“Mental Health, Direction and Challenges”

Dopaminergic neurotransmission in lymphocytes as an indicator to evaluate effectiveness of antipsychotics

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28 April 2016

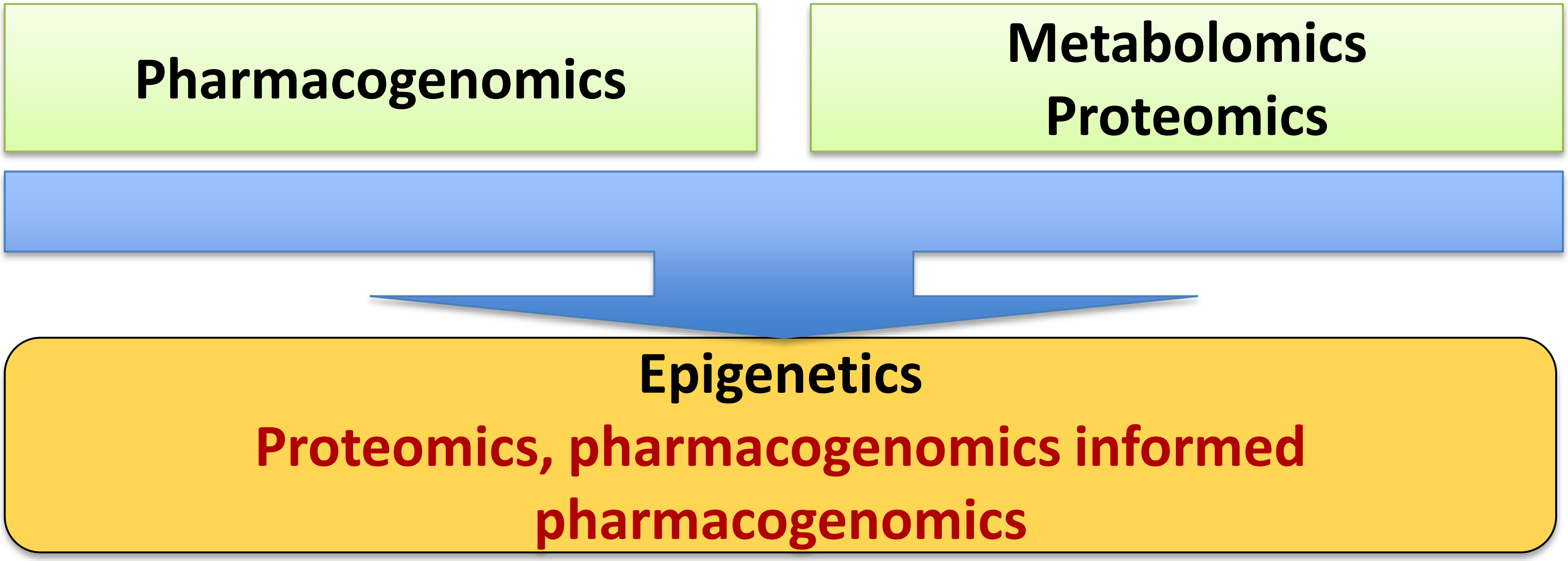
Personalized medicine

Genotype

- Gene polymorphisms
- The level of mRNA gene

Phenotype

- Gene expression level
- Enzyme activity
- Molecular biomarkers



Pharmacogenomics

Metabolomics
Proteomics

Epigenetics

Proteomics, pharmacogenomics informed pharmacogenomics

Study design

«Antipsychotics: the development of personalized approaches to therapy based on the individual characteristics of the receptor neurotransmission lymphocytes»

