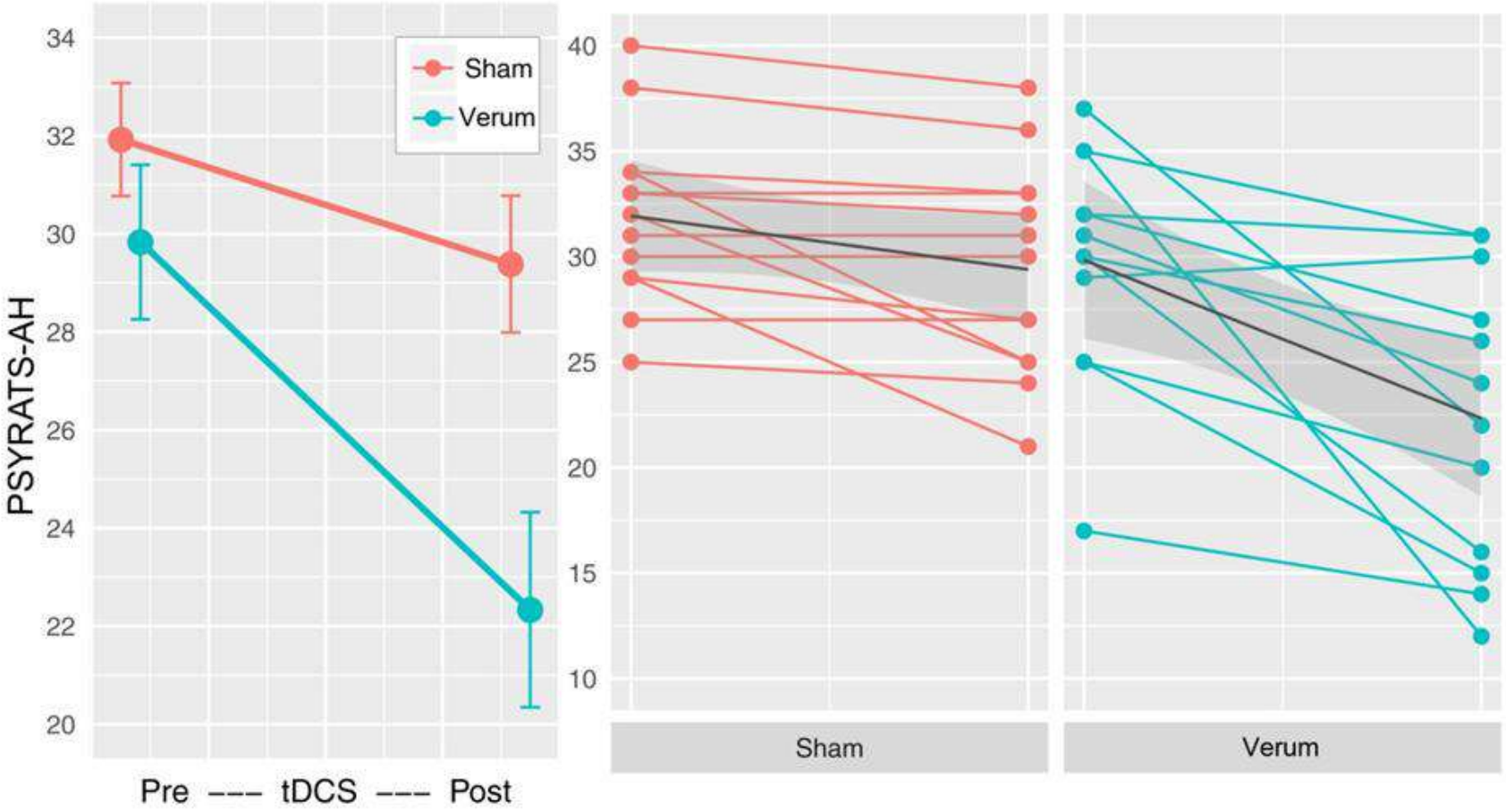
Bose… Venkatasubramanian, 2017

tDCS for Persisting Auditory Hallucinations in Schizophrenia: Randomized, Double-blind, Sham-controlled Design



Bose… Venkatasubramanian, 2017

tDCS for Persisting Auditory Hallucinations in Schizophrenia: Randomized, Double-blind, Sham-controlled Design: Results



RMANOVA (tDCS (Verum [N=12] vs. Sham [N=13]) significant tDCS type x time-point interaction [$F(1,23) = 5.5$, $p = 0.03$, partial $\eta 2 = 0.19$] indicating significantly greater reduction of auditory hallucinations in true tDCS group as compared to sham group

Bose… Venkatasubramanian, 2017

Early Course Schizophrenia: Response & Relapse

How well do patients with a first episode of schizophrenia respond to antipsychotics: A systematic review and meta-analysis

- Randomized controlled trials that compared antipsychotic drugs with each other or with placebo in first-episode schizophrenia
- 17studies with a total of 3156 participants
- Data were pooled in a single-group summary meta-analysis & several potential moderators of response to antipsychotics were examined by meta-regression.
- More than 80% of first-episode patients achieved 20% PANSS/BPRS reduction from baseline and around 50% achieved a 50% PANSS/BPRS reduction

Zhu et al 2017

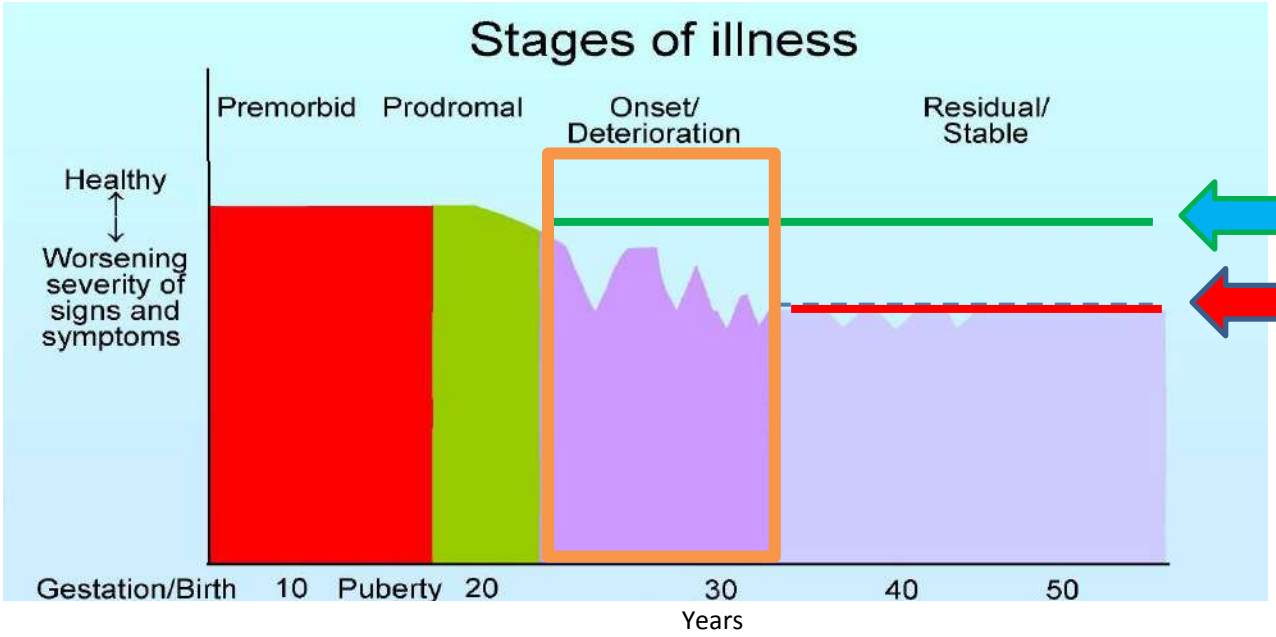
Relapse in Schizophrenia

- Reviews of outcomes in first episode psychosis concluded that up to 22% of subjects may recover within the first 5 years without further relapses.

