Revisiting the Cerebral Diabetes Hypothesis of Schizophrenia:

Clinical Perspectives & Translational Potential in Contemporary Psychiatry

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Dr. G. Venkatasubramanian MD PhD

Professor of Psychiatry

National Institute of Mental Health And Neurosciences

Bangalore

InSTAR
Individualized Schizophrenia Treatment And Reintegration

TRANS PSYCH
Translational Psychiatry Laboratory
Cognitive Neurobiology Division
Neurobiology Research Centre
NIMHANS, India

NIMHANS
Department of Psychiatry – Then [1940s]

Department of Psychiatry - Now

NIMHANS
An Institute of National Importance

NIMHANS
An Institute of National Importance

InSTAR
Individualized Schizophrenia Treatment And Reintegration

Individualized Schizophrenia Treatment And Reintegration Program (InSTAR Program)

A dedicated clinical research program for schizophrenia

InSTAR Psychiatry Team

Prof B.N. Gangadhar MD DSc
Prof G. Venkatasubramanian MD PhD
Prof Shivarama Varambally MD
Dr. Naren P Rao MD
Dr. Vijaya Kumar MD

Dr. Sreeraj MD
Dr. Dinakaran MD
Dr. Shivakumar PhD
Dr. Sowmya MD
Dr. Anushree Bose PhD

www.instar-

InSTAR
Individualized Schizophrenia Treatment And Reintegration

www.instar-program.org

- Schizophrenia Clinic @ NIMHANS since 2000
- Multi-disciplinary team: psychiatry, psychiatric social work & clinical psychology
- **Uniqueness**: Caters to the clinical needs of untreated early course as well as multi-episode / treatment resistant patients with schizophrenia spectrum disorders
- InSTAR Program involves an outpatient (weekly) and inpatient services
- About 600+ schizophrenia patients are being followed up in this clinic with varying follow-up period ranging from monthly to yearly visits as per their clinical needs.
- Metabolic Clinic in Psychiatry: Innovative clinical program (SZ-Metabolic Disorder)
- Inclusive Treatment: Medications, Neuromodulation, Psychosocial & Yoga Therapy

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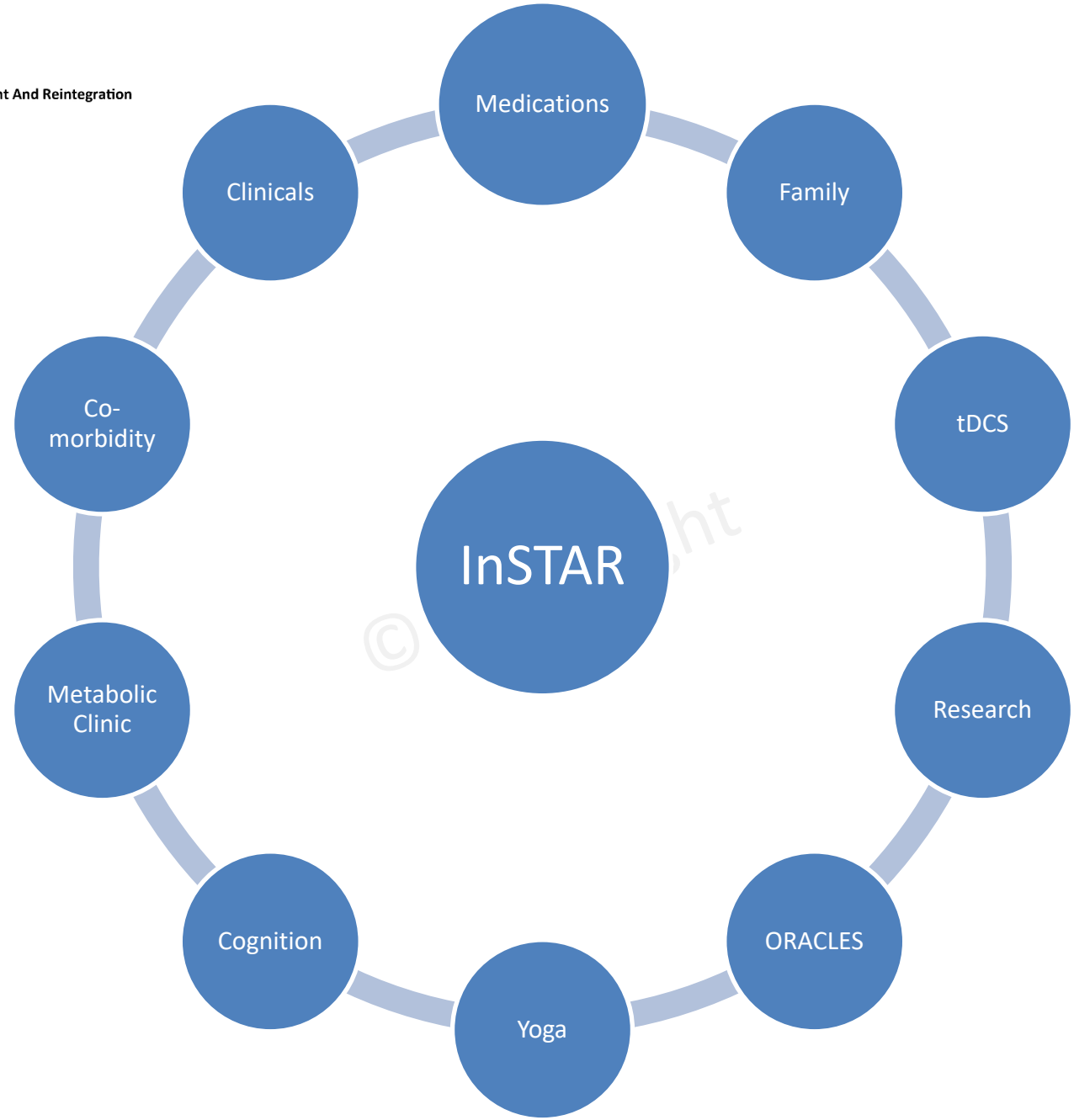
InSTAR
Individualized Schizophrenia Treatment And Reintegration



TRANS PSYCH
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Cognitive Neurobiology Division
Neurobiology Research Centre
NIMHANS, India

InSTAR
Individualized Schizophrenia Treatment And Reintegration

Bench → **Bed-Side**

"Translational Neurobiology Research On Schizophrenia"

InSTAR Clinical Research Program

Cutting-edge clinical and neurobiological research studies examining patients with schizophrenia spectrum as well as their unaffected first-degree relatives through brain imaging (sMRI, fMRI, MRS & DTI), eye movement, genetics, immunological / metabolic assays & transcranial Direct Current Stimulation.

The overarching focus of these studies is to evaluate
the systems biology interactions in schizophrenia
within a translational research paradigm to
discover biomarkers for diagnosis, treatment optimization & innovations

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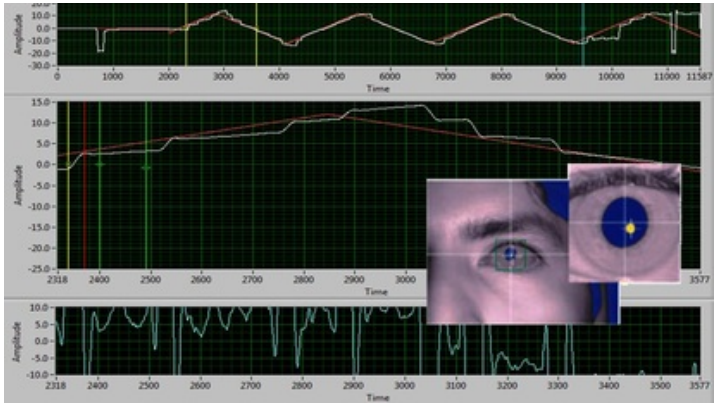
Ministry of Science and Technology

Department of Science & Technology
Ministry of Science & Technology

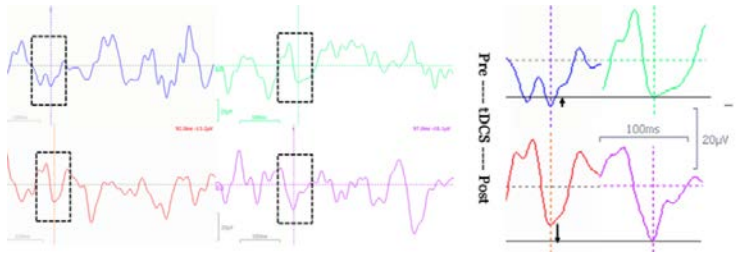
Schizophrenia: Electrophysiology & Psychophysics Research

High-Speed Eye Tracking



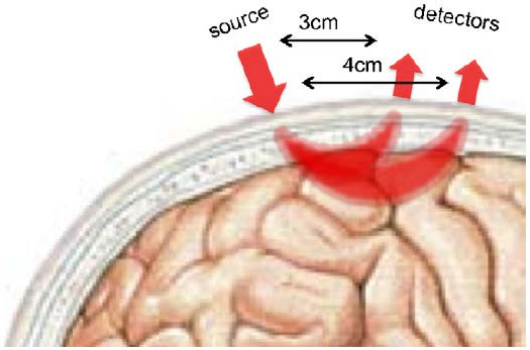
Subramaniam et al 2017

EEG / ERP Studies



Bose et al 2018

fNIRS



760 / 850 nm

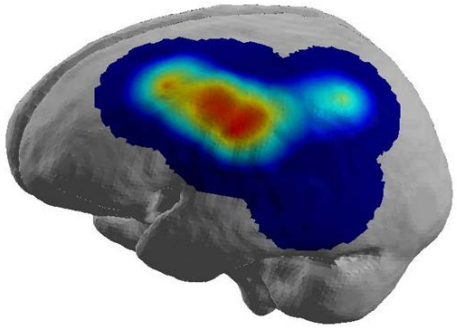


Figure 1(c)

Chhabra et al 2018

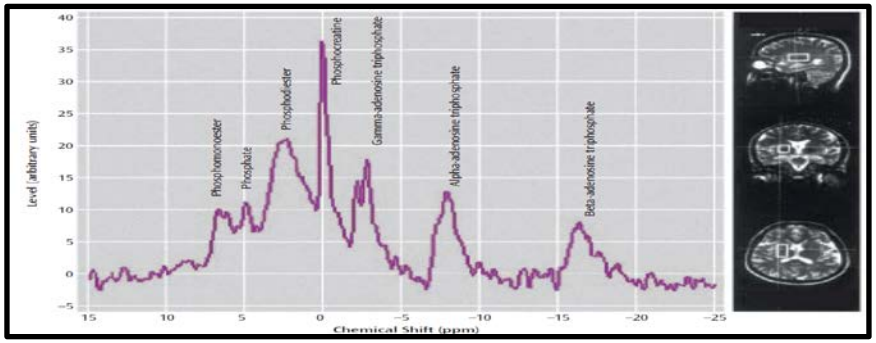
InSTAR Research Program – Brain Imaging Studies in Schizophrenia

Contents lists available at ScienceDirect

Progress in Neuro-Psychopharmacology & Biological Psychiatry

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

Schneiderian first rank symptoms and inferior parietal lobule cortical thickness in antipsychotic-naïve schizophrenia



ORIGINAL ARTICLE www.indianjpsychiatry.org

A functional Magnetic Resonance Imaging study of neurohemodynamic abnormalities during emotion processing in subjects at high risk for schizophrenia

ORIGINAL ARTICLE

Neuroanatomical correlates of psychopathology in antipsychotic-naïve schizophrenia

Contents lists available at ScienceDirect

Psychiatry Research: Neuroimaging

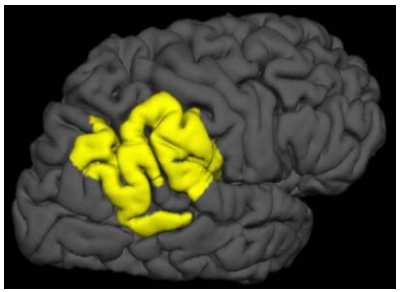
journal homepage: www.elsevier.com/locate/psychresns

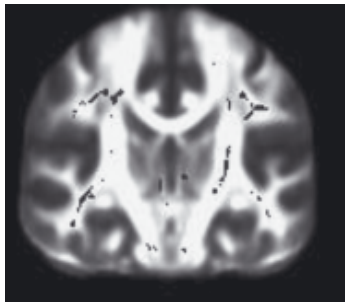
Corpus callosum deficits in antipsychotic-naïve schizophrenia: Evidence for neurodevelopmental pathogenesis

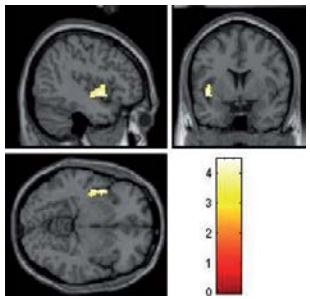
Original Article

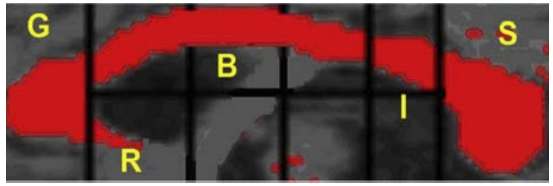
www.ijpm.info

Orbitofrontal Lobe Volume Deficits in Antipsychotic-Naïve Schizophrenia: A 3-Tesla MRI Study

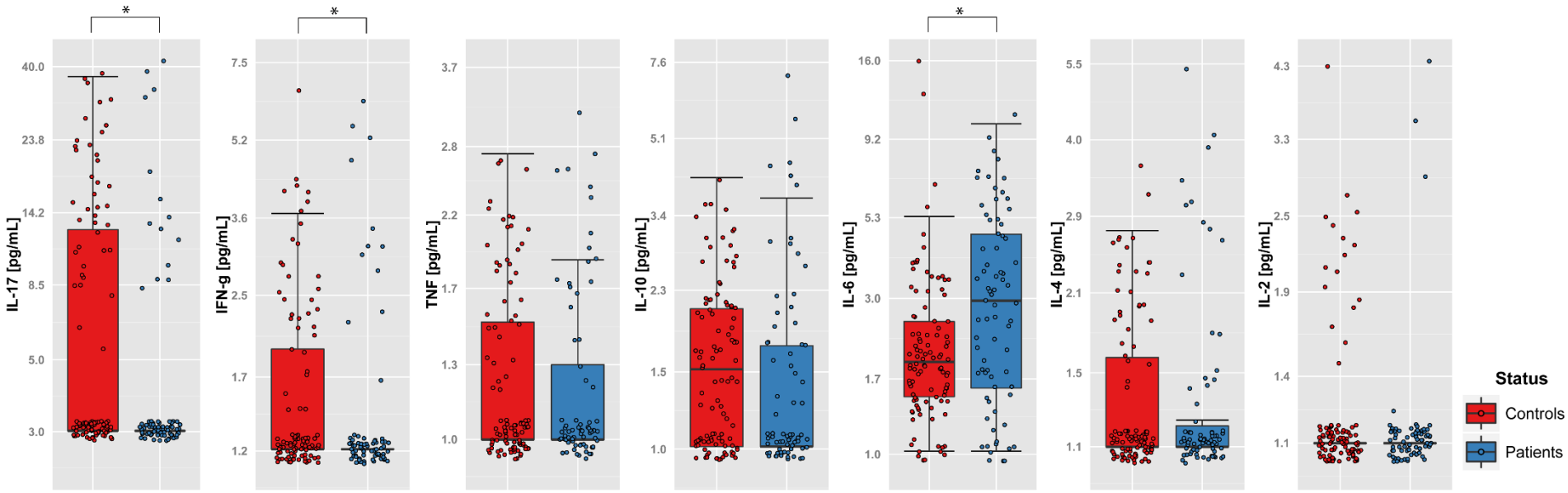








InSTAR Research: Cytokine Abnormalities in Schizophrenia



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

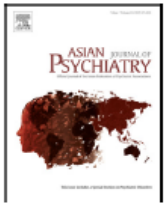
Patients had significantly greater plasma levels of IL-6 &
lower levels of IL-17a as well as IFN-g in comparison to healthy controls