Patients with alcohol dependence syndrome

Patients with schizophrenia

Patients with comorbidity of schizophrenia and alcohol dependence syndrome

Schizophrenia

Causes disability in adult population

Significantly improves quality of life

It requires prolonged, often lifelong therapy

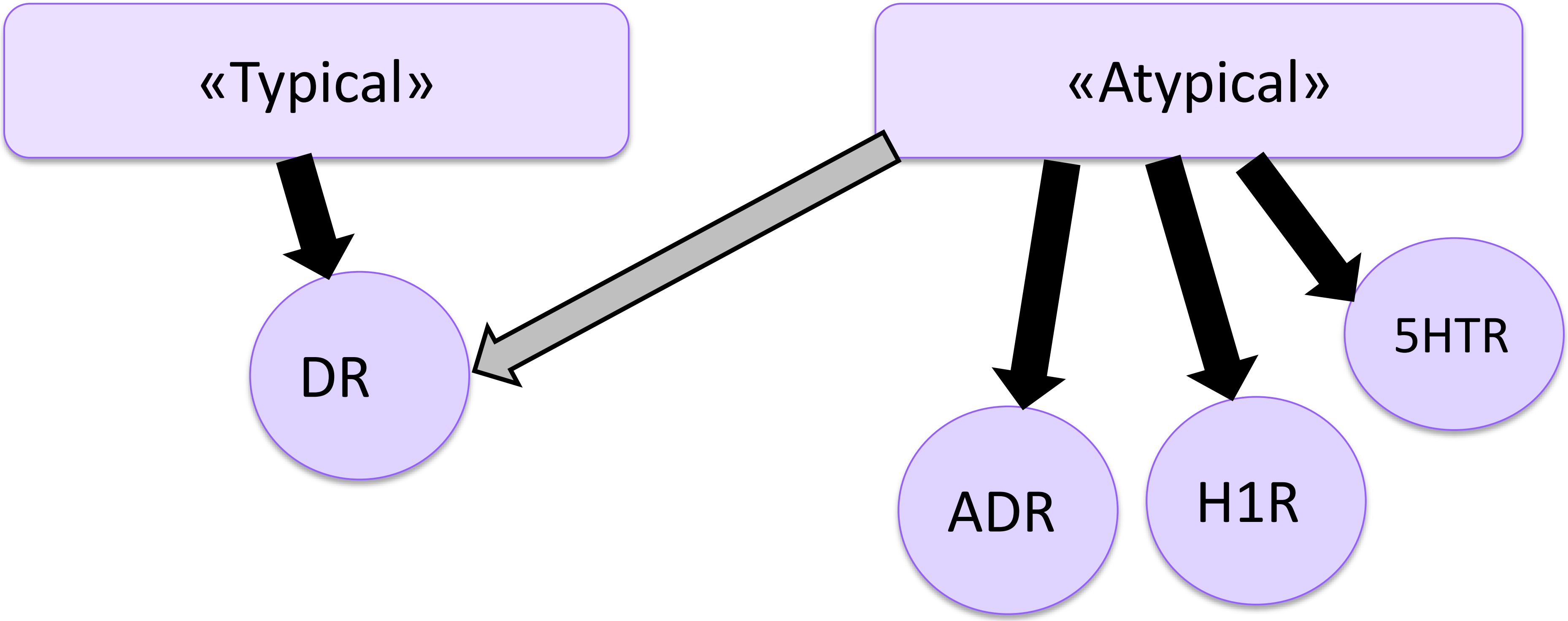
Lammers S.M. et al, 2014; Ustun T.B. et al,1999

Relevance

Dopamine is involved into pathogenesis of majority of mental disorders

Beaulieu J.M., Gainetdinov R.R. 2011

Antipsychotics



«Typical»

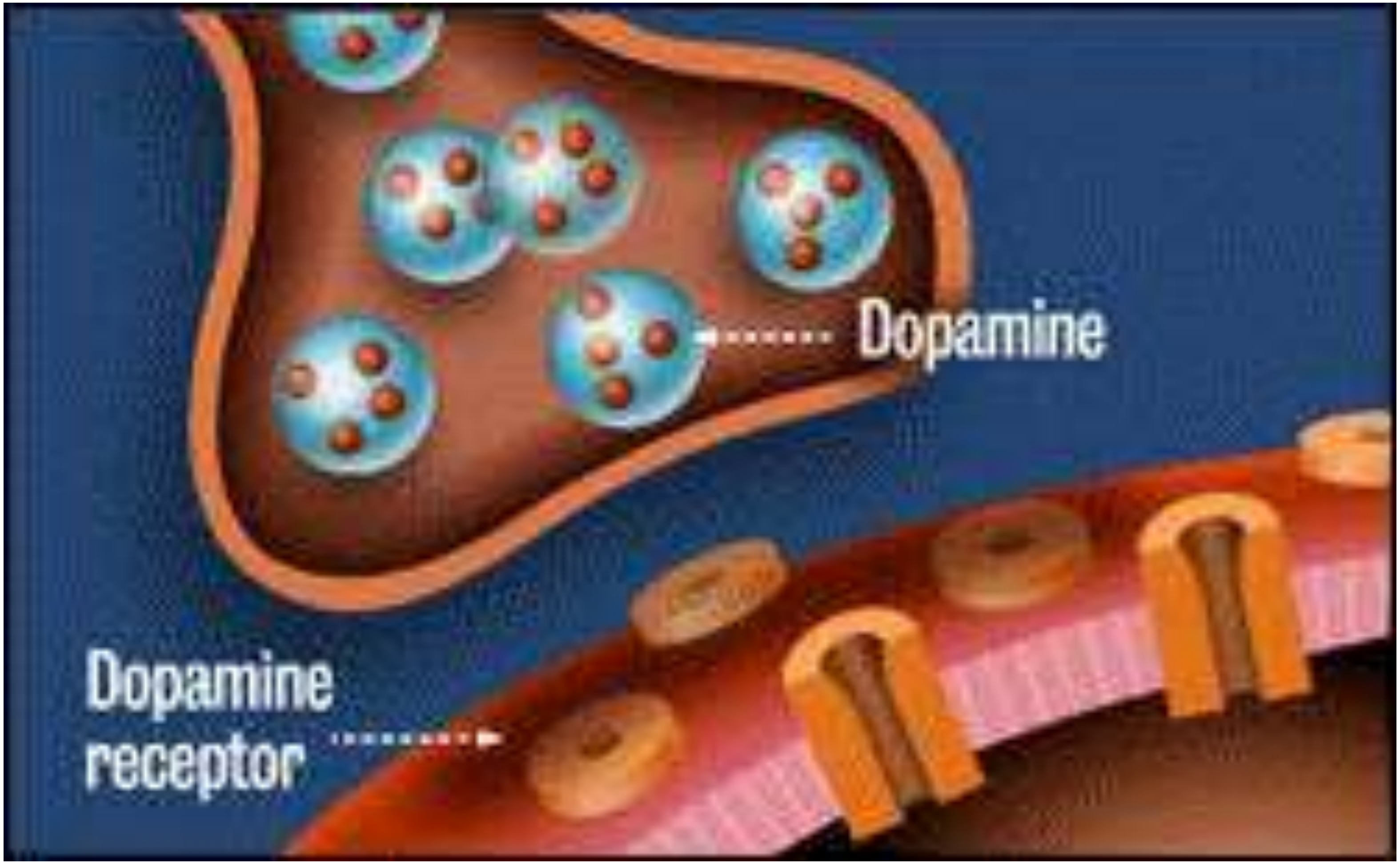
«Atypical»