- However, in subjects meeting full criteria for schizophrenia as opposed to other psychoses, relapse rates reach 80% to 85% during the first 5 years of illness.

Carbon & Correll, 2014

Differential Relapse Rates: Effect of Time – Early vs Late Course



Relapse Rates: ~ 10%
Remission: 70-85%

Relapse rates: 30-50%Remission: 30-35%

Henry et al 2010; Emsley et al 2012

Review

The evidence for illness progression after relapse in schizophrenia

Schizophrenia is associated with disease progression in so far as time to response is longer, negative and other symptoms persist, some patients become treatment refractory

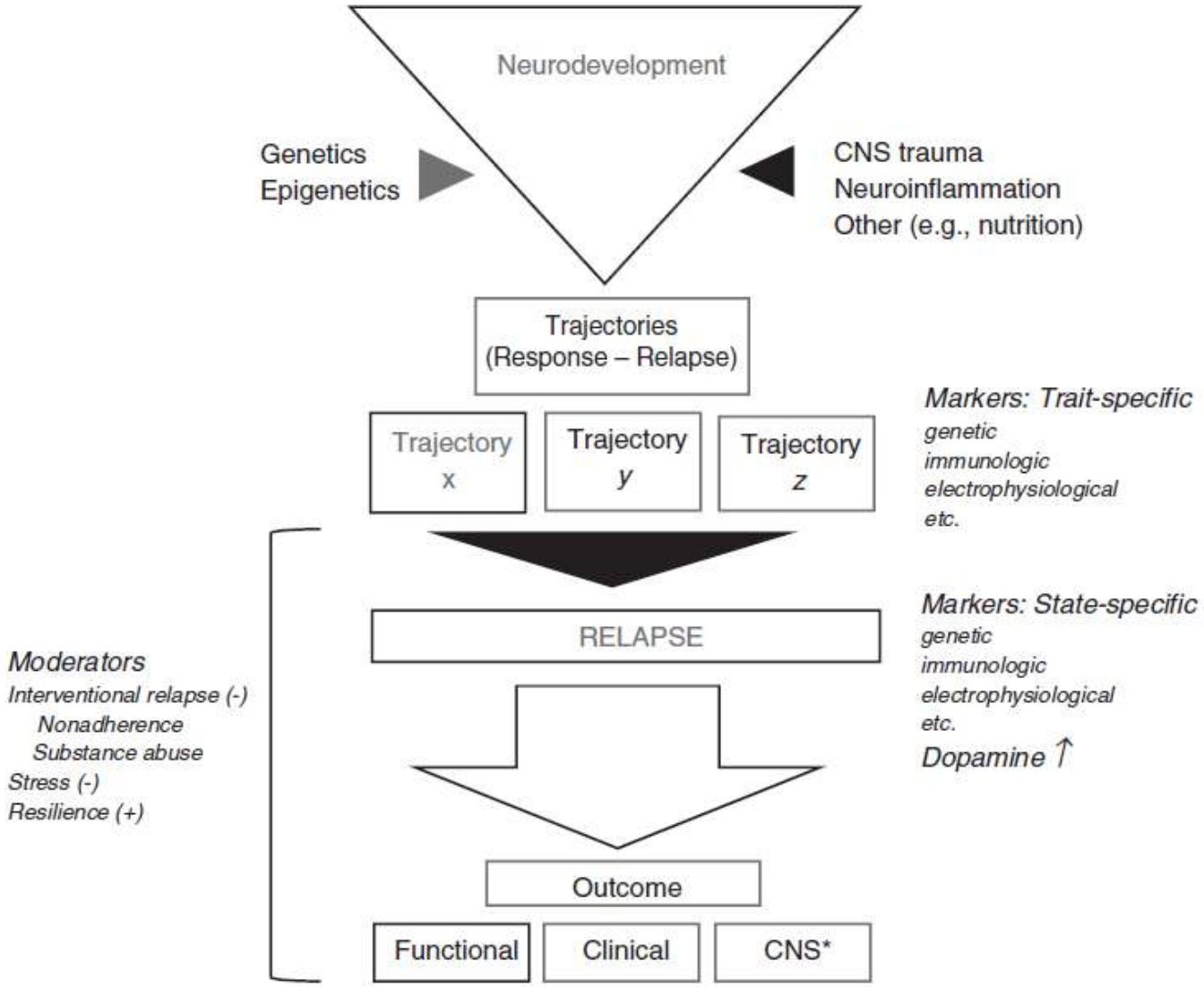
Neuroprogression in terms of structural brain changes may occur

Treatment response after relapse is variable, with many patients responding rapidly, others exhibiting protracted impairment of response and a subgroup displaying emergent refractoriness.

This subgroup comprises about 1 in 6 patients, irrespective of whether it is the first or a subsequent relapse, and even when the delay between onset of first symptoms of relapse and initiation of treatment is brief.

Emsley et al 2013

The neurobiology of relapse in schizophrenia



Remington et al 2014

THE LANCET

Antipsychotic drugs versus placebo for relapse prevention in schizophrenia: a systematic review and meta-analysis

Antipsychotic drugs significantly reduced relapse rates at 1 year (drugs 27% vs placebo 64%).

Fewer patients given antipsychotic drugs than placebo were readmitted, but less than a third of relapsed patients had to be admitted.

Limited evidence suggested better quality of life and fewer aggressive acts with antipsychotic drugs than with placebo.

More patients given antipsychotic drugs than placebo gained weight, had movement disorders, and experienced sedation.

Leucht et al 2012

Schizophrenia Research

Risk factors for relapse following treatment for first episode psychosis: A systematic review and meta-analysis of longitudinal studies

Factors that demonstrated a consistent and significant association with relapse included:

- Non-adherence with medication,
- Substance use disorder
- Carers' critical comments & hostility
- Poor premorbid adjustment

Alvarez-Jimenez et al 2012

Two distinct patterns of treatment resistance: clinical predictors of treatment resistance in first-episode schizophrenia spectrum psychoses

PSYCHOLOGICAL MEDICINE

- Quasi-prospective cohort design (N=246)
- First-episode schizophrenia spectrum (FESS) patients [ICD-10]
  - Schizophrenia (F20), Schizoaffective (F25), Other (F28) / Unspecified (F29) Non-organic Psychoses
- 5-year longitudinal assessment of clinical outcomes
- Treatment Resistance: 81 of 240 patients (34%)
  - Earlier age of contact for treatment (< 20 years)
  - Men
  - Black Ethnicity

Lally et al 2016

Two distinct patterns of treatment resistance: clinical predictors of treatment resistance in first-episode schizophrenia spectrum psychoses

PSYCHOLOGICAL MEDICINE

- **<u>Early Resistant (70% of Treatment-resistant patients)</u>**
  - who met criteria for treatment-resistance and did not experience a symptomatic remission from the time of the first presentation
- **<u>Late Resistant (30% of Treatment-resistant patients)</u>**
  - Response to antipsychotics and attained a symptomatic remission (of at least 6 months duration), but at a later stage failed to respond to the ongoing use of non-clozapine antipsychotics

Lally et al 2016

A neurobiological hypothesis for the classification of schizophrenia: type A (hyperdopaminergic) and type B (normodopaminergic)

Oliver D. Howes and Shitij Kapur

BJPsych

2014

Review of evidence supports that dopaminergic alterations to the onset of psychosis in the majority of patients with schizophrenia but also highlights emerging evidence that this is not the case in all patients.