Kalmady…Venkatasubramanian. Schizophrenia Research 2018

InSTAR Research Program – Immunogenetic Studies in Schizophrenia

The impact of HLA-G 3′ UTR variants and sHLA-G on risk and clinical correlates of schizophrenia

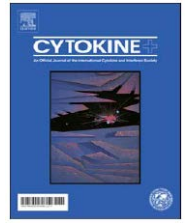
The impact of IL10 polymorphisms and sHLA-G levels on the risk of schizophrenia



Soluble human leukocyte antigen (sHLA)-G levels may predict early onset of schizophrenia in male patients

TISSUE ANTIGENS
IMMUNE RESPONSE GENETICS

Influence of correlation between HLA-G polymorphism and Interleukin-6 (IL6) gene expression on the risk of schizophrenia



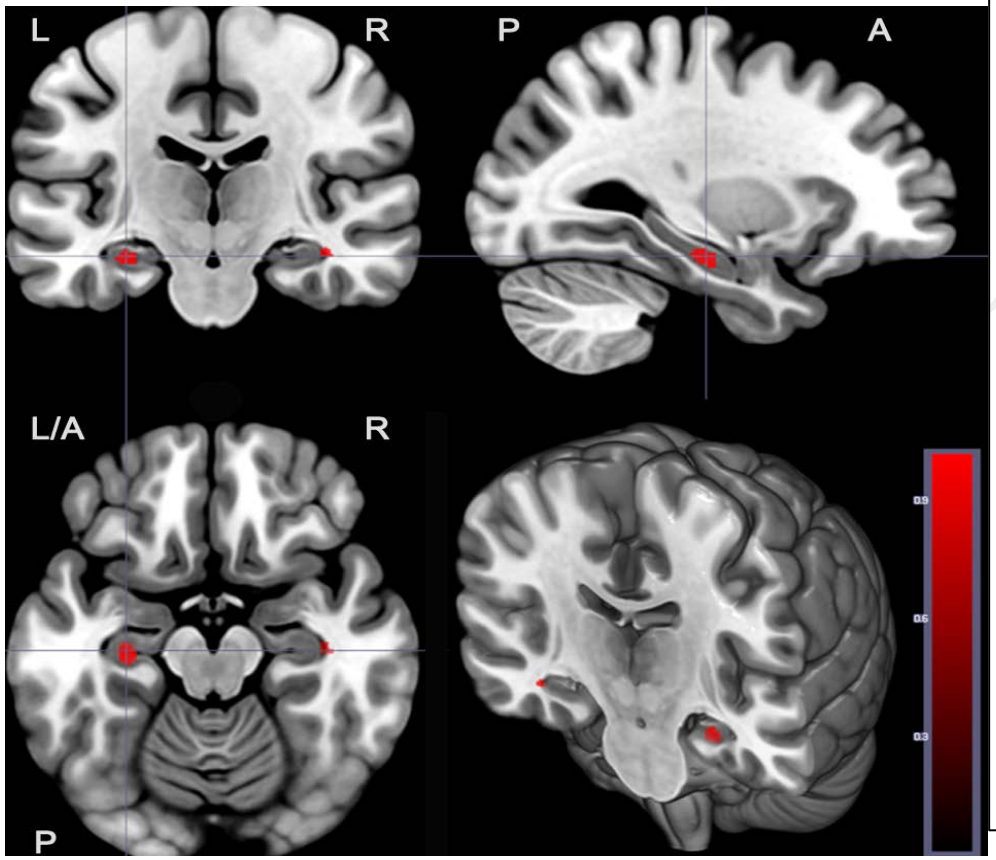
Impact of antipsychotic treatment on methylation status of Interleukin-6 [IL-6] gene in Schizophrenia

InSTAR Research Program – Imaging Genetics in Schizophrenia

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]



Various lines of evidence involving epidemiological, genetic and foetal pathogenetic models suggest a compelling role for Interleukin-6 (IL-6) in the pathogenesis of schizophrenia.

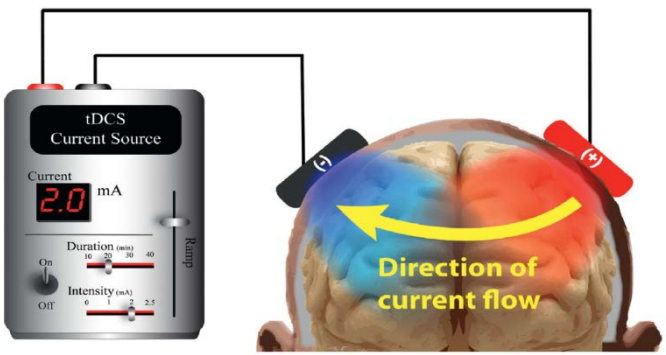
IL-6 mediated inflammatory response triggered by maternal infection or stress

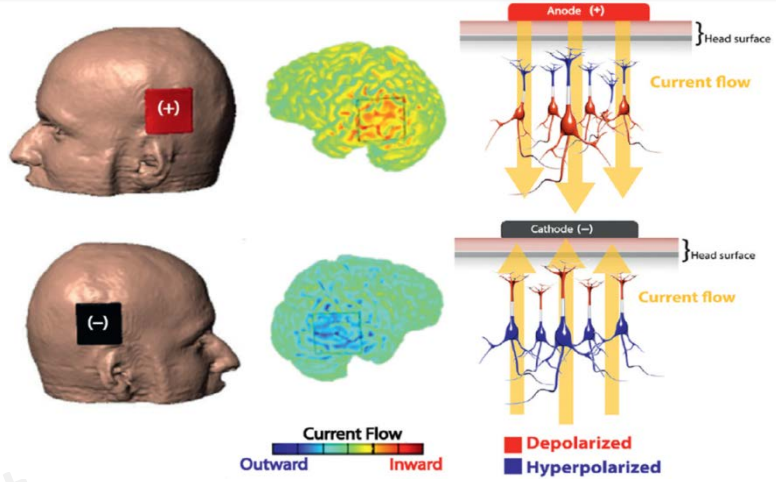
This can lead to disrupted prenatal hippocampal development which might contribute towards psychopathology during adulthood.

A recent NIMHANS study examined antipsychotic-naïve schizophrenia patients for hippocampal volume, plasma IL-6 & IL-6 gene promoter polymorphism; findings suggest differential susceptibility effects of IL-6 promoter polymorphism on hippocampal volume in schizophrenia patients.

Kalmady, Venkatasubramanian et al. PLoS One 2014

WISER Neuromodulation Program for Schizophrenia



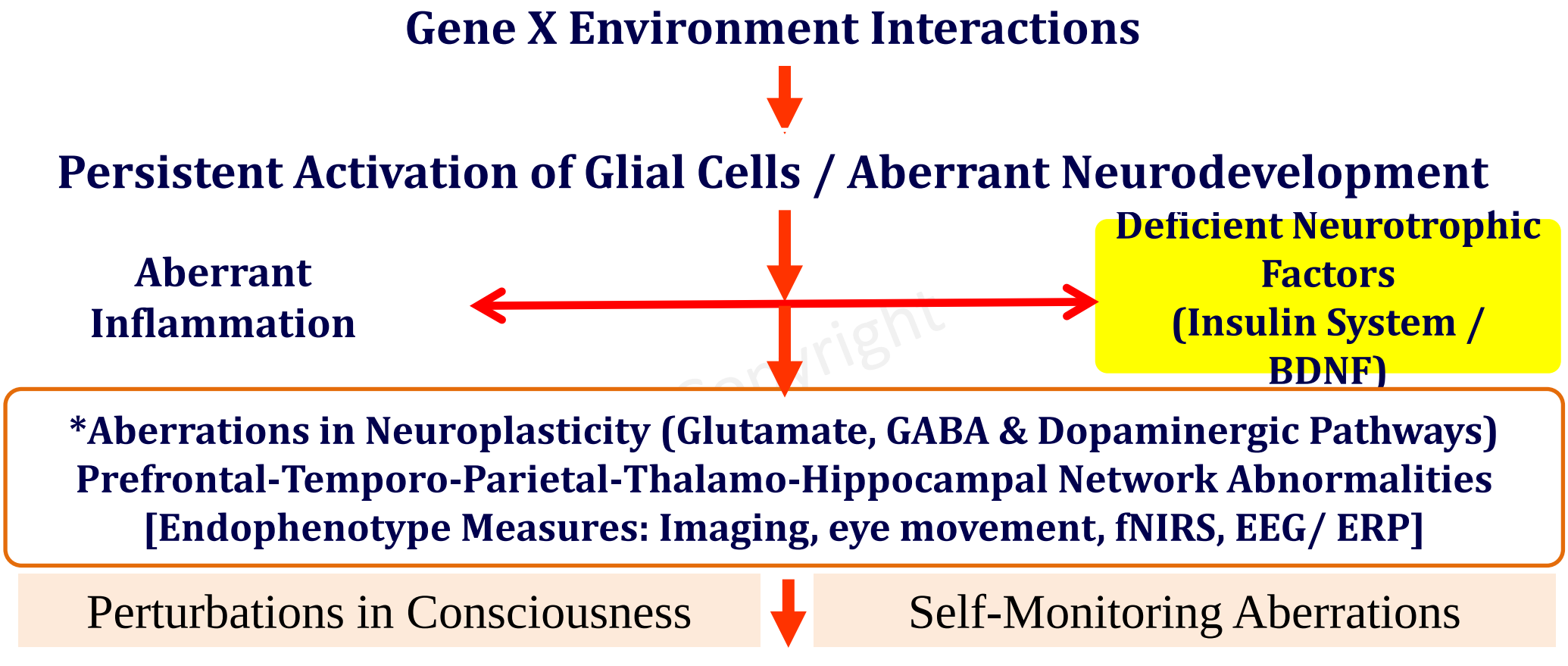


"**W**eak **I**ntensity **S**timulation for **E**nhancement and **R**e-integration"
"**WISER**" Neuromodulation Program

"Modulation of Neuroplasticity using
several neuromodulation techniques that apply
weak intensity electric current to
understand & treat schizophrenia / other psychiatric disorders through
enhancement of deficient brain functions as well as
amelioration of resistant symptoms facilitating **re-integration**"

Transcranial Direct Current Stimulation (tDCS) & its variants

InSTAR Research Program – Clinical Neurobiology of Schizophrenia



Neurobiological correlates of treatment (antipsychotics neuromodulation – tDCS)

*Select Representation of Parameters

Venkatasubramanian et al 2007; 2008, 2015

Revisiting the Cerebral Diabetes Hypothesis of Schizophrenia:

Clinical Perspectives & Translational Potential in Contemporary Psychiatry

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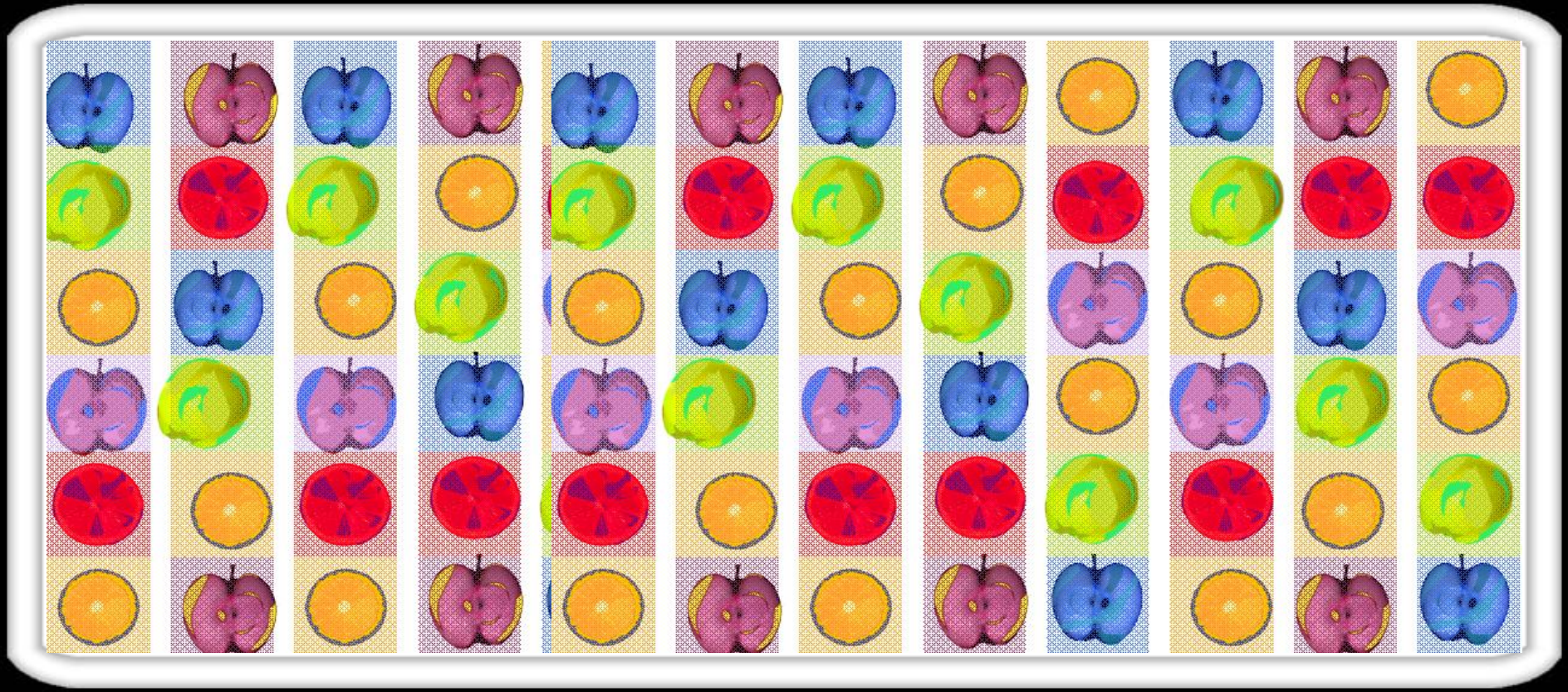
Schizophrenia – The Elusive Enigma

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

Lovestone et al 2007

"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]

Schizophrenia and Systems Biology

Intriguing Interactions

Schizophrenia: The Red Queen Effect

'Schizophrenia might be associated with decreased risk for Certain types of Cancer

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Grinshpoon et al. Sch Res 2005; Venkatasubramanian, Med Hypotheses 2009

Genetic correlates of medical comorbidity associated with schizophrenia and treatment with antipsychotics

- Based on clinical genetic studies in schizophrenia, comorbid impaired glucose tolerance/type 2 diabetes mellitus, most autoimmune disorders and cardiac autonomic dysregulation have the strongest evidence for familial predisposition.

- Similarly, of antipsychotic-induced adverse drug reactions, tardive dyskinesia, neuroleptic malignant syndrome, and antipsychotic-induced weight gain have some evidence for familial clustering.

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- On the molecular genetic level, schizophrenia seems to share specific genes with type 2 diabetes mellitus and with autoimmune disorders.