Based on this we propose two subtypes of schizophrenia:

type A (hyperdopaminergic)

characterised by

elevated striatal dopamine synthesis and release capacity, and

type B (normodopaminergic)

where these dopaminergic alterations are not present.

type A (hyperdopaminergic) schizophrenia will respond to dopamine-blocking drugs, whereas type B, where there is no elevation in dopamine, will not.

(? May benefit with early treatment with clozapine)

Treatment Resistant Schizophrenia
versus
Pseudo-Resistant Schizophrenia

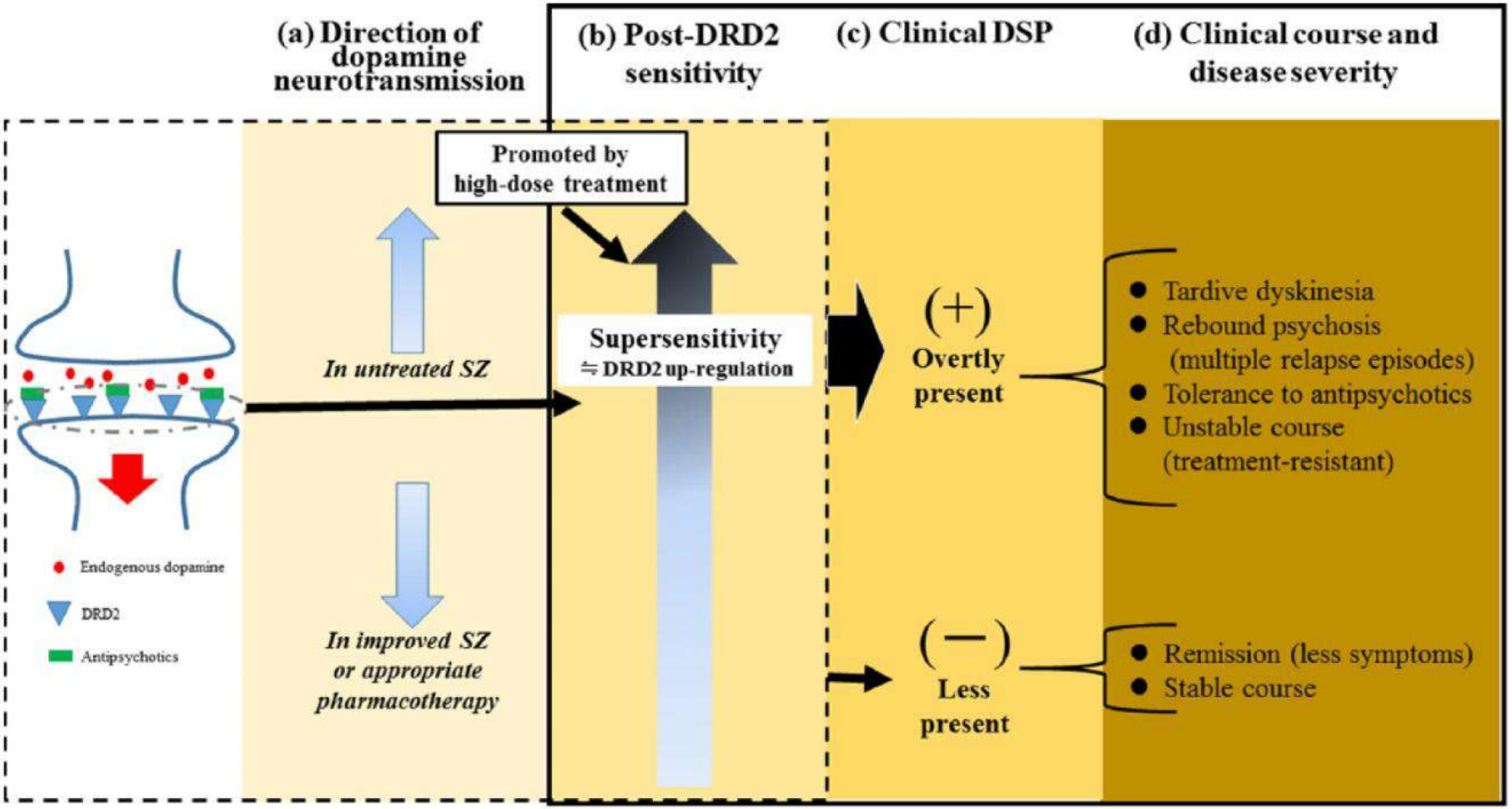
Treatment Resistant Schizophrenia versus Pseudo-Resistant Schizophrenia

- Non-Adherence
- Concomitant substance abuse
- Medical disorders or medications affecting antipsychotic pharmacokinetics/pharmacodynamics
- Adverse and detrimental psychosocial conditions
- ?? Dopamine supersensitivity psychosis

Dold & Leucht 2014; de Bartolomeis et al 2017

Dopamine Supersensitivity Psychosis (DSP)

Dopamine supersensitivity psychosis in schizophrenia: Concepts and implications in clinical practice



Nakata et al 2017

Dopamine supersensitivity psychosis in schizophrenia: Concepts and implications in clinical practice

Psychopharm

- The concept of DSP originated with reports by Chouinard and colleagues in the 1970s.
- Patients whose psychotic symptoms worsened immediately upon cessation of treatment
- Thereafter higher dosages of drugs were needed to control the patients' psychosis, and eventually tardive dyskinesia appeared.

Nakata et al 2017

Dopamine Supersensitivity Psychosis (DSP)

- When a patient with schizophrenia is diagnosed as having DSP, he or she should continuously take antipsychotic(s) for more than 3 months.
- In addition, one of the following three criteria must met:
- (i) **the presence of rebound psychosis**, i.e., a psychotic relapse that occurs immediately after the reduction, cessation, or change of antipsychotics ("immediately" = within six weeks for oral agents and within three months for depot injectable antipsychotics) has occurred
- (ii) **tolerance to the antipsychotics' effect** is observed: that is, when severe psychotic symptoms and/or other positive symptoms emerge, a higher dosage of antipsychotics is needed to control the psychotic symptoms compared to the dose(s) for previous treatment, and in some cases even high-dosage treatment cannot control the psychosis
- (iii) **the presence or history of Tardive Dyskinesia**: TD appears at the withdrawal of medication, or disappears after a re-administration of antipsychotics.

Chouinard, 1991; Nakata et al 2017

A prospective comparative study of risperidone long-acting injectable for treatment-resistant schizophrenia with dopamine supersensitivity psychosis

Kimura et al 2014

Risperidone long-acting injectable in the treatment of treatment-resistant schizophrenia with dopamine supersensitivity psychosis: Results of a 2-year prospective study, including an additional 1-year follow-up

Psychopharm

Kimura et al 2016

"Long-acting injectable of an atypical antipsychotic combined with reduced doses of oral antipsychotic(s) provided beneficial effects, particularly for treatment resistant schizophrenia patients with DSP"

Potential role for treatment with Clozapine
Prevention potential: Quetiapine, Aripiprazole & Valproate

Nakata et al 2017

Role of Depot Antipsychotics in Early Course Schizophrenia: Current Perspectives

- A growing body of literature demonstrates that LAIs also are effective for early intervention or when used for first-episode treatment of schizophrenia rather than delaying treatment
- Mechanistic Basis: Neuroprotective pro-myelination effects, ? avoidance of supersensitivity
- More research is needed on the differential efficacy in terms of head-to-head comparisons

Stevens et al 2015

Early Course Schizophrenia

Treatment Resistance
vs
Resistance to Treatment

Treatment resistant or resistant to treatment? Antipsychotic plasma levels in patients with poorly controlled psychotic symptoms

- Patients with treatment-resistant schizophrenia / psychosis referred for clozapine (N=36)
- 16 patients (44%) had sub-therapeutic plasma antipsychotic level.
- Undetectable level in 7 of these 16 patients (i.e. 19% of 36 patients)
- A significantly higher proportion of patients taking olanzapine and amisulpride had therapeutic plasma levels (68% therapeutic) compared to other medications (27% therapeutic).

McCutcheon et al 2015

Treatment resistant or resistant to treatment? Antipsychotic plasma levels in patients with poorly controlled psychotic symptoms

- A sub-therapeutic plasma level could be due to
  - Non-adherence to treatment
  - Poor absorption
  - Rapid metabolism

- In early treatment phase, if there is poor clinical response, there is a potential role for plasma level monitoring of antipsychotic
- Cost-benefit aspect of routine plasma level monitoring needs further research
- Plasma level can potentially clarify adherence / pharmacokinetic factors, thereby accelerating the route to suitable alternatives

McCutcheon et al 2015

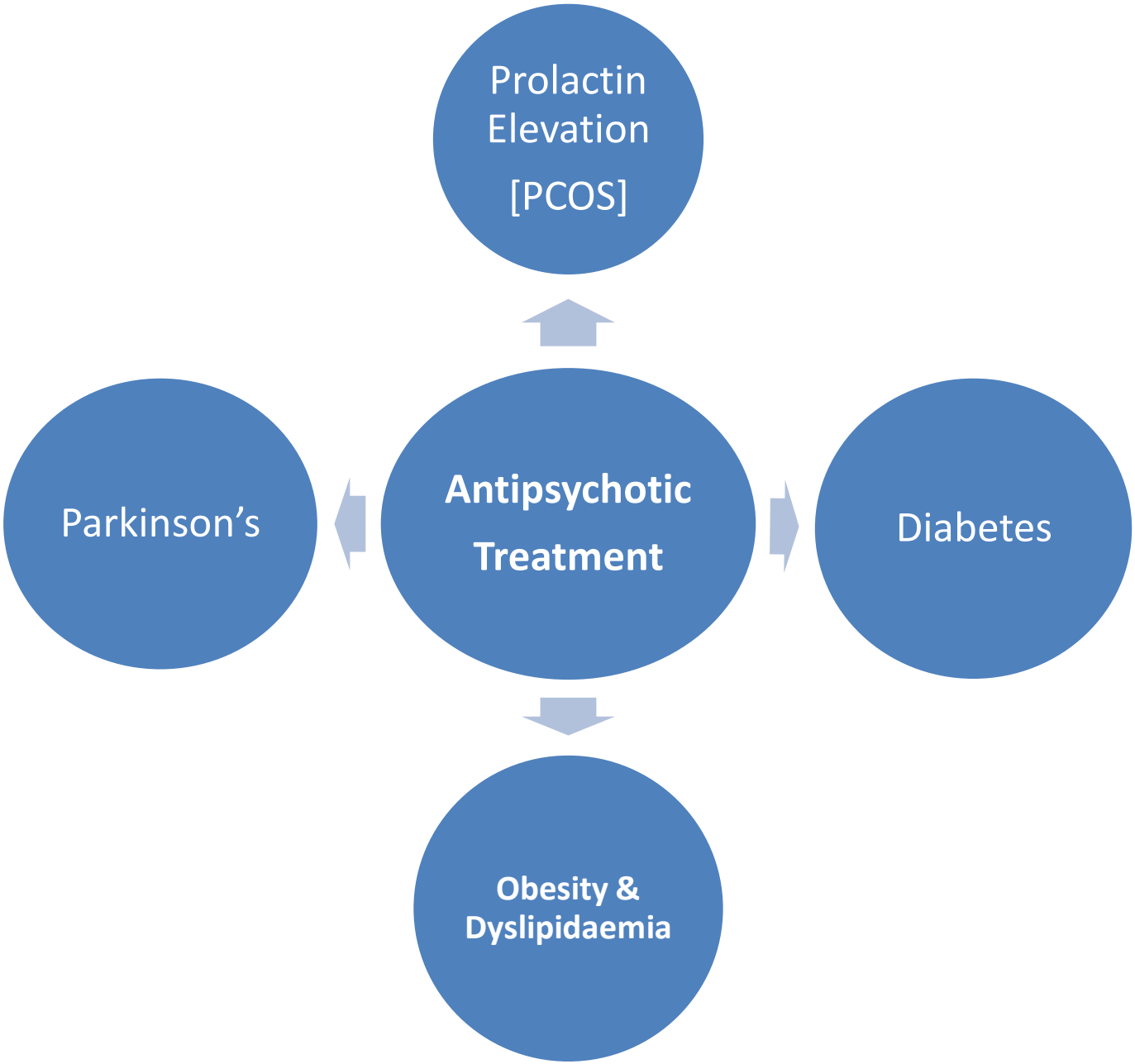
Antipsychotic plasma levels in the assessment of poor treatment response in schizophrenia

Acta Psychiatrica Scandinavica

- Antipsychotic plasma levels were measured in 99 individuals provisionally diagnosed with treatment-resistant schizophrenia by their treating clinicians, but not prescribed clozapine
- Thirty-five per cent of plasma levels were subtherapeutic, and of these, 34% were undetectable.
- Individuals with subtherapeutic/undetectable levels were significantly more likely to be admitted to hospital ($P = 0.02$).
- The presence of subtherapeutic plasma levels may suggest a need to address adherence or pharmacokinetic factors as opposed to commencing clozapine treatment.

McCutcheon et al 2018

Early Course Schizophrenia: The Burden of Side-Effects


Prolactin Elevation [PCOS]
Parkinson's
Antipsychotic Treatment
Diabetes
Obesity & Dyslipidaemia

Review

Early Intervention IN PSYCHIATRY

Antipsychotic-induced weight gain in first-episode psychosis patients: a meta-analysis of differential effects of antipsychotic medications

Tek et al 2015

- Most antipsychotic medications were associated with significant body weight gain and BMI increase in first-episode psychosis patients, except for ziprasidone
- Olanzapine and clozapine caused the highest weight gain compared to placebo
- Cardiovascular risk doubles in the first year of psychotic illness

Article

Metformin for Weight Loss and Metabolic Control in Overweight Outpatients With Schizophrenia and Schizoaffective Disorder

- Metformin (1000 mg; twice-daily for 16 weeks) was modestly effective in reducing weight and other risk factors for cardiovascular disease in clinically stable, overweight outpatients with chronic schizophrenia or schizoaffective disorder over 16 weeks.

- A significant time-by-treatment interaction suggests that benefits of metformin may continue to accrue with longer treatment.

- Metformin may have an important role in diminishing the adverse consequences of obesity and metabolic impairments in patients with schizophrenia.

Jarskog et al 2013

JAMA Psychiatry | Original Investigation

Effect of Liraglutide Treatment on Prediabetes and Overweight or Obesity in Clozapine- or Olanzapine-Treated Patients With Schizophrenia Spectrum Disorder

A Randomized Clinical Trial

Glucagon-like peptide-1 (GLP-1) is an incretin hormone secreted from the L cells in the intestinal mucosa in response to nutrients.

Glucagon-like peptide-1 stimulates insulin secretion and inhibits glucagon secretion, thereby lowering plasma glucose levels.