- Various genes have been proposed to account for the reduced incidence of rheumatoid arthritis and cancer in schizophrenic patients and their relatives.

Ferentinos & Dikeos, 2012

Schizophrenia and Systems Biology

Arm Chair Theorist versus Astute Clinician

Exciting Hypotheses versus Effective Interventions

The Bottom-line is that one cannot deny the intricate and possibly intrinsic link between

Schizophrenia & Other Medical Diseases

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Schizophrenia and Systems Biology

Restating the 'problem' of Schizophrenia

Schizophrenia is a neuropsychiatric disorder with complex systems biology interactions that are relevant at pathogenetic as well as therapeutic dimensions

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Schizophrenia and Systems Biology

What does it offer clinically?

If Schizophrenia has intricate links with other medical diseases, interventions that are likely to alter the pathways of schizophrenia pathogenesis are equally likely to have an impact on the risk for other medical diseases as well

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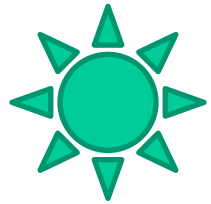

"SCHIZOPHRENIA AS A METABOLIC BRAIN DISORDER"

An Attempt to Understand the 'Enigma'

A Disorder of Mind / Brain ?

A Disorder of Metabolism ?

Is it a Metabolic Brain Disorder??

Schizophrenia and Systems Biology

Intriguing Interactions

Schizophrenia & Diabetes Mellitus

'Diabetes is a disease which often shows itself in families in which insanity prevails'

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Maudsley, 1897

BRAIN
A JOURNAL OF NEUROLOGY
1919

HYPERGLYCEMIA IN MENTAL DISORDERS

F.H. KOOY

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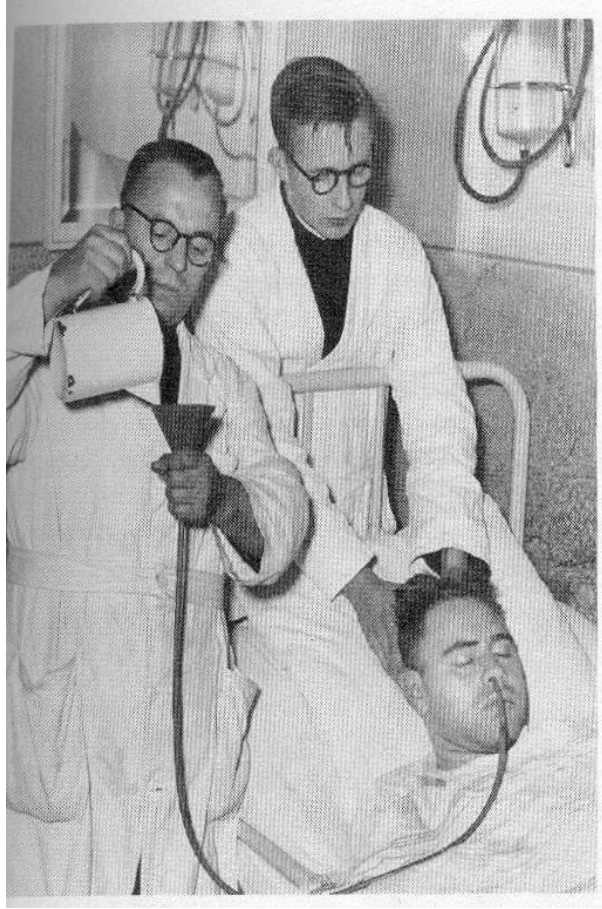
"the daily account and mental state of
10 patients with hebephrenic schizophrenia,
the conclusion was that
their constant hyperglycaemic curve meant that
they had both dementia praecox and hyperglycaemia"



Insulin Coma Therapy

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"an intensification of the tonus of the parasympathetic end of the autonomic nervous system, by blockading the nerve cell, and by strengthening the anabolic force which induces the restoration of the normal function of the nerve cell and the recovery of the patient."

(Sakel, 1956)

Medical Hypotheses

Medical Hypotheses (1994) 43, 420–435
©Longman Group Ltd 1994

Schizophrenia is a Diabetic Brain State: An Elucidation of Impaired Neurometabolism

R.J. HOLDEN* and P.A. MOONEY*

Schizophrenia & Diabetes Mellitus – Pre-neuroleptic Era

"Case studies and thoughtful naturalistic publications
prior to the availability of phenothiazines,
albeit poor in design,
still help the modern clinician to
ask valid questions and gain an insight into
possible pathological conditions associated with schizophrenia."

"They raise the intriguing possibility that diabetes and disturbed
carbohydrate metabolism could be an integral part of
the schizophrenia disease process."

Kohen, 2004

The Brain Connection of Diabetes

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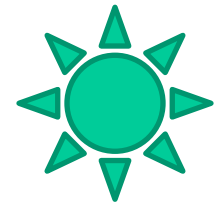

REVIEW

nature

Cooperation between brain and islet in glucose homeostasis and diabetes

Michael W. Schwartz[1], Randy J. Seeley[2], Matthias H. Tschöp[3], Stephen C. Woods[4], Gregory J. Morton[1], Martin G. Myers[5] & David D'Alessio[2]

REVIEW nature

Cooperation between brain and islet in glucose homeostasis and diabetes

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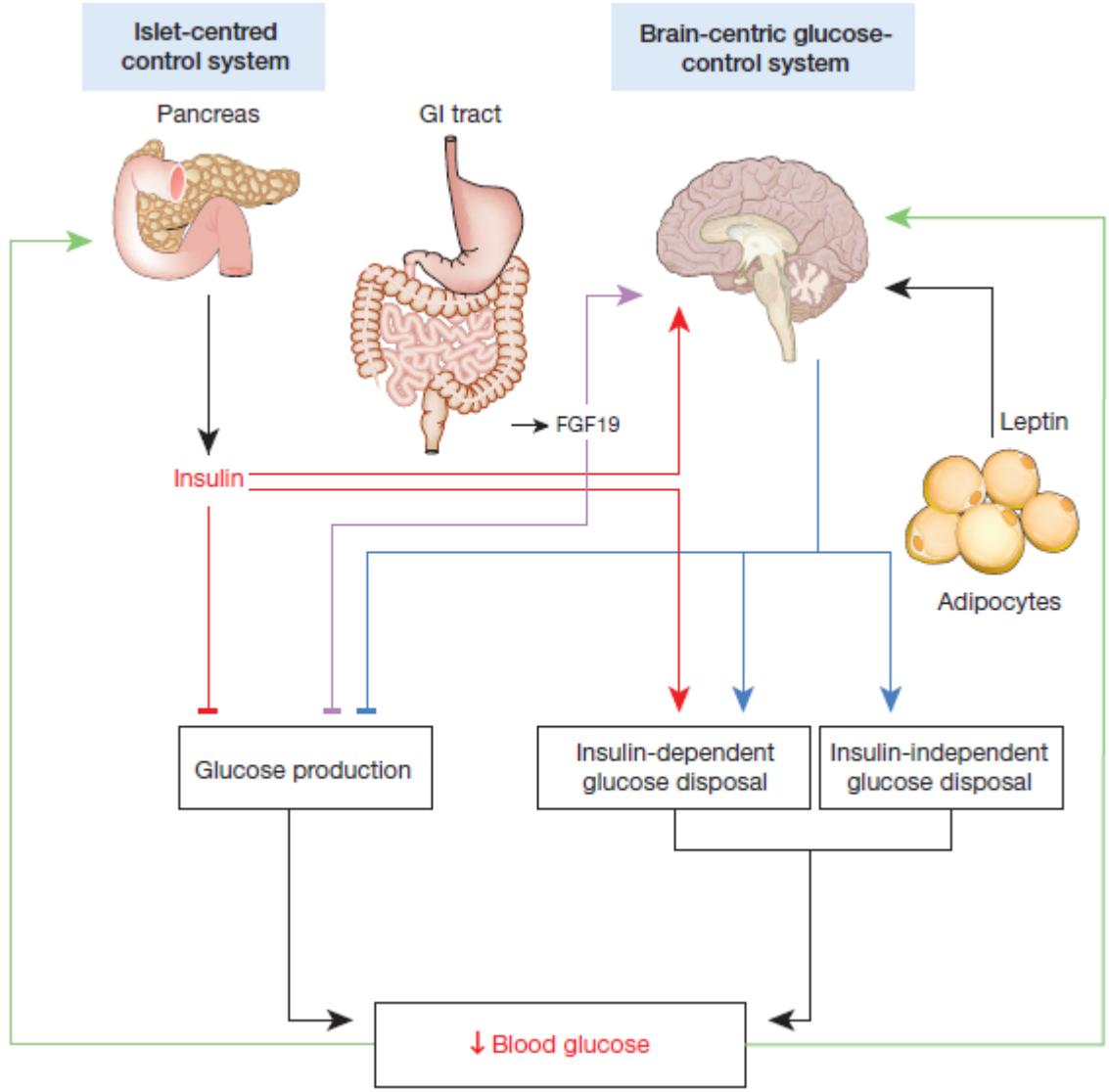

REVIEW nature

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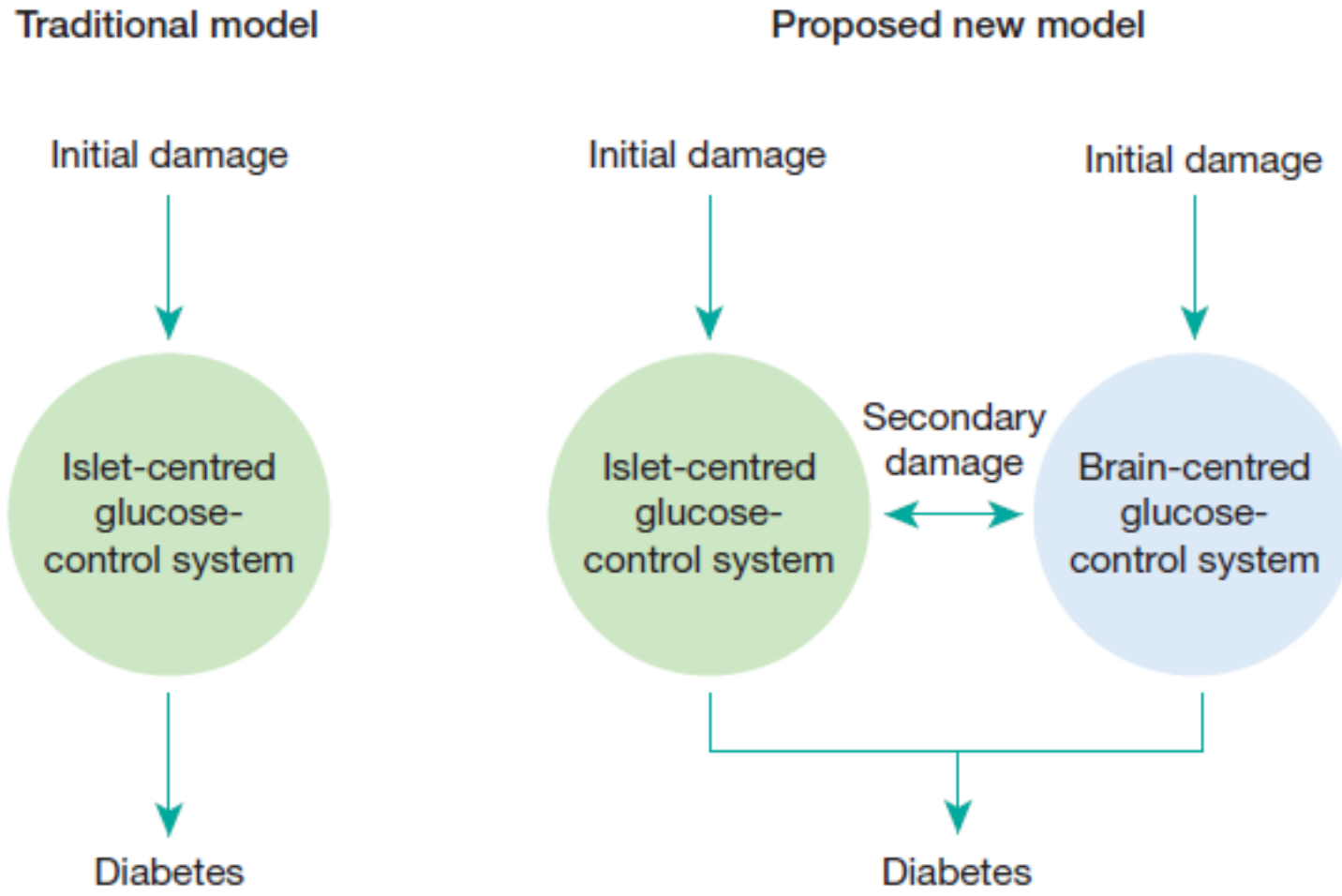

DIABETES, OBESITY AND METABOLISM
A JOURNAL OF PHARMACOLOGY AND THERAPEUTICS

Effect of the antipsychotic agent amisulpride on glucose lowering and insulin secretion

"Amisulpride has anti-diabetic actions in diet-induced obese mice resulting from increased insulin secretion.

This provides some explanation for why amisulpride, unlike other atypical antipsychotics, is not diabetogenic in man.

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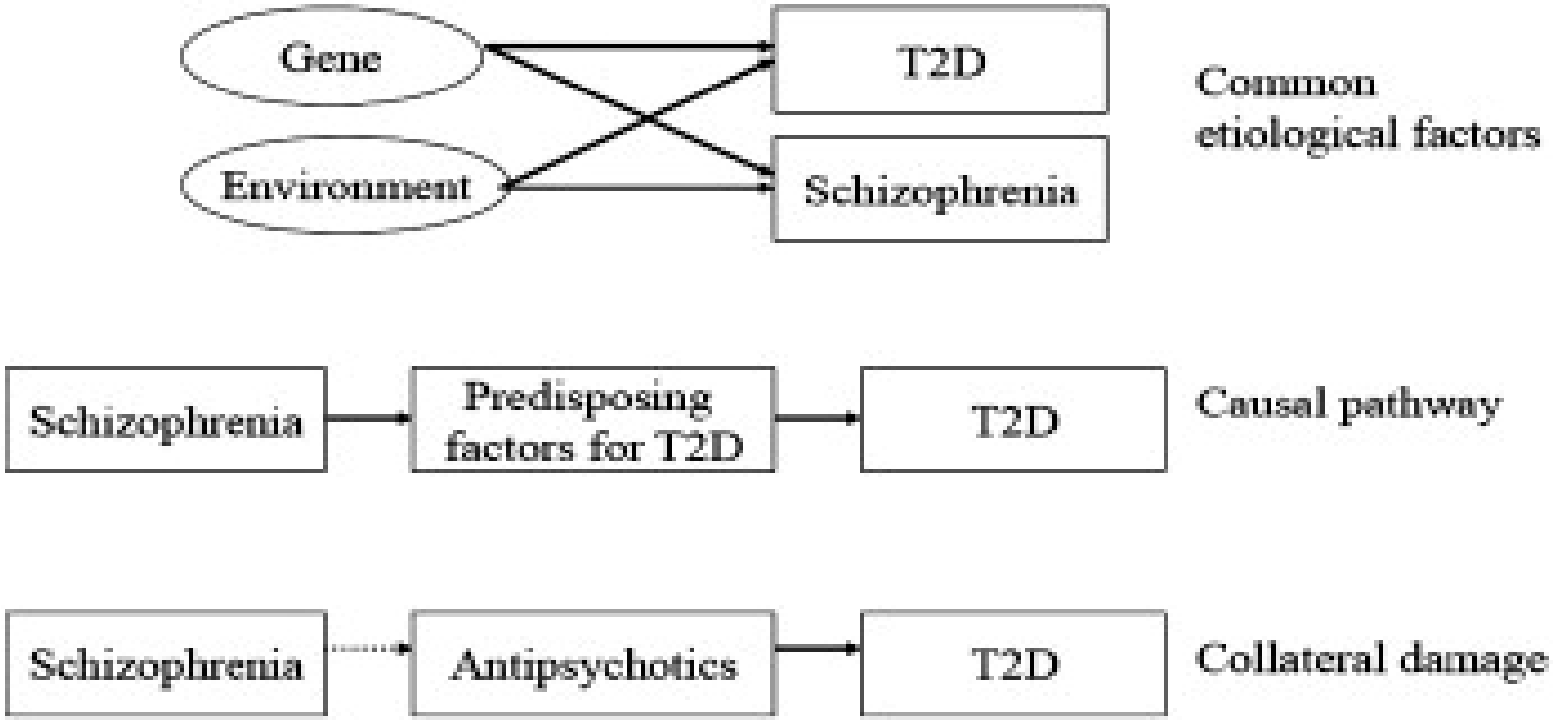
Roix et al 2011

SCHIZOPHRENIA & INCREASED RISK FOR DIABETES MELLITUS

- Two family studies have found that the relatives of people with schizophrenia (Mukherjee et al. 1989; Spelman et al. 2007) as well as non-affective psychoses (Fernandez-Egea et al. 2008) have an increased risk of Type 2 diabetes.



Insulin Abnormalities in Schizophrenia

Insulin and Insulin-Like Growth Factor-1 Abnormalities in Antipsychotic-Naive Schizophrenia

THE AMERICAN JOURNAL OF PSYCHIATRY

Ganesan Venkatasubramanian, M.D.

Seetharamaiah Chittiprol, Ph.D.

Narendran Neelakantachar, M.B.B.S.

Magadi N. Naveen, M.D.

Jagadisha Thirthall, M.D.

Bangalore N. Gangadhar, M.D.

K. Taranath Shetty, Ph.D.

Objective: The purpose of this study was to examine the evidence for the insulin-like growth factor-1 (IGF-1) deficiency hypothesis in the pathogenesis of schizophrenia.

Method: The authors examined the fasting plasma levels of glucose, insulin, IGF-1, and cortisol in antipsychotic-naive schizophrenia patients (N=44) relative to age- and sex-matched healthy comparison subjects (N=44). Patients and comparison subjects were also matched for anthropometric measures and physical activity.

Results: Schizophrenia patients had a significantly higher mean plasma insulin level as well as a significantly higher mean insulin resistance score relative to healthy comparison subjects. The mean plasma IGF-1 level was significantly lower in patients. IGF-1 levels had a significant negative correlation with plasma insulin levels. The total positive symptoms score as well as the hallucinations subscore had a significant inverse relationship with IGF-1 levels.

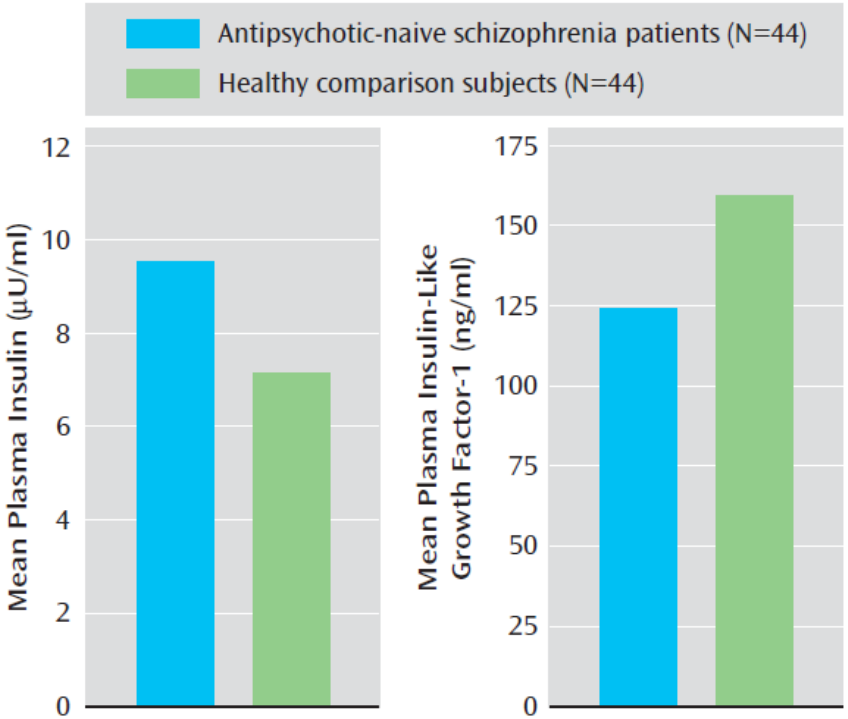
Conclusions: Deficient IGF-1 might underlie insulin resistance in schizophrenia. The IGF-1 deficit in antipsychotic-naive schizophrenia patients and its significant correlation with psychopathology scores suggest that IGF-1 might be potentially involved in the pathogenesis of schizophrenia.

(Am J Psychiatry 2007; 164:1557–1560)

Schizophrenia-Diabetes Interface: Insulin System Abnormalities

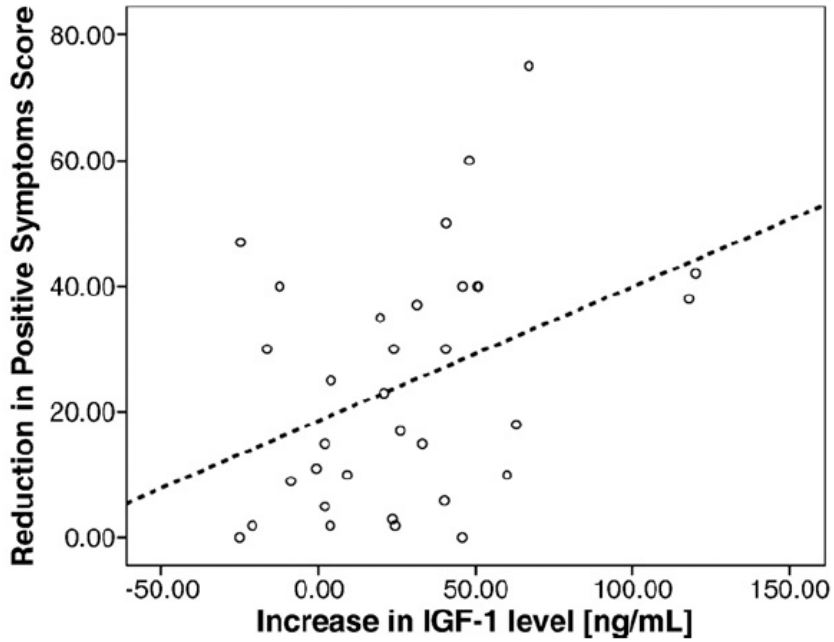
Insulin and Insulin-Like Growth Factor-1 Abnormalities in Antipsychotic-Naive Schizophrenia

THE AMERICAN JOURNAL OF PSYCHIATRY



Venkatasubramanian et al. American Journal of Psychiatry 2007

Effect of antipsychotic treatment on Insulin-like Growth Factor-1 and cortisol in schizophrenia: A longitudinal study



Venkatasubramanian et al. Schizophrenia Research 2010

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Insulin, Insulin-like Growth Factor-1 & the Insulin Signaling pathway

- Insulin & Insulin-like Growth Factor-1 (IGF-1) receptors share similar structures and signaling pathways (Bondy et al 2002)
- IGF-1 has neuroprotective, anti-apoptotic properties that are crucial for optimal neurodevelopment – especially prefrontal & hippocampal cortices (Dore et al 1997)
- Prefrontal (Goldman-Rakic and Selemon, 1997) & Hippocampal (Harrison, 2004) cortices are critically implicated in the pathogenesis of schizophrenia
- It is possible that low IGF-1 might render the brain more vulnerable to neurodevelopmental insults potentially culminating in schizophrenia.

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Insulin & IGF-1 Abnormalities in Antipsychotic-naïve Schizophrenia

IGF-1 levels had a significant negative correlation with plasma insulin levels.

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

Venkatasubramanian et al 2007

Neuroendocrinology Letters

Fasting insulin serum levels and psychopathology profiles in male schizophrenic inpatients treated with olanzapine or risperidone

Olanzapine-related
changes in endogenous fasting insulin levels
were correlated with
clinical improvement in
acutely ill non-diabetic schizophrenia patients

Konarzewska et al 2013

The activation of the Akt/PKB signalling pathway in the brains of clozapine-exposed rats is linked to hyperinsulinemia and not a direct drug effect

Defects in Akt/PKB and GSK3 signalling can contribute to development of psychiatric diseases.

Clozapine is known to activate Akt/PKB in the brain, and some studies have indicated that this is due to a direct effect of the drug on the neurons.

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Elevated insulin levels induced by clozapine are in fact the real cause of the drug's effects on Akt/PKB and GSK3 in the brain.

This suggests that the elevated levels of insulin induced by clozapine may contribute to this drug's therapeutic efficacy

Smith et al 2014

Effectiveness & Metabolic Side-Effects

Clinical and biochemical measures	*Comparisons between SGAs*
Effectiveness	$\mathrm{Clz} > \mathrm{Olz} \geqslant \mathrm{Risp} \backsimeq \mathrm{Quet} \backsimeq \mathrm{Zip} \backsimeq \mathrm{Ari}$
Degree of metabolic disturbances	$\mathrm{Clz} \geqslant \mathrm{Olz} > \mathrm{Risp} \backsimeq \mathrm{Quet} \geqslant \mathrm{Zip} \backsimeq \mathrm{Ari}$

Girgis et al 2008

The American Journal of Psychiatry

Basal Ganglia High-Energy Phosphate Metabolism in Neuroleptic-Naive Patients With Schizophrenia: A 31-Phosphorus Magnetic Resonance Spectroscopic Study

Gangadhar et al 2004

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Psychiatry Research: Neuroimaging 181 (2010) 237–240

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

Brief report

High energy phosphate abnormalities normalize after antipsychotic treatment in schizophrenia: A longitudinal ^{31}P MRS study of basal ganglia

Peruvumba N. Jayakumar[a], Bangalore N. Gangadhar[b,*], Ganesan Venkatasubramanian[b], Sunali Desai[a], Latha Velayudhan[b], Dattathreya Subbakrishna[c], Matcheri S. Keshavan[d,e]

Summary Points

1. Schizophrenia – hyperinsulinemia even in untreated state
2. Therapeutic correlates of insulin levels as well as energy metabolism aberrations in schizophrenia argues for “metabolic” component to underlie the pathogenesis

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SCHIZOPHRENIA AS A METABOLIC BRAIN DISORDER: A CLINICIAN'S PERSPECTIVE

A SHIFT IN APPROACH TOWARDS UNDERSTANDING SCHIZOPHRENIA

BRAIN / MIND DISORDER

METABOLICALLY DISORDERED BRAIN / MIND

CRTICAL QUERY: IS THERE A LINK BETWEEN INSULIN & DOPAMINE?

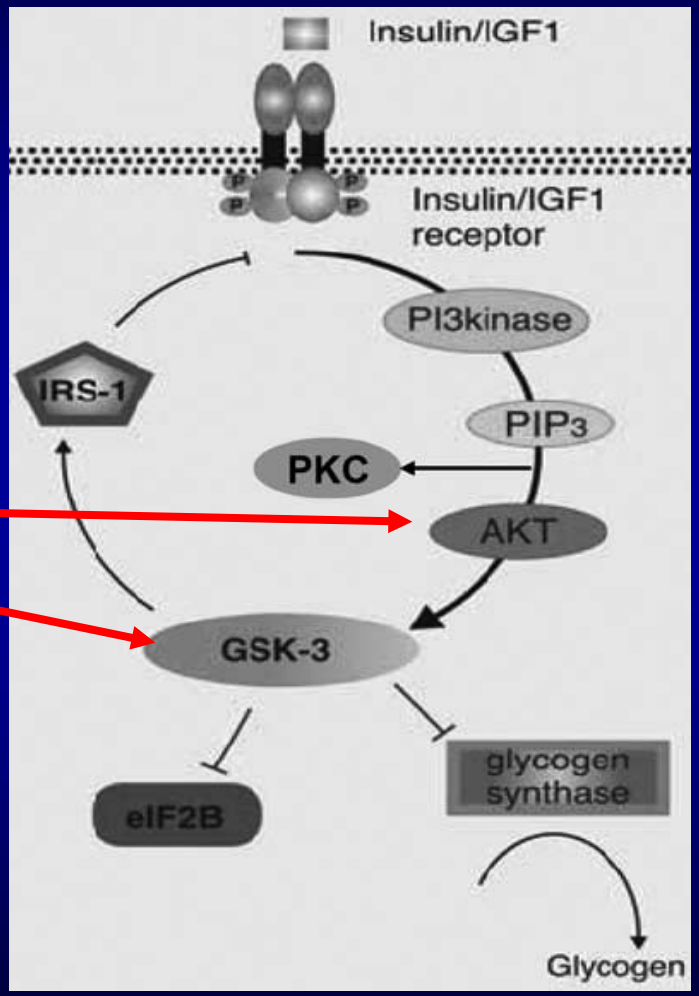
SCHIZOPHRENIA & INCREASED RISK FOR DIABETES MELLITUS

At-Risk Variant in *TCF7L2* for Type II Diabetes Increases Risk of Schizophrenia

- Recently, a single nucleotide polymorphism of the gene TCF7L2 (Transcription factor 7-like 2) [rs7903146] was found to be associated with schizophrenia [Hansen et al 2011]
- Importantly, this gene has been most consistently replicated in the risk towards type-2 diabetes mellitus [Ioannidis et al 2007]
- Interestingly, this gene modulate important signaling pathways that underlie schizophrenia pathogenesis – Wnt & GSK-3β [Cauchi & Froguel, 2008]
- Critically, these signaling pathways are also linked to various genes that are robustly implicated in the pathogenesis of schizophrenia like DISC1, dopamine signaling and several others [Lin & Shuldiner, 2010]

GSK-3 & The Insulin Signaling Pathway

Antipsychotics



Chlorpromazine
Haloperidol
Fluphenazine
Risperidone
Olanzapine
Clozapine

Dwyer et al 2005; Girgis et al 2008

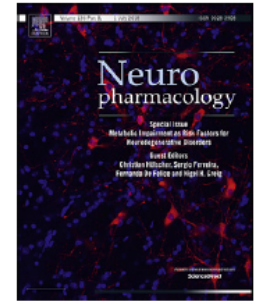
Hippocampus

Akt1 Deficiency in Schizophrenia and Impairment of Hippocampal Plasticity and Function

Contents lists available at ScienceDirect

Neuropharmacology

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



Insulin-mediated synaptic plasticity in the CNS: Anatomical, functional and temporal contexts

Neuroplasticity

Neural plasticity is the neurophysiological process through which the brain adapts to changing environment by altering its molecular and structural features

ERNESTO LUGARO

The first to coin the term plasticity to synaptic modification (1898)

JERZY KORNOSKI

Morphological Changes in the Neuronal Synaptic Connections are the substrate of Learning (1948)

DONALD HEBB

Cells that fire together wire together (1949)