Larsen et al 2017

JAMA Psychiatry | Original Investigation

Effect of Liraglutide Treatment on Prediabetes and Overweight or Obesity in Clozapine- or Olanzapine-Treated Patients With Schizophrenia Spectrum Disorder

A Randomized Clinical Trial

- Recent study reported findings on Glucagon-like peptide-1 receptor agonist liraglutide added to clozapine or olanzapine treatment of schizophrenia spectrum disorders

- Liraglutide significantly improved glucose tolerance, body weight, and cardiometabolic disturbances in patients with schizophrenia spectrum disorders treated with clozapine or olanzapine

Larsen et al 2017

Antipsychotic-induced Side-Effect: Beyond Metabolic Syndrome

Melka *et al. Clinical Epigenetics* 2014, **6**:1
http://www.clinicalepigeneticsjournal.com/content/6/1/1

CLINICAL EPIGENETICS

RESEARCH Open Access

The effects of olanzapine on genome-wide DNA methylation in the hippocampus and cerebellum

Epigenetic changes involving DNA methylation may underlie
the amelioration of symptoms
as well as
certain adverse effects including the metabolic syndrome.

These epigenetic alterations give insights into
the mechanism of action of olanzapine,
therapeutic effects and the side effects of
antipsychotics

Contents lists available at ScienceDirect

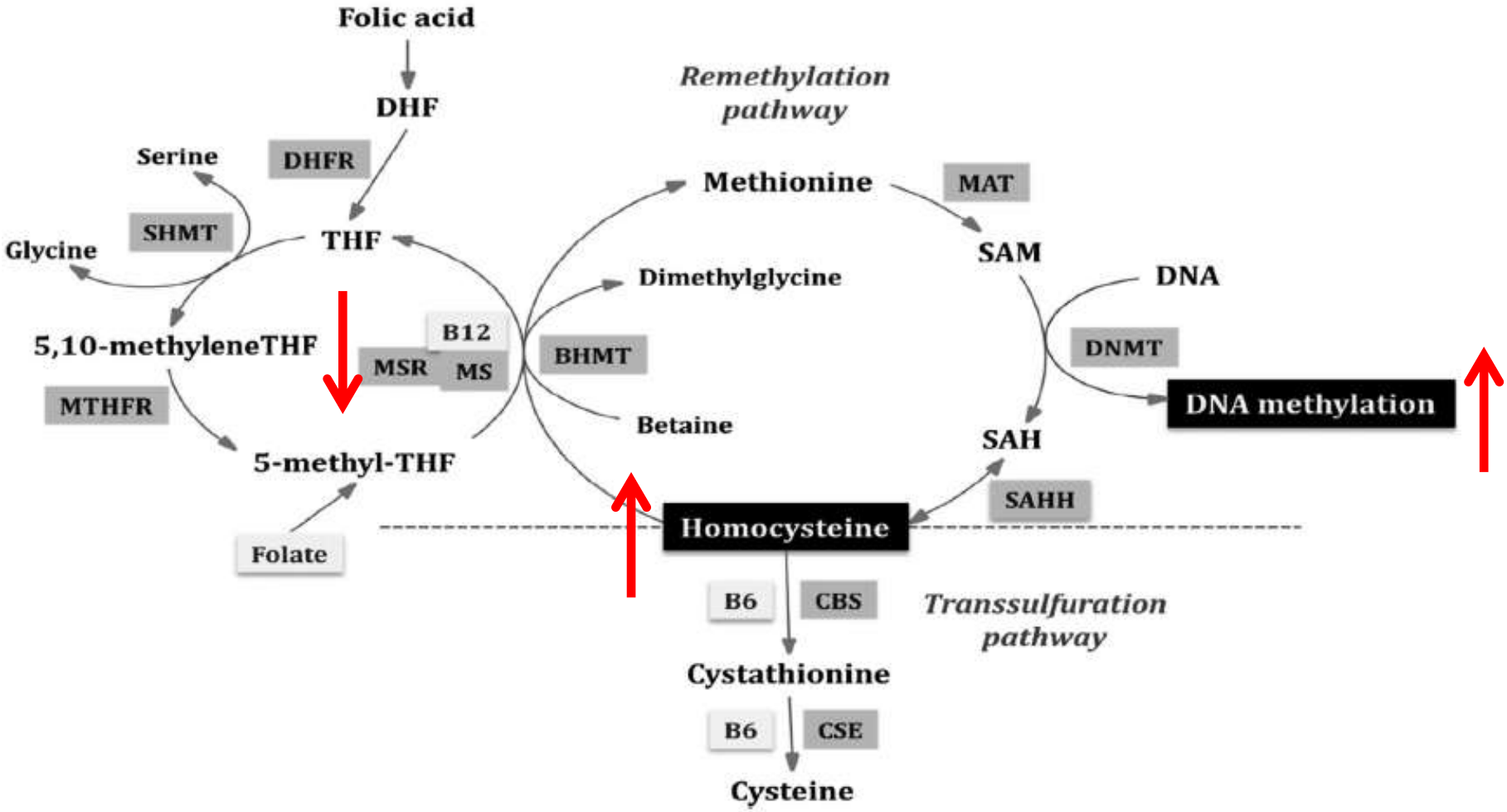
Molecular Genetics and Metabolism

journal homepage: www.elsevier.com/locate/ymgme

Mandaviya et al. 2014

Mini review

Homocysteine and DNA methylation: A review of animal and human literature



Eur J Clin Pharmacol

Effects of second-generation antipsychotics on selected markers of one-carbon metabolism and metabolic syndrome components in first-episode schizophrenia patients

- 39 First Episode Schizophrenia Patients
- 12 weeks of treatment with risperidone or olanzapine,
- At Follow-up, all patients had significantly higher body mass index (BMI), serum levels of total cholesterol (TC), low-density lipoproteins, triglycerides (TG) and homocysteine together with significantly lower levels of folate and vitamin B_{12}

Misiak et al 2014

Eur J Clin Pharmacol

Effects of second-generation antipsychotics on selected markers of one-carbon metabolism and metabolic syndrome components in first-episode schizophrenia patients

- There was a significantly higher increase in BMI and TC in patients treated with olanzapine in comparison with those treated with risperidone.
- Patients receiving olanzapine had a higher decrease in vitamin B_{12} than those assigned to the treatment with risperidone.
- Changes in folate, vitamin B_{12}, homocysteine and TC levels were significant only in males

Misiak et al 2014

ONLINE FIRST

JAMA Psychiatry 2013

Randomized Multicenter Investigation of Folate Plus Vitamin B_{12} Supplementation in Schizophrenia

- Both Vitamin-B12 as well as Folate deficiency can increase cardio-metabolic risk as well as worsen the sequel of hyperprolactinemia

- Pre-emptive assessment & treatment of deficiency can potentially reduce the risk for these metabolic side-effects

- Interestingly in a recent report, Vitamin-B12 + Folate supplementation has been shown to improve negative symptoms as well

Roffman et al 2013

Nutritional Deficiencies and Clinical Correlates in First-Episode Psychosis: A Systematic Review and Meta-analysis

SCHIZOPHRENIA BULLETIN
The Journal of Psychoses and Related Disorders

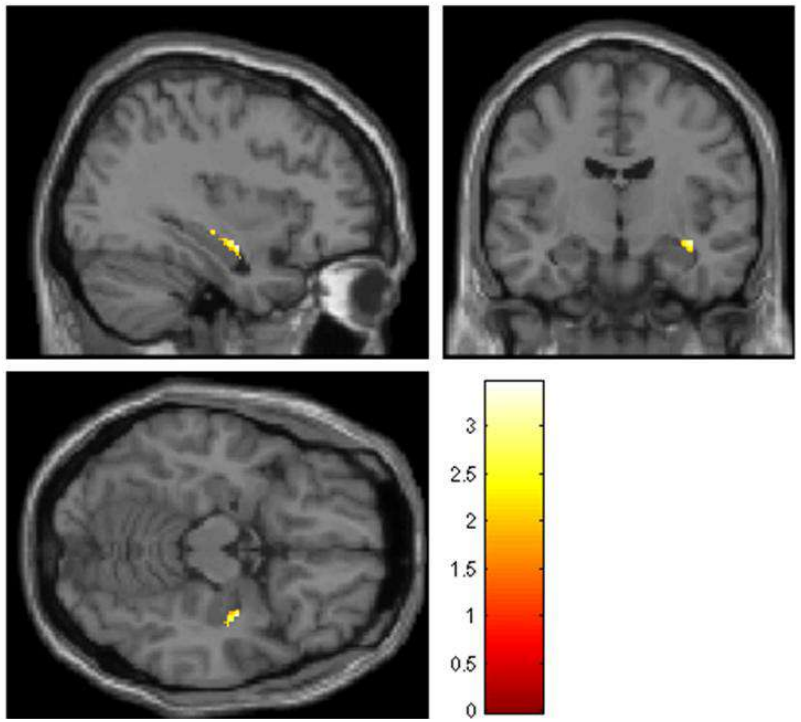
- Deficits in vitamin D and folate previously observed in long-term schizophrenia appear to exist from illness onset, and are associated with worse symptomology.