THE MUTABLE BRAIN

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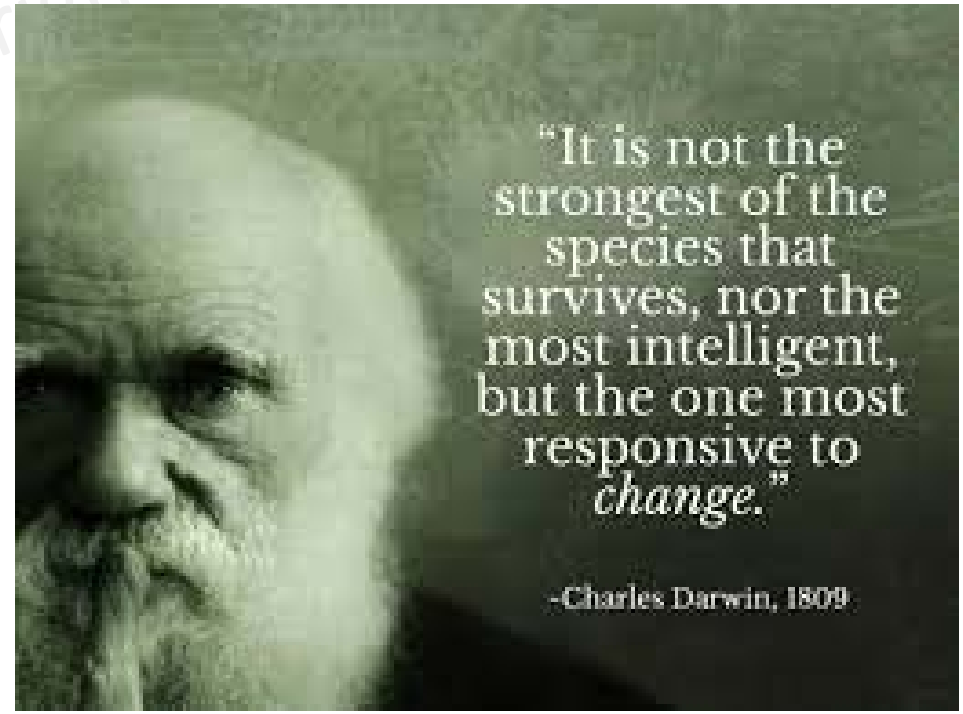
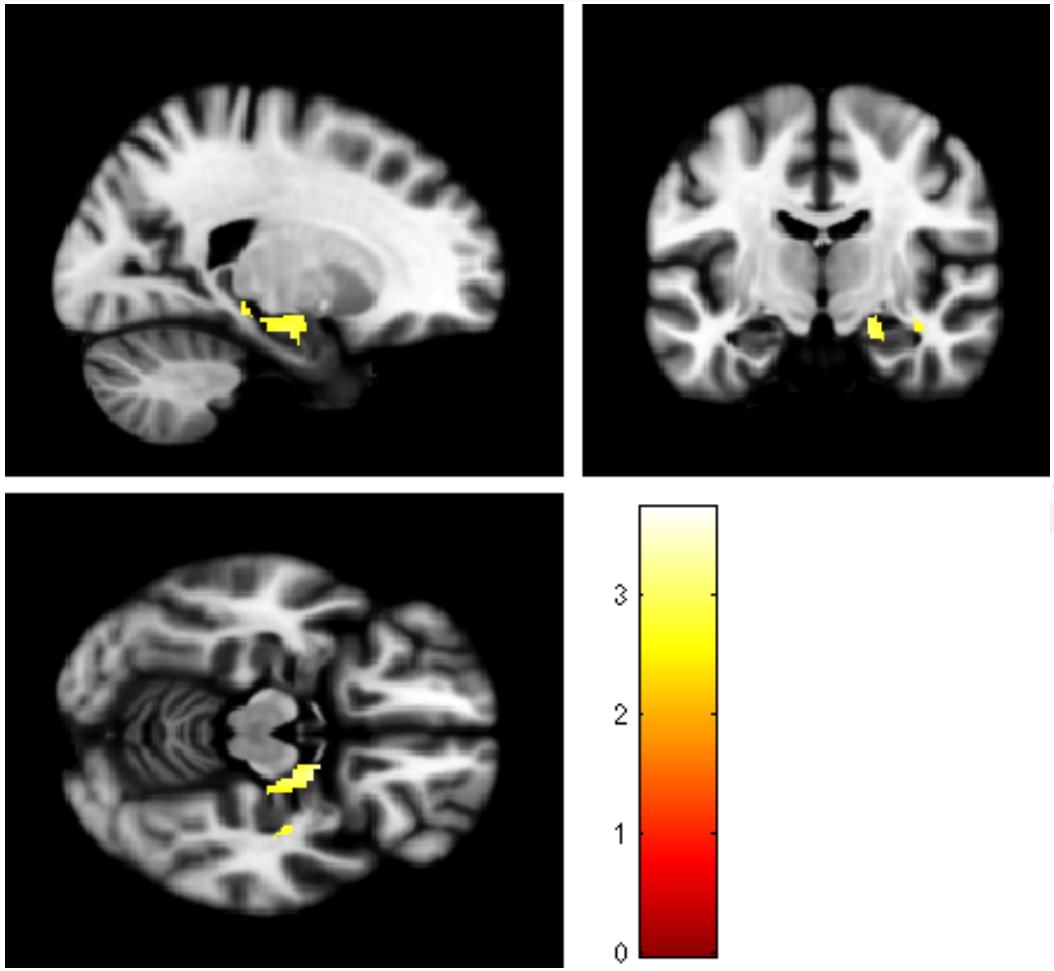
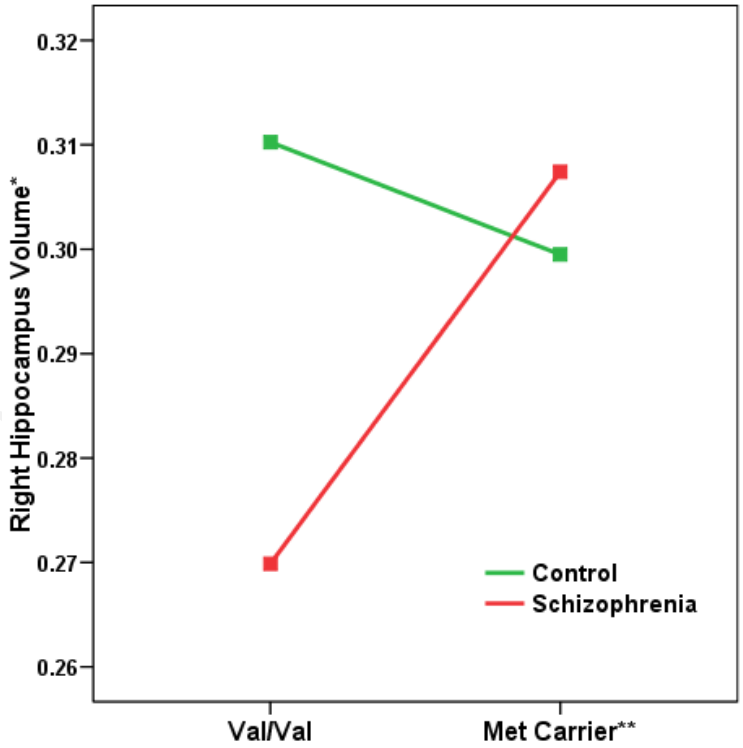
“Neuroplasticity changed the view of brain as a hard-wired black box”

“The Brain was constructed to change”



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)

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]*

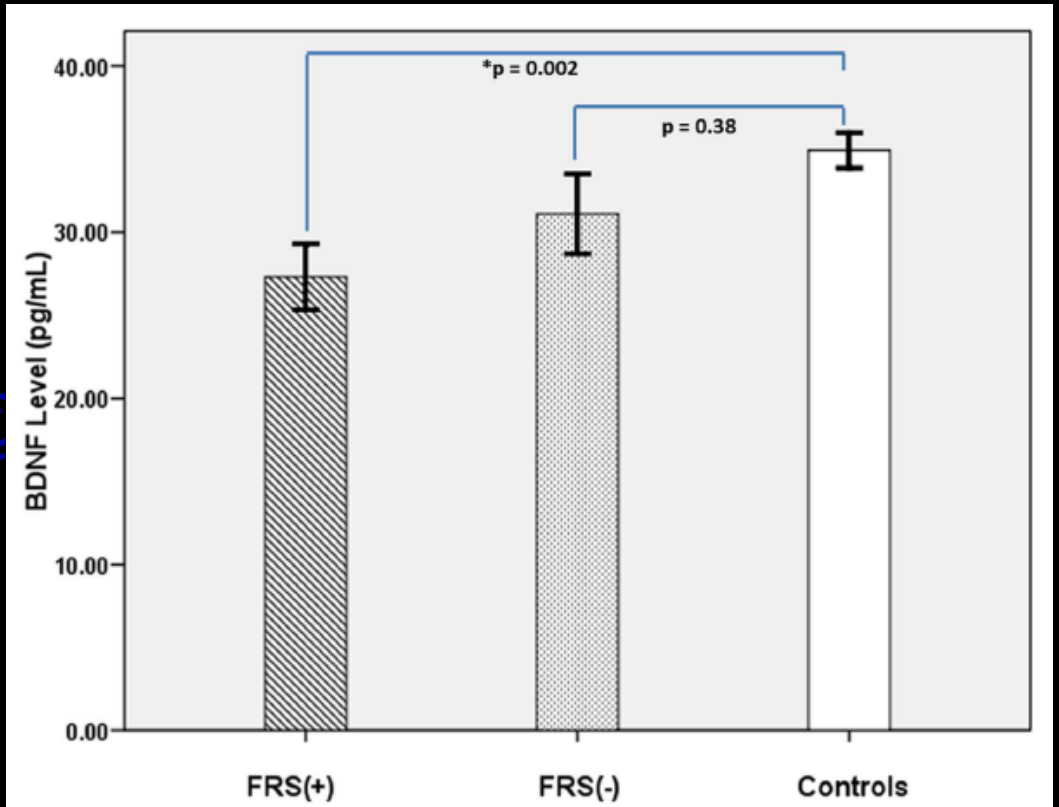


FIGURE 1 | It shows comparative profile of serum BDNF levels in FRS(+) patients ($N = 36$), FRS(−) ($N = 23$), and healthy controls ($N = 60$).

SUMMARY POINTS

1. Schizophrenia – hyperinsulinemia even in untreated state
2. Therapeutic correlates of insulin levels as well as energy metabolism aberrations in schizophrenia argues for “metabolic” component to underlie the pathogenesis
3. The underlying signalling pathways are critically linked with neuroplasticity

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INSULIN & DOPAMINE LINKED

- Recently, a cyclic AMP-independent mechanism of dopaminergic behaviours and signalling at the D_2 receptor also invovlve the Akt/GSK pathway

- Critically, this pathway has been shown to underlie the behavioral abnormalities secondary to dopaminergic aberrations

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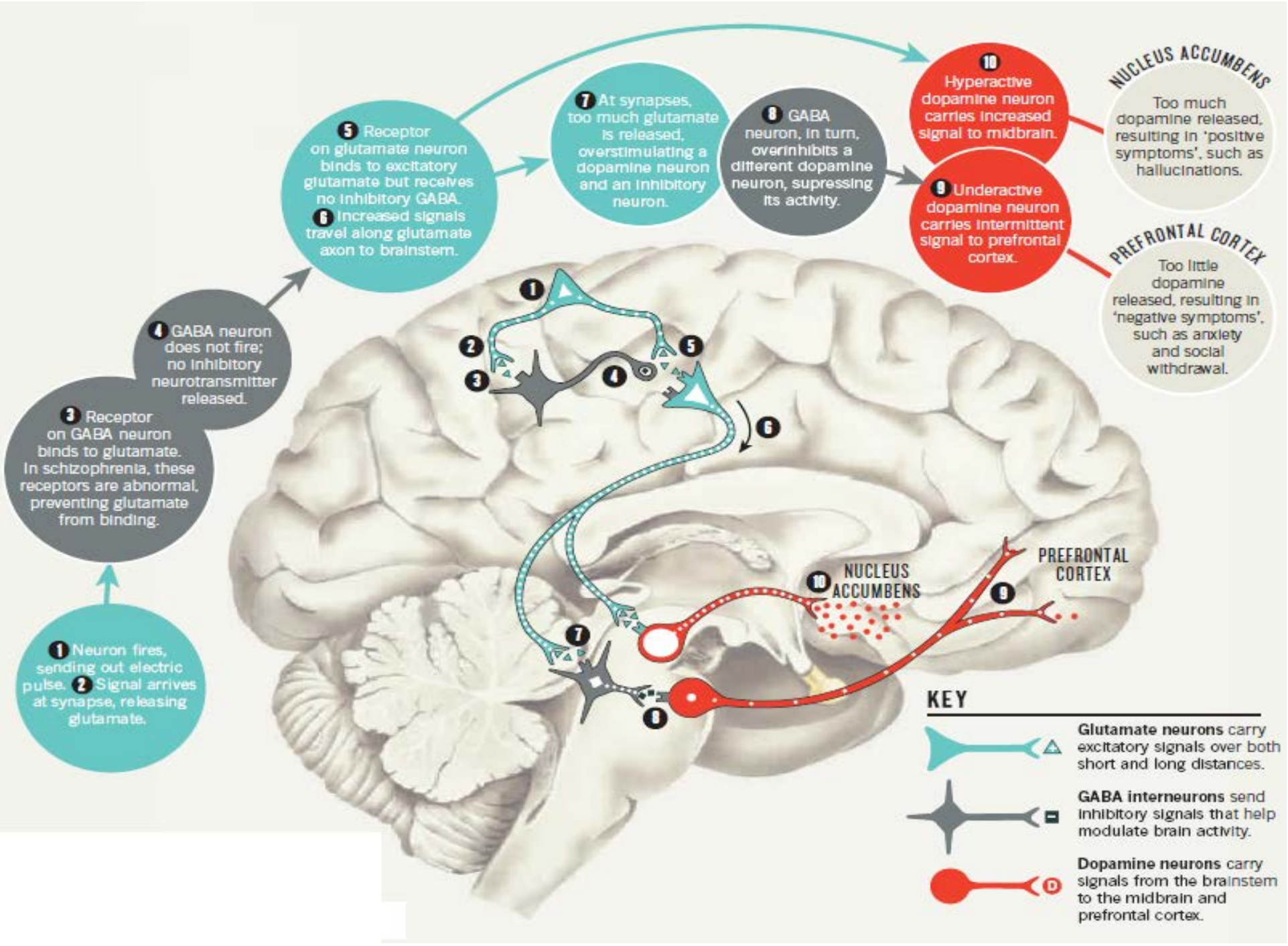
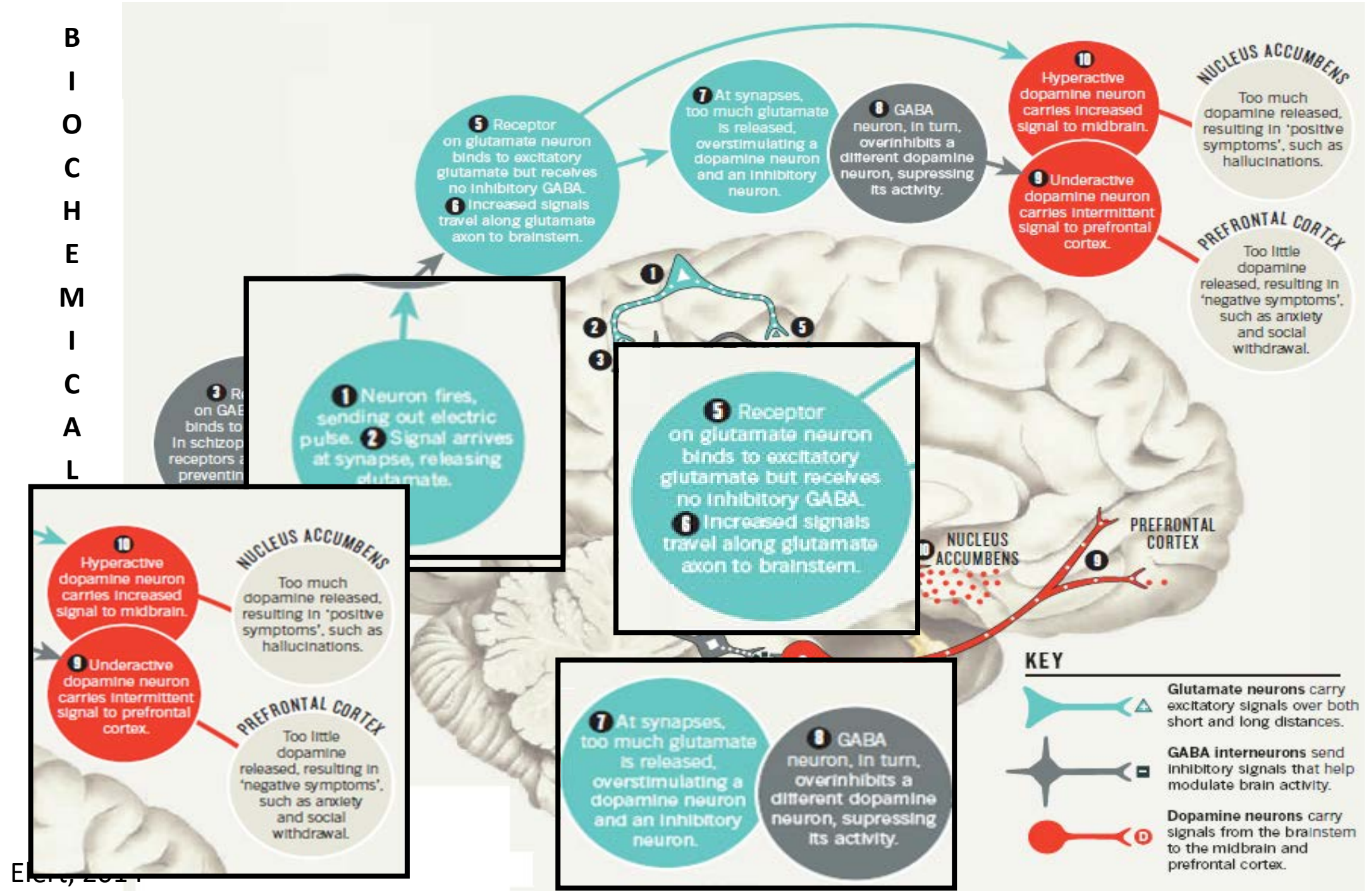
Beaulieu et al 2004