- Further research must examine the direction and nature of these relationships (mediator, moderator, or marker) with clinical status in first-episode psychosis.

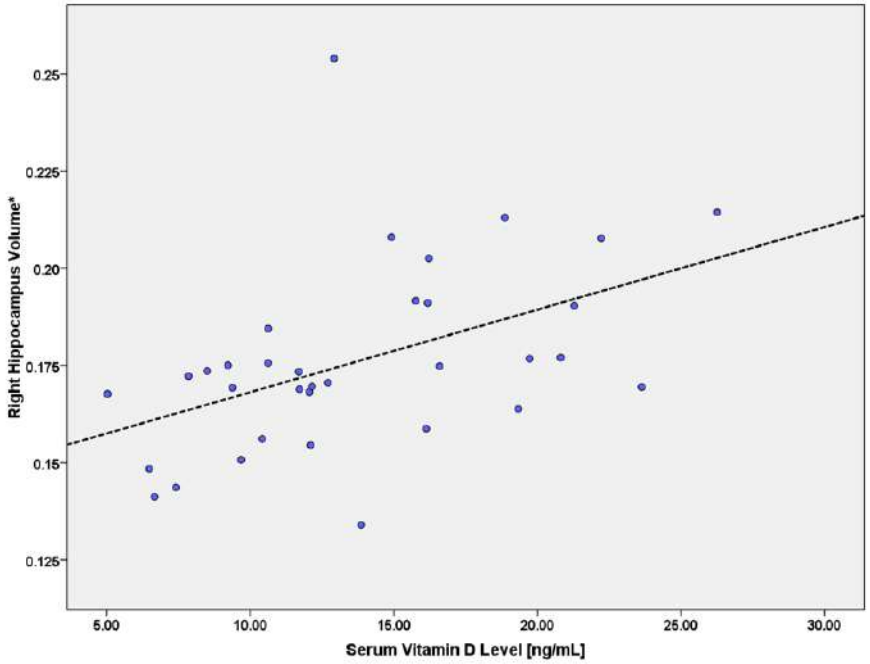
- Future trials assessing efficacy of nutrient supplementation in FEP samples should consider targeting and stratifying for baseline deficiency

Firth et al 2018

Serum vitamin D and hippocampal gray matter volume in schizophrenia



Lower levels of serum vitamin D levels were associated with decreased grey matter volume in the right hippocampus (X=33, Y= -18, Z = -8) pFWE = 0.027.



Statistical parametric maps Image signal intensity at the voxel of coordinates (X=33, Y= -18, Z = -8) plotted against serum vitamin D levels. (p = 0.001)

Shivakumar … Venkatasubramanian, 2017

Minimizing Treatment Resistance in Schizophrenia

Current Perspectives on Clozapine

Comparative efficacy and tolerability of 15 antipsychotic drugs in schizophrenia: a multiple-treatments meta-analysis

Stefan Leucht, Andrea Cipriani, Loukia Spineli, Dimitris Mavridis, Deniz Örey, Franziska Richter, Myrto Samara, Corrado Barbui, Rolf R Engel, John R Geddes, Werner Kissling, Marko Paul Stapf, Bettina Lässig, Georgia Salanti, John M Davis

Clozapine was ranked first & Amisulpride was found to rank second (the first being clozapine) efficacy in acute treatment for schizophrenia patients (6-week)

Assessment of tolerance & acceptability (ascertained by odds ratio with placebo for all-cause discontinuation) showed that amisulpride was best tolerated when compared with all other antipsychotics

[clozapine, amisulpride, olanzapine, risperidone, paliperidone, zotepine, haloperidol, quetiapine, aripiprazole, sertindole, ziprasidone, chlorpromazine, asenapine, lurasidone, and iloperidone]

Leucht et al. LANCET 2013

JAMA Psychiatry | Original Investigation

Real-World Effectiveness of Antipsychotic Treatments in a Nationwide Cohort of 29 823 Patients With Schizophrenia

- Prospectively gathered nationwide databases were linked to study the risk of re-hospitalization and treatment failure from July 1, 2006, to December 31, 2013, among all patients in Sweden with a schizophrenia diagnosis who were 16 to 64 years of age in 2006.

- Clozapine and long-acting injectable antipsychotic medications were the pharmacologic treatments with the highest rates of prevention of relapse in schizophrenia

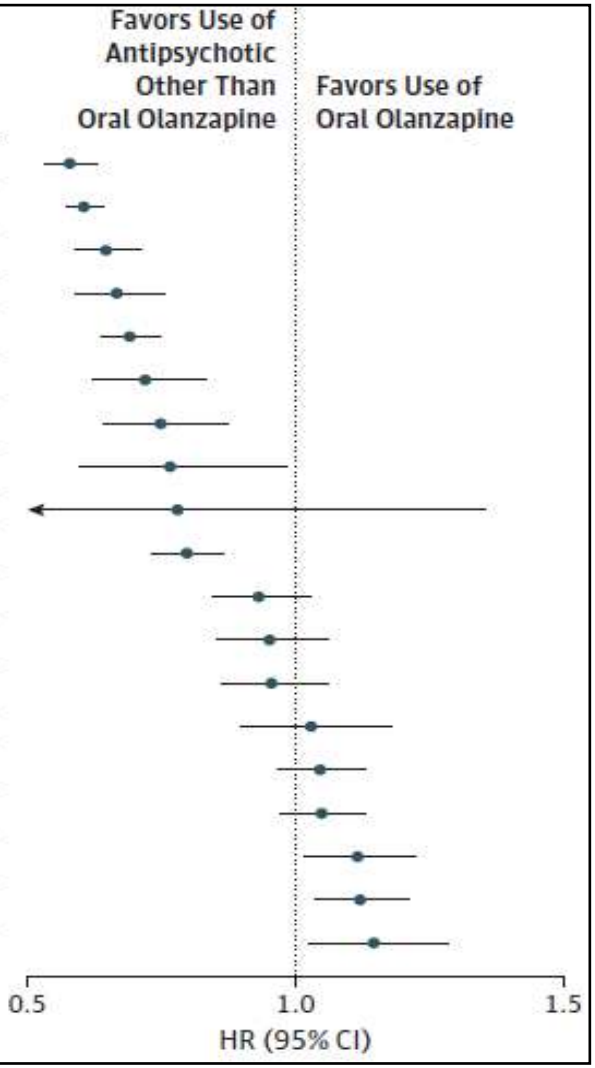
Tiihonen et al 2017

JAMA Psychiatry | Original Investigation

Real-World Effectiveness of Antipsychotic Treatments in a Nationwide Cohort of 29 823 Patients With Schizophrenia