BIOCHEMICAL CASCADE



Elert, 2014

BIOCHEMICAL

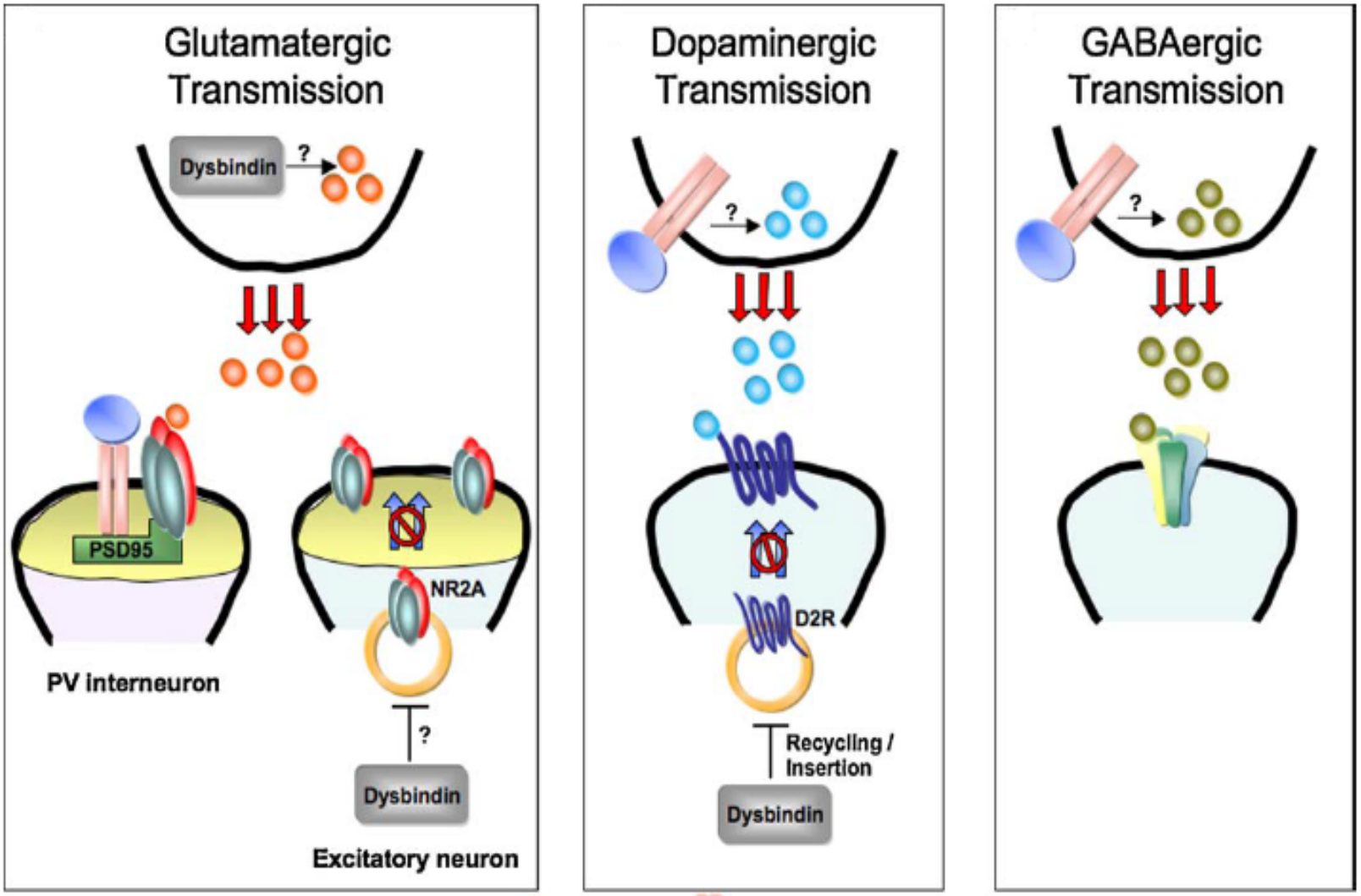


Ehrt, 2014

Multiple risk pathways for schizophrenia converge in serine racemase knockout mice, a mouse model of NMDA receptor hypofunction

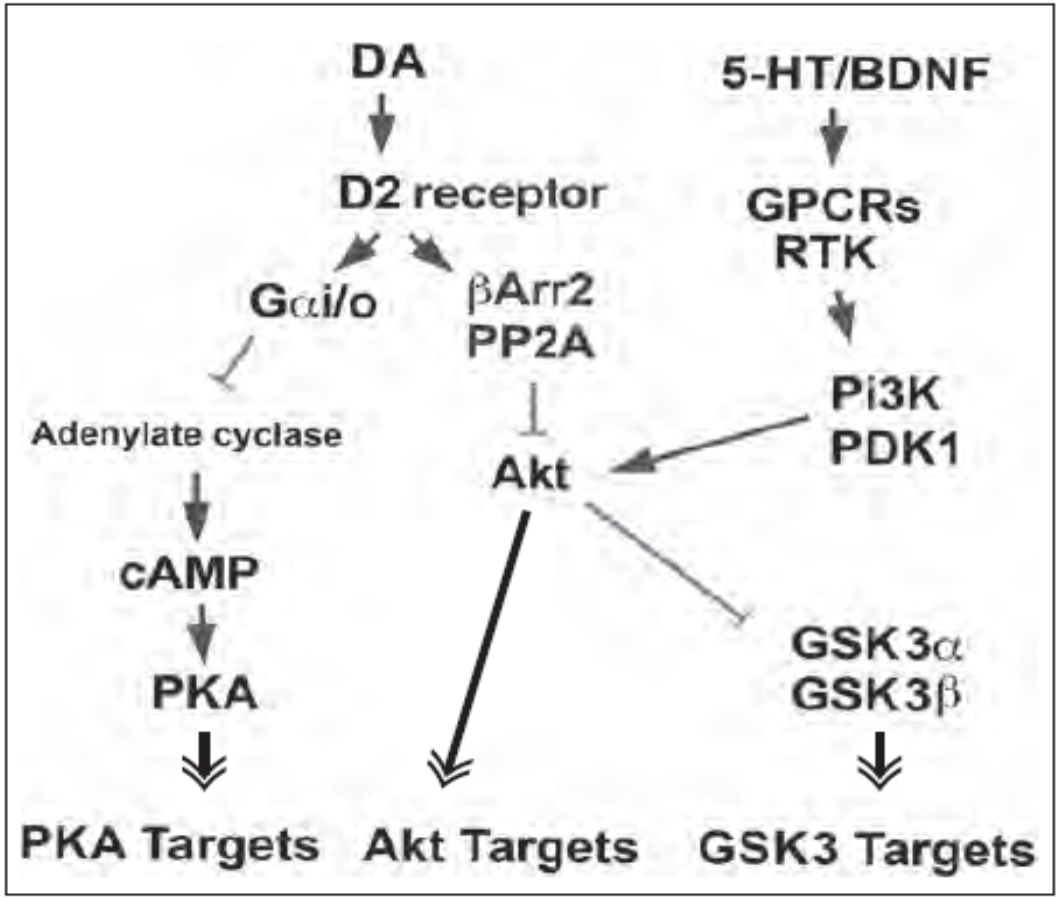
NMDAR hypofunction alters numerous pathways, including
BDNF/TrkB,
Akt/mTOR/GS3K, and
miR-132
that not are not only potent regulators of plasticity and spine dynamics, but have been found to be
genetically associated with or perturbed in schizophrenia

Plasticity Signaling Pathways Play Key Role – Hippocampus Network



Balu & Coyle, 2011

A role for Akt and glycogen synthase kinase-3 as integrators of dopamine and serotonin neurotransmission in mental health



D_2 as well as 5-HT_2 antagonism result in similar downstream effects on insulin signalling pathway – i.e. – GSK3β inhibition

GSK3β inhibition has been associated with potential antipsychotic effects

Future drug target

Beaulieu 2012

SUMMARY POINTS

1. Schizophrenia – hyperinsulinemia even in untreated state
2. Therapeutic correlates of insulin levels as well as energy metabolism aberrations in schizophrenia argues for “metabolic” component to underlie the pathogenesis
3. The underlying signalling pathways are critically linked with neuroplasticity
4. Schizophrenia: Key neurotransmitters modulate neuroplasticity

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“Weak Direct Current can modulate neuroplasticity”

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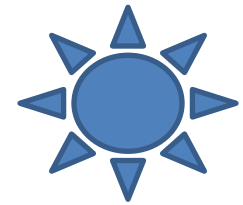


Weak Intensity Stimulation: Effects on Neurons

- Several lines of research evidence strongly support the sensitivity of neuronal networks to weak electric field applications.

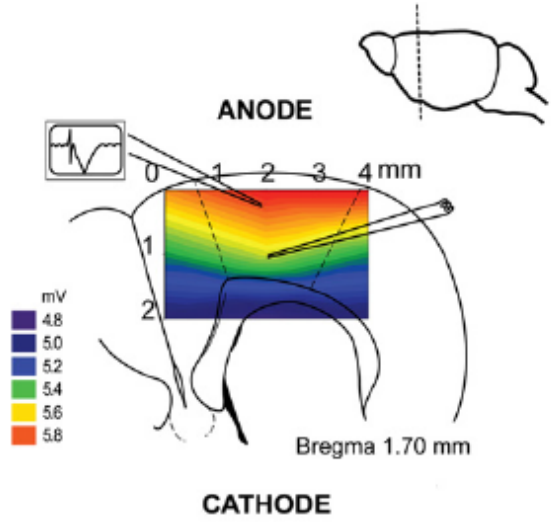
- These studies have applied methodologically rigorous techniques to establish that weak electric fields modulated neuronal activity by accurately characterizing the dosimetry of applied current strength, mapping subtle changes in the neuronal membrane voltage without several potential confounding factors (Frohlich, 2014).

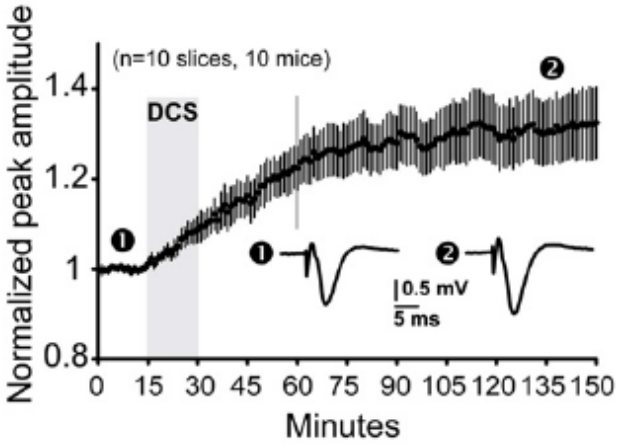
- Evidence accumulated from a series of neuroimaging studies further adds to the support for neural effects of tDCS in human subjects as well (Baeken et al., 2016; Downar et al., 2016).

Cell PRESS

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

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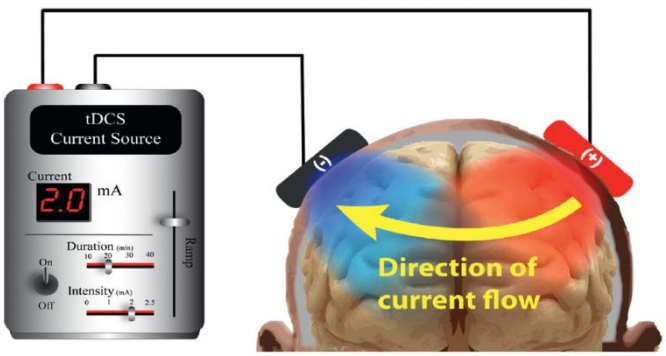
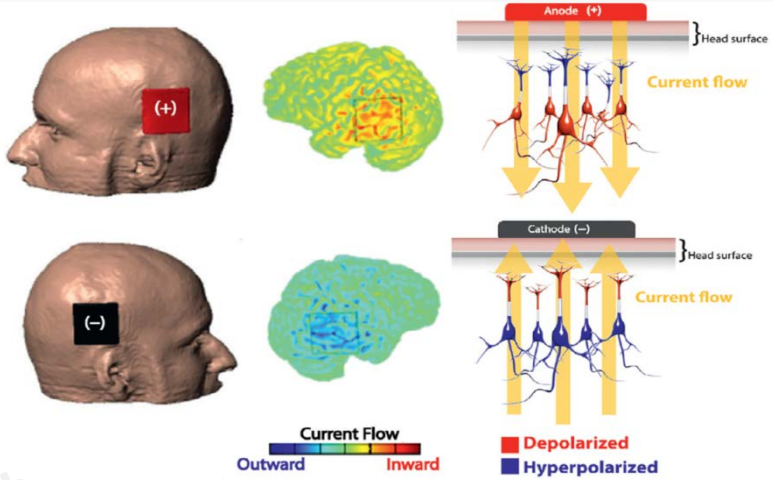
Fritsch et al, NEURON, 2010

Transcranial Direct Current Stimulation (tDCS)





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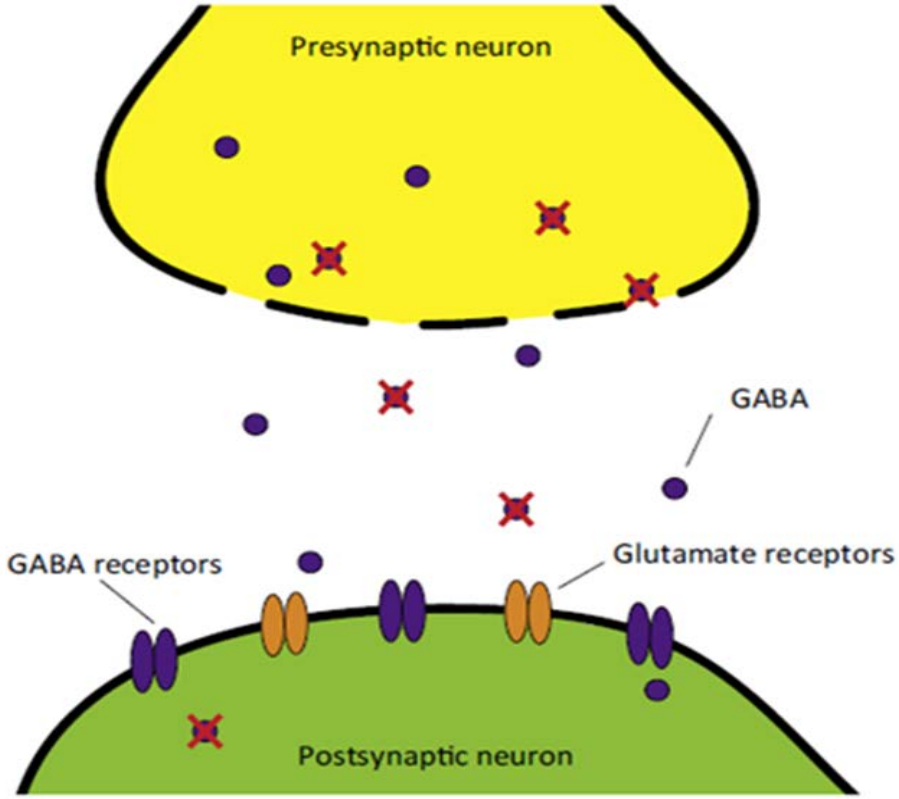
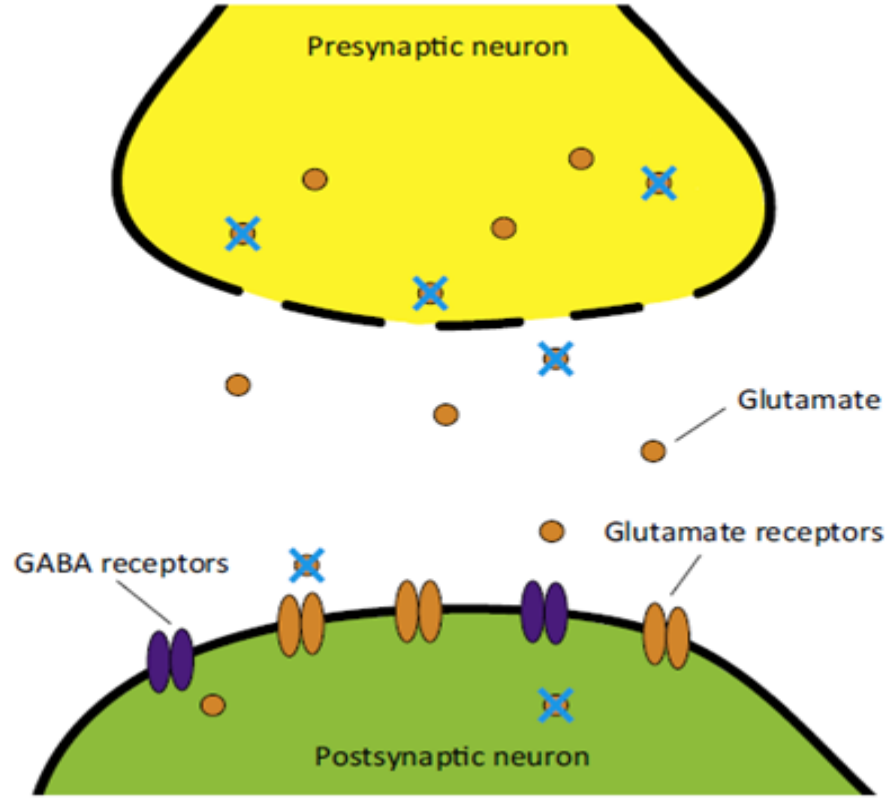
tDCS is a non-invasive, safe technique that involves application of low intensity, direct current (1-2 mA) using electrodes placed on the scalp resulting in polarity specific neuromodulation & adaptive neuroplasticity changes .
(Nitsche & Paulus, 2000)

tDCS: Neurobiological Effects

Anodal tDCS inhibits GABAergic transmission



Cathodal tDCS inhibits Glutamatergic transmission

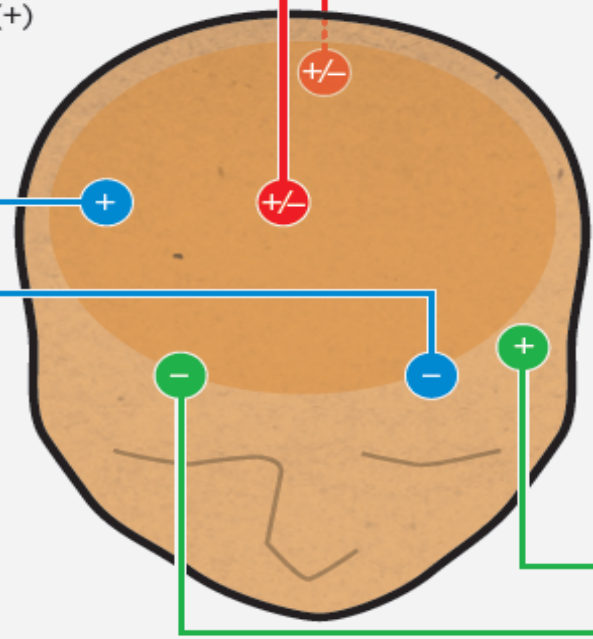


Filmer et al. Trends in Neurosciences 2014

nature International weekly journal of science

WIRED UP

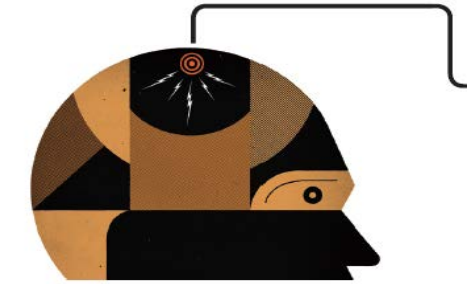
In transcranial direct-current stimulation, electrodes placed on the scalp deliver low currents that can penetrate the skull and affect brain tissue. Differing effects have been documented, depending on the placement of the anode (+) and cathode (–).



VISUAL PERCEPTION
Alterations in visual perception have been noted under both cathodal and anodal stimulation of the occipital lobes.
• Up to 2 milliamps for as long as 15 minutes.

MOTOR CONTROL
Anodal stimulation over the motor cortex on the side of the brain affected by stroke has been shown to improve movement for arms and hands.
• Up to 4 milliamps for as long as 20 minutes.

WORKING MEMORY
Anodal stimulation of the dorsolateral prefrontal cortex has been associated with improved working memory and verbal fluency.
• Up to 2 milliamps for as long as 20 minutes.



BRAIN BUZZ

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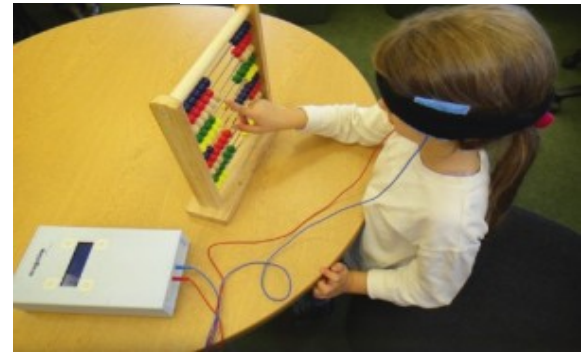
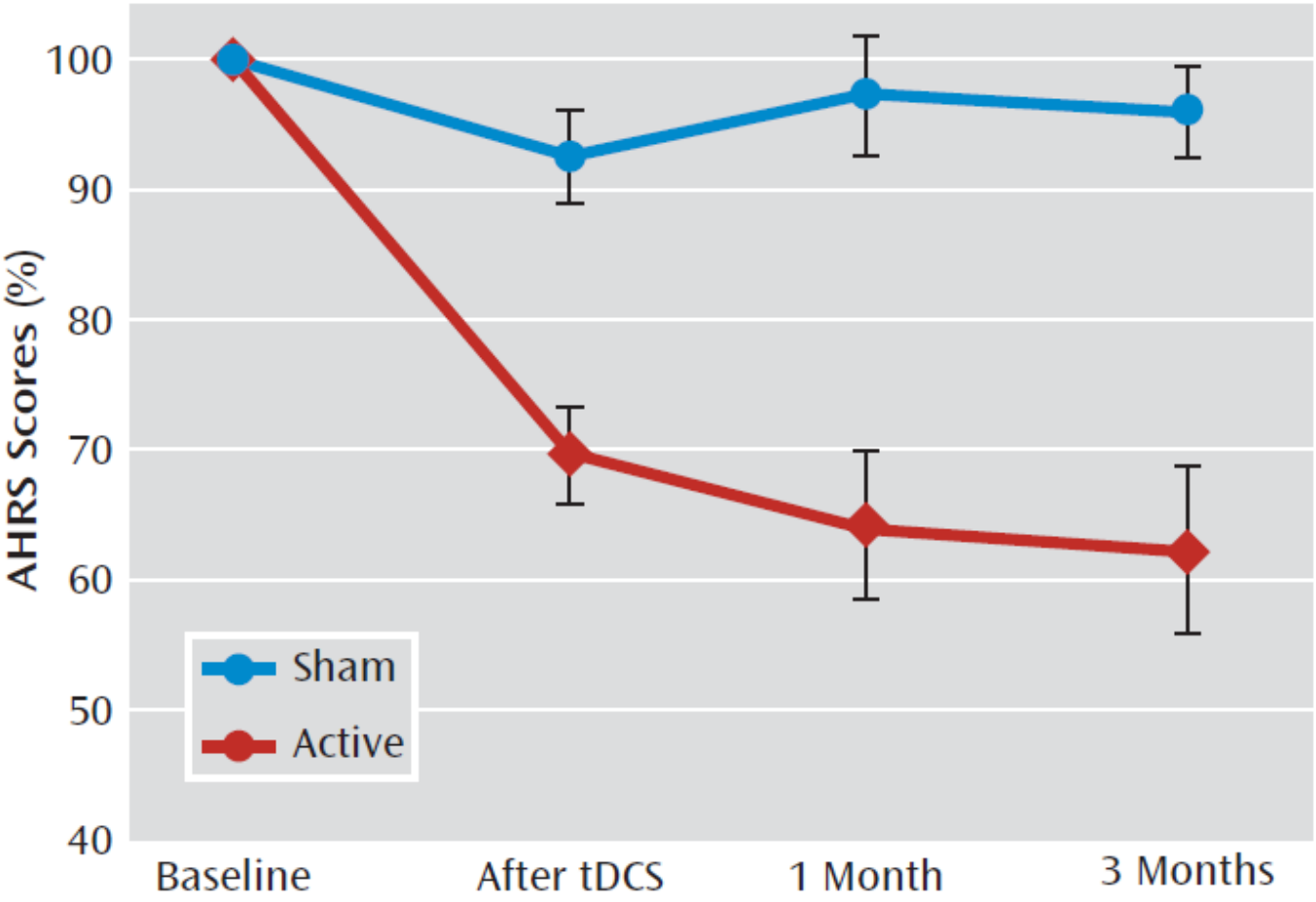


Examining Transcranial Direct-Current Stimulation (tDCS) as a Treatment for Hallucinations in Schizophrenia

THE AMERICAN JOURNAL OF PSYCHIATRY



- Auditory verbal hallucinations were robustly reduced by tDCS relative to sham stimulation, with a mean diminution of 31%.
- The beneficial effect on hallucinations lasted for up to 3 months.
- Significant improvement in negative and positive dimensions of PANSS was observed

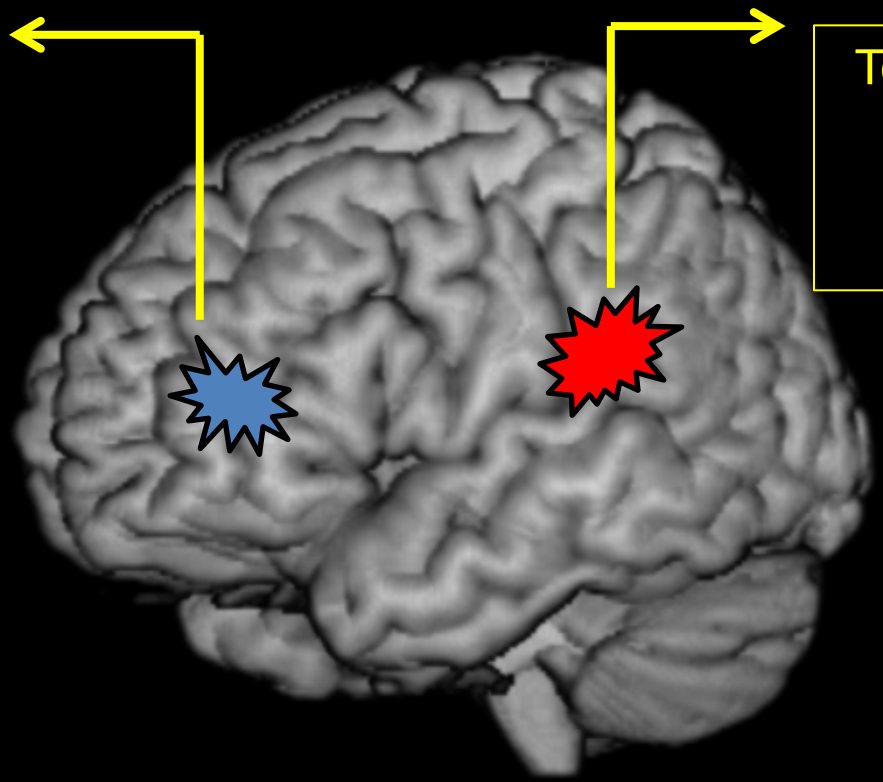
Brunelin et al American Journal of Psychiatry 2012

tDCS for Schizophrenia:
Distinctive Neural Correlates of Treatment Resistant Symptoms

Negative Symptoms
(Amotivation, Avolition, Alogia)

Positive Symptoms
(Delusions, Hallucinations)