Treatment Failure During Each Monotherapy Compared With Oral Olanzapine Use*

Treatment	HR (95% CI)
Oral clozapine	0.58 (0.53-0.63)
Polytherapy	0.61 (0.57-0.64)
LAI perphenazine	0.65 (0.59-0.71)
LAI haloperidol	0.67 (0.59-0.75)
LAI zuclopenthixol	0.69 (0.64-0.75)
LAI paliperidone	0.72 (0.62-0.83)
LAI flupentixol	0.75 (0.64-0.87)
LAI olanzapine	0.77 (0.60-0.98)
LAI fluphenazine	0.78 (0.45-1.35)
LAI risperidone	0.80 (0.73-0.87)
Oral perphenazine	0.93 (0.84-1.03)
Oral zuclopenthixol	0.95 (0.85-1.06)
Oral haloperidol	0.96 (0.86-1.06)
Oral flupentixol	1.03 (0.90-1.18)
Oral quetiapine	1.05 (0.97-1.13)
Oral risperidone	1.05 (0.97-1.13)
Other oral formulations	1.12 (1.02-1.22)
Oral aripiprazole	1.12 (1.04-1.21)
Oral levomepromazine	1.15 (1.02-1.28)



Significantly differed from Oral Olanzapine

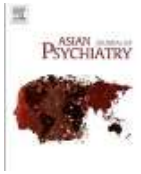
- Oral Clozapine
- LAI Perphenazine
- LAI Haloperidol
- LAI Zuclopenthixol
- LAI Paliperidone
- LAI Flupentixol
- LAI Risperidone

[$p < 0.001$, Significant after Bonferroni correction]

* - Adjusted Hazard Ratios & 95%CIs

Tiihonen et al 2017

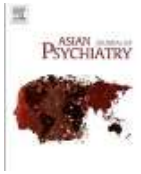
Clozaphobia: Is avoidance of clozapine in diabetes warranted?



- Clozapine is one of the most underutilized psychotropic agents.
- The risk of metabolic syndrome which includes obesity, hyperlipidemia and diabetes mellitus, with their subsequent complications counts among the top most reasons for the reluctance
- Emerging literature suggests that clozapine is less likely to induce diabetes at any rate higher than general population

Sreeraj et al 2017

Clozaphobia: Is avoidance of clozapine in diabetes warranted?



- Recently, we reported our clinical experience with nine patients having schizophrenia/schizoaffective disorders with comorbid diabetes mellitus and treated with clozapine.

- Interestingly, all patients could be maintained on optimal glycemic control even after clozapine with significant improvement in schizophrenia symptoms as well.

- A critique on the potential risks versus benefits of clozapine amidst our observations from this case series adds further supporting evidence to the emerging literature on the clinical utility of clozapine in treating schizophrenia patients with diabetes mellitus.

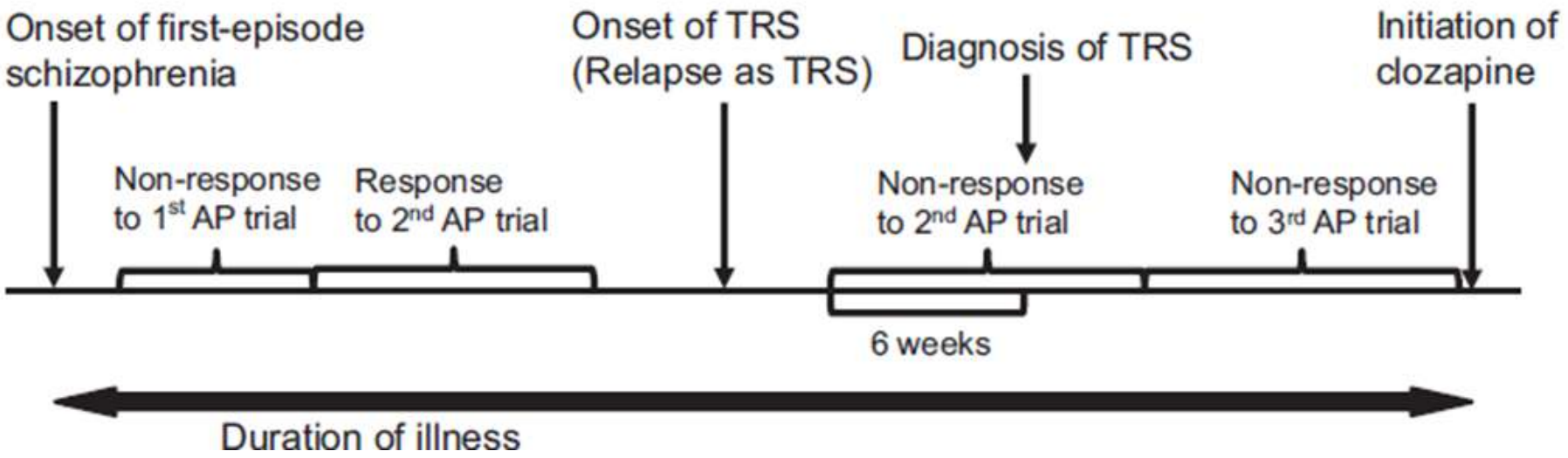
Sreeraj et al 2017

The critical treatment window of clozapine in treatment-resistant schizophrenia: Secondary analysis of an observational study

- 40–70% of patients with treatment resistant schizophrenia do not respond sufficiently to clozapine even with adequate blood levels
- SCZ patients whose treatment with clozapine was delayed after a diagnosis of treatment-resistance gained less benefit from this treatment
- Long delay in initiating clozapine (mean delay in initiating clozapine, 2–5 years) during routine clinical practice

Yoshimura et al 2017

The critical treatment window of clozapine in treatment-resistant schizophrenia: Secondary analysis of an observational study



Yoshimura et al 2017

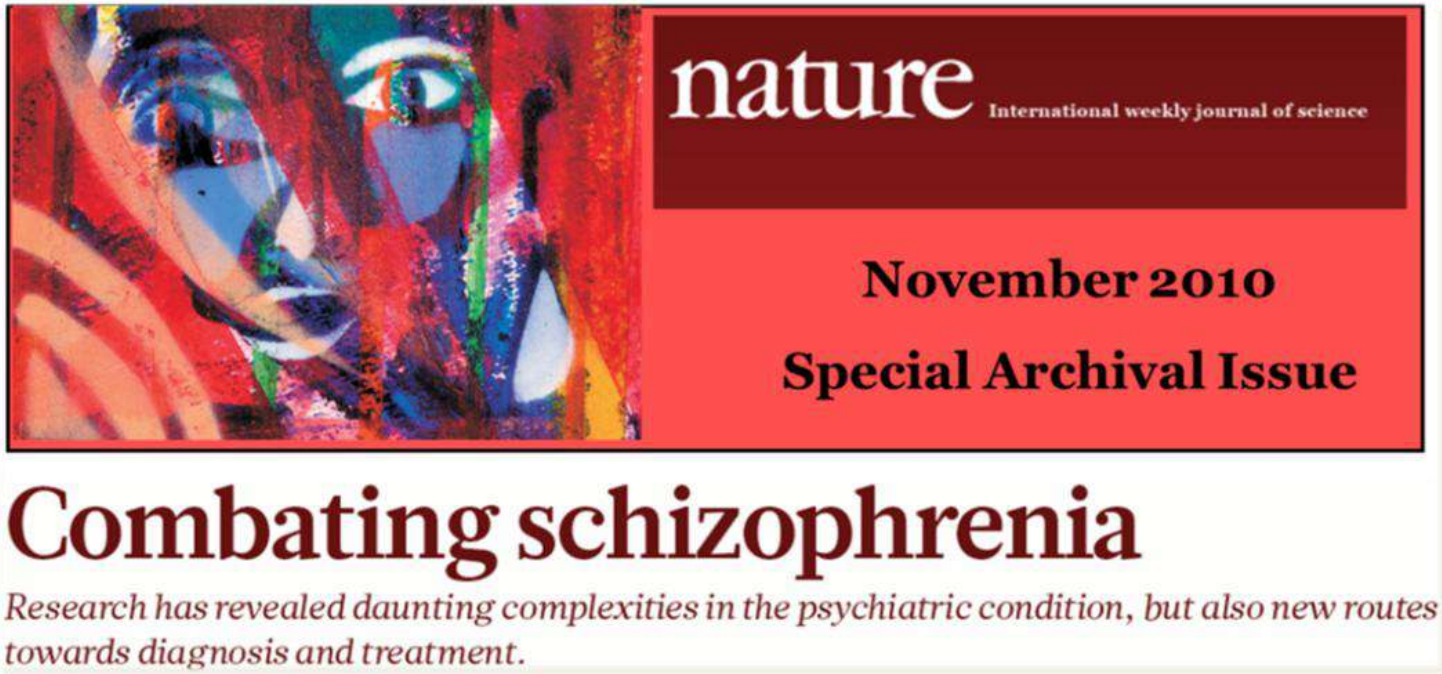
The critical treatment window of clozapine in treatment-resistant schizophrenia: Secondary analysis of an observational study