Deficient Activation of Prefrontal Cortex with Decreased N-Acetyl Aspartate level



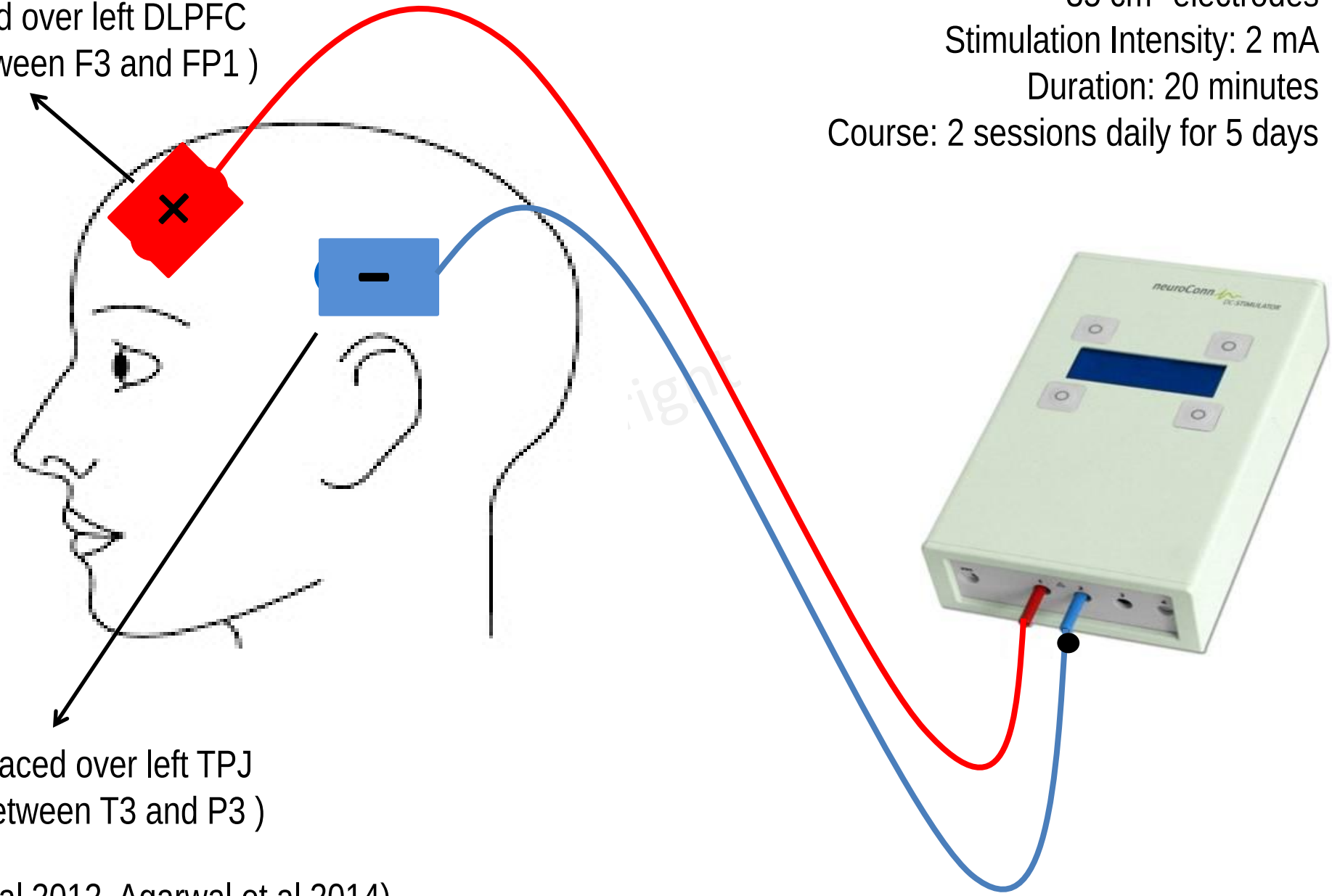
Temporo-Parietal Junction Hyperactivity with significantly increased Glutamate level

Venkatasubramanian et al American Journal of Psychiatry2005
Venkatasubramanian et al NeuroImage 2005

tDCS in Schizophrenia: Application Schema

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, Agarwal et al 2014)

Contents lists available at ScienceDirect

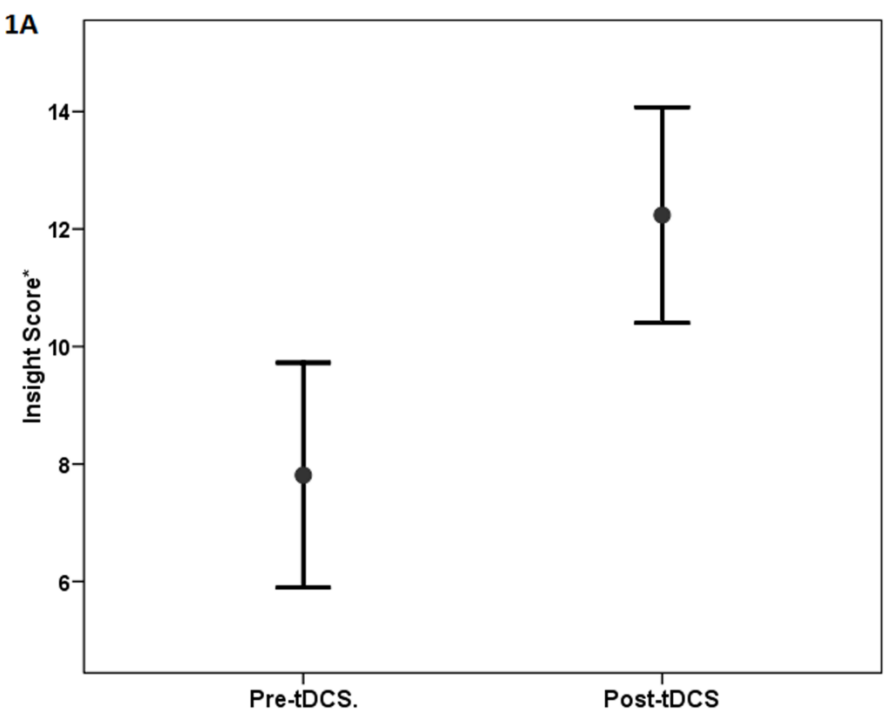
Schizophrenia Research

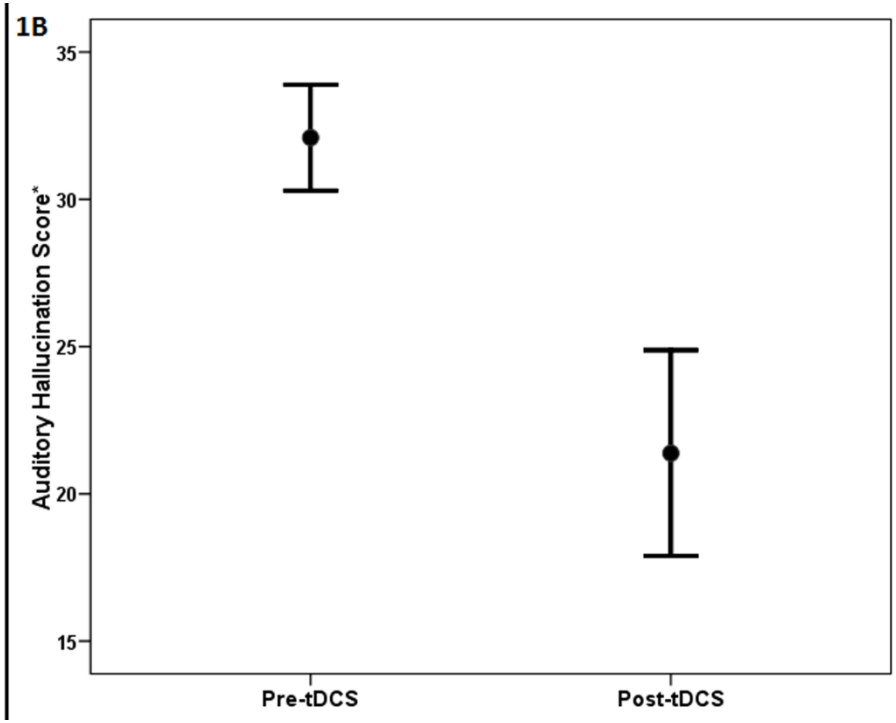
journal homepage: www.elsevier.com/locate/schres

Insight facilitation with add-on tDCS in schizophrenia

Anushree

Shiv



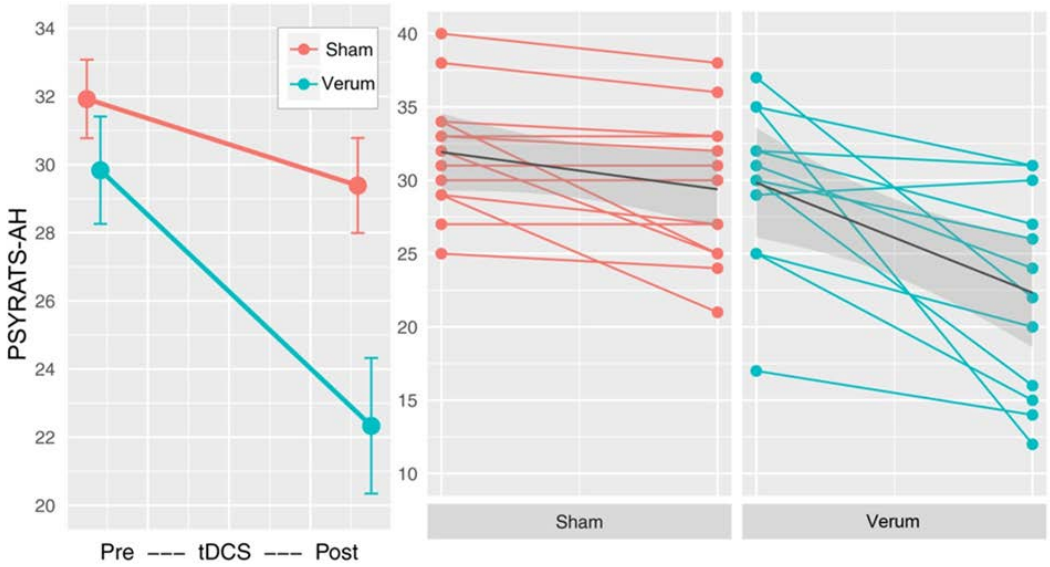


Improvement in insight had a significant positive correlation with reduction in auditory hallucinations (r= 0.65; p = 0.002)

Bose et al, Schizophrenia Research, 2014

WISER Neuromodulation in Schizophrenia: Neuroplasticity

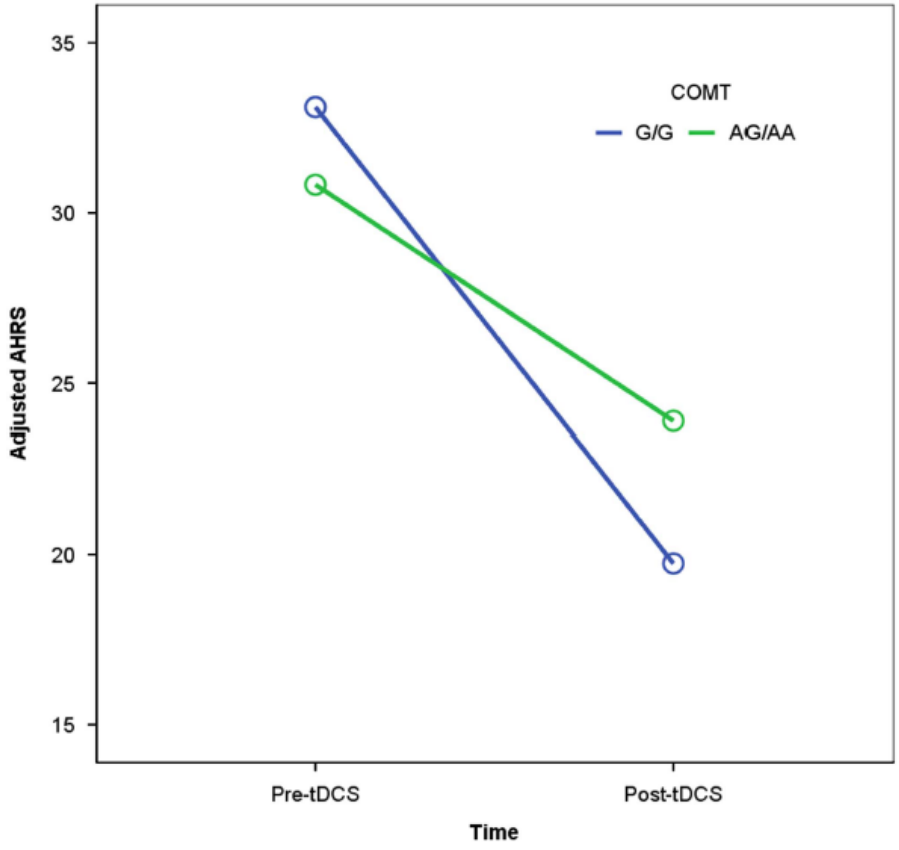
Efficacy of fronto-temporal transcranial direct current stimulation for refractory auditory verbal hallucinations in schizophrenia: A randomized, double-blind, sham-controlled study



Bose et al 2018

Gene polymorphisms and response to transcranial direct current stimulation for auditory verbal hallucinations in schizophrenia

Acta Neuropsychiatrica



Chhabra et al 2018

Schizophrenia: Other Avenues to Modulate Neuroplasticity

1. Other Brain Stimulation Techniques: ECT & TMS
2. Yoga Therapy
3. Aerobic Physical Exercises
4. Systematic Cognitive Re-training
5. Diet and Nutraceuticals

? Specific components that are differentially implicated in schizophrenia pathogenesis and ameliorative effects need to be elucidated.

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CNS Spectrums (2018), page 1 of 2. © Cambridge University Press 2018
doi:10.1017/S1092852918001256

Insulin-growth-factor-1 (IGF-1): just a few steps behind the evidence in treating schizophrenia and/or autism

Rami Bou Khalil *

Schizophrenia: Contemporary Relevance of "Cerebral Diabetes" Hypothesis

Gene X Environment Interactions

Persistent Activation of Glial Cells / Aberrant Neurodevelopment

Aberrant Inflammation

Deficient Neurotrophic Factors (Insulin System / BDNF)

***Aberrations in Neuroplasticity (Glutamate, GABA & Dopaminergic Pathways)**
Prefrontal-Temporo-Parietal-Thalamo-Hippocampal Network Abnormalities
[Endophenotype Measures: Imaging, eye movement, fNIRS, EEG/ ERP]

Perturbations in Consciousness

Self-Monitoring Aberrations

Clinical Symptoms of Schizophrenia

Neurobiological correlates of treatment (antipsychotics neuromodulation – tDCS)

*Select Representation of Parameters

Venkatasubramanian et al 2007; 2008, 2015

Summary Points

1. Schizophrenia – hyperinsulinemia even in untreated state
2. Therapeutic correlates of insulin levels as well as energy metabolism aberrations in schizophrenia argues for “metabolic” component to underlie the pathogenesis – i.e. metabolic brain disorder
3. The underlying signalling pathways are critically linked with neuroplasticity
4. Schizophrenia: Key neurotransmitters modulate neuroplasticity
5. Clinical Implications: Psychopharmacology, brain stimulation, complementary / alternative techniques

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Acknowledgements

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Dr. M.S. Keshavan

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Individualized Schizophrenia Treatment And Reintegration

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