- Delay in initiating clozapine is a predictor of outcomes in response to clozapine, similar to the duration of untreated psychosis in first-episode schizophrenia
- The longer the delay the poorer was the response
- 2.8 years was the best predictive cut-off value of a delay in initiating clozapine for outcome of treatment with clozapine, and the response rate and improvement in BPRS total score in patients
- Clinicians should strive to reduce the delay in initiating clozapine to less than 3 years to improve symptomatic outcomes in TRS and to prevent clozapine-resistant schizophrenia.

Yoshimura et al 2017

Optimized Treatment for Early Course Schizophrenia

SUMMARY



"Antipsychotic drugs may not be the elusive silver bullet; Nonetheless, they have been strikingly efficacious in treating symptoms of schizophrenia"

The "Other" Side of Antipsychotics

*"Some drugs make me **Stiff***
*Others make me **Stout***
*I am told that a few might make my bones **Brittle***
*And sometimes **Infertile***
Incidentally – the voices might stop talking"

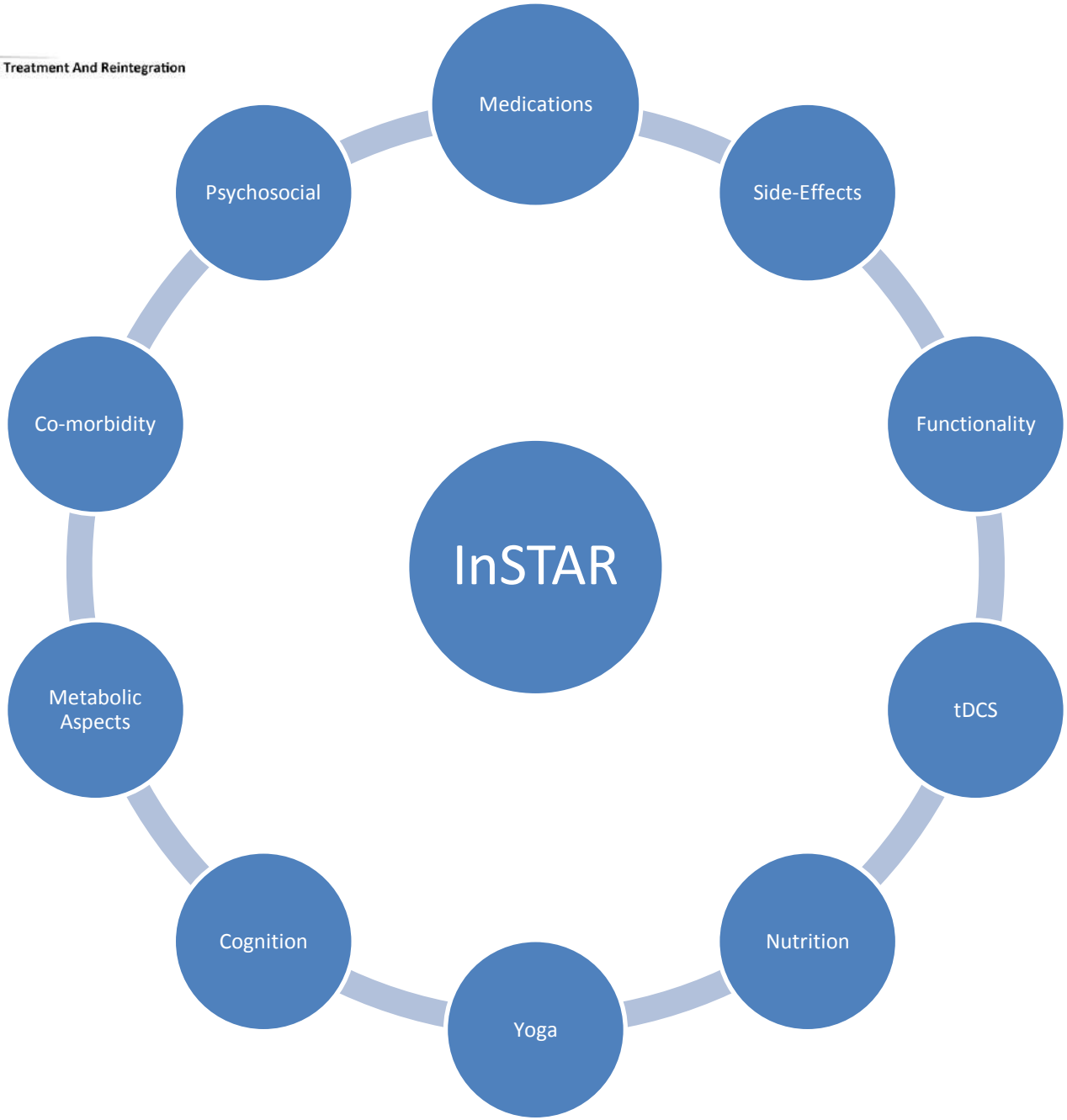
InSTAR

Individualized Schizophrenia Treatment And Reintegration

A Program with Personalized Approach for Treatment of Schizophrenia @ NIMHANS

www.instar-program.org

InSTAR
Individualized Schizophrenia Treatment And Reintegration



Optimized Treatment for Early Course Schizophrenia
SUMMARY

- Early course SCZ – a critical window of opportunity for treatment
- Antipsychotics – appropriately chosen & dosed – mainstay treatment
- Neurobiological aberrations involving inflammation, oxidative stress and neuroplasticity offer complementary avenues for further optimized treatment
- Relapse of symptoms in schizophrenia worsens illness course
- Certain risk factors for relapse are modifiable
- Optimizing adherence using long-acting injectable antipsychotic is a clinical impactful strategy

Optimized Treatment for Early Course Schizophrenia

SUMMARY

- Treatment-Resistant versus Resistant-to-Treat Schizophrenia
- The significance of plasma level monitoring of antipsychotics
- Antipsychotics cause a panorama of side-effects
- Recent evidence suggests potential nutritional deficiencies that can arise due to metabolic side effects of antipsychotics
- Early course schizophrenia patients are likely to have nutritional deficiencies & comprehensive systems-biology treatment approach
- Despite all these interventions, if symptoms persist, treatment with clozapine need to be initiated at the earliest.

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InSTAR

Individualized Schizophrenia Treatment And Reintegration

www.instar-program.org

Acknowledgement – InSTAR Team

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Dr. Shivakumar
Dr. Sowmya
Dr. Anushree Bose

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Thank You

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www.transpsychlab.org

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