DR

ADR

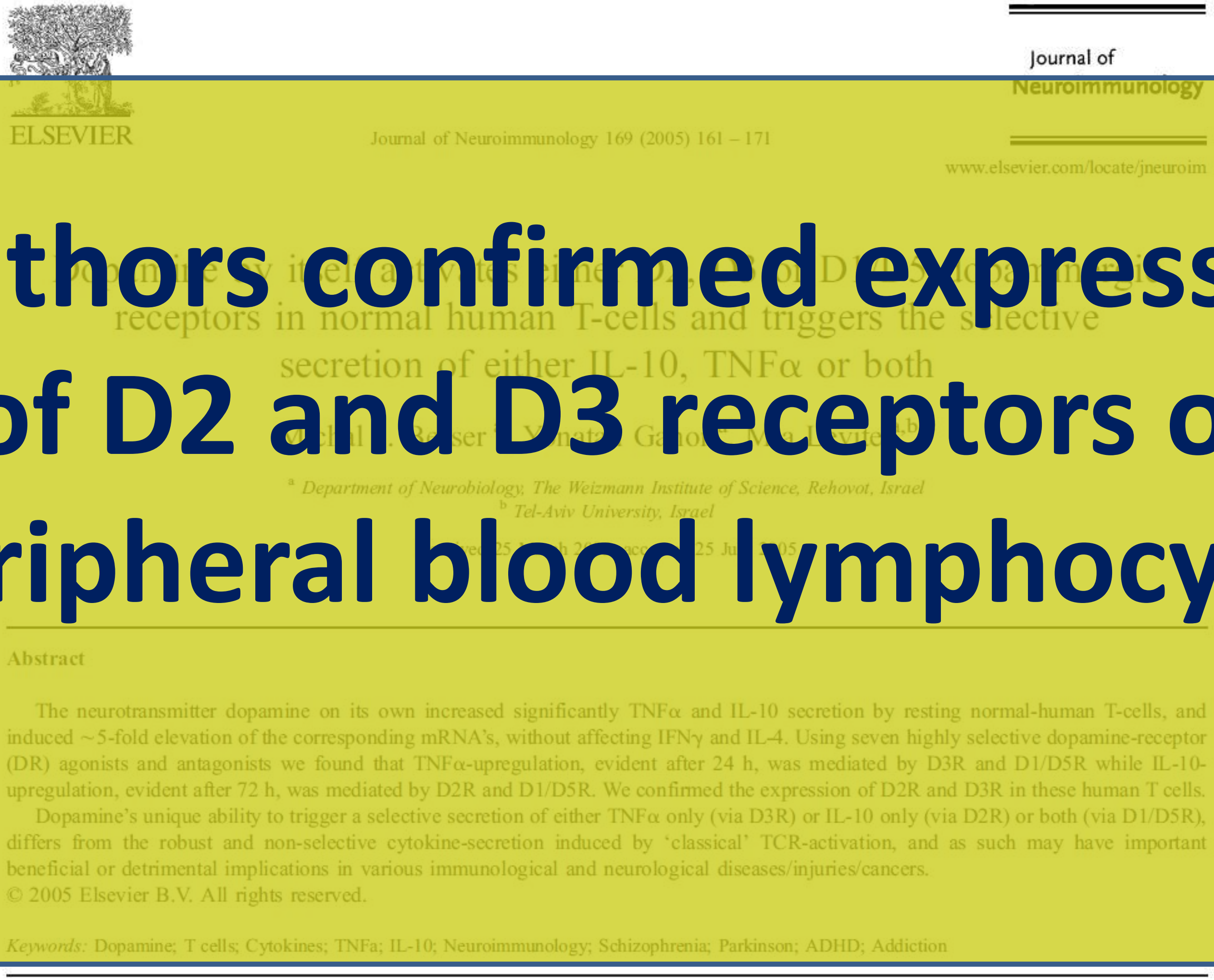
H1R

5HTR



Is it possible to assess the dopaminergic neurotransmission in alive person?

Authors confirmed expression of D2 and D3 receptors on peripheral blood lymphocytes.



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receptors in normal human T-cells and triggers the selective
secretion of either IL-10, TNFα or both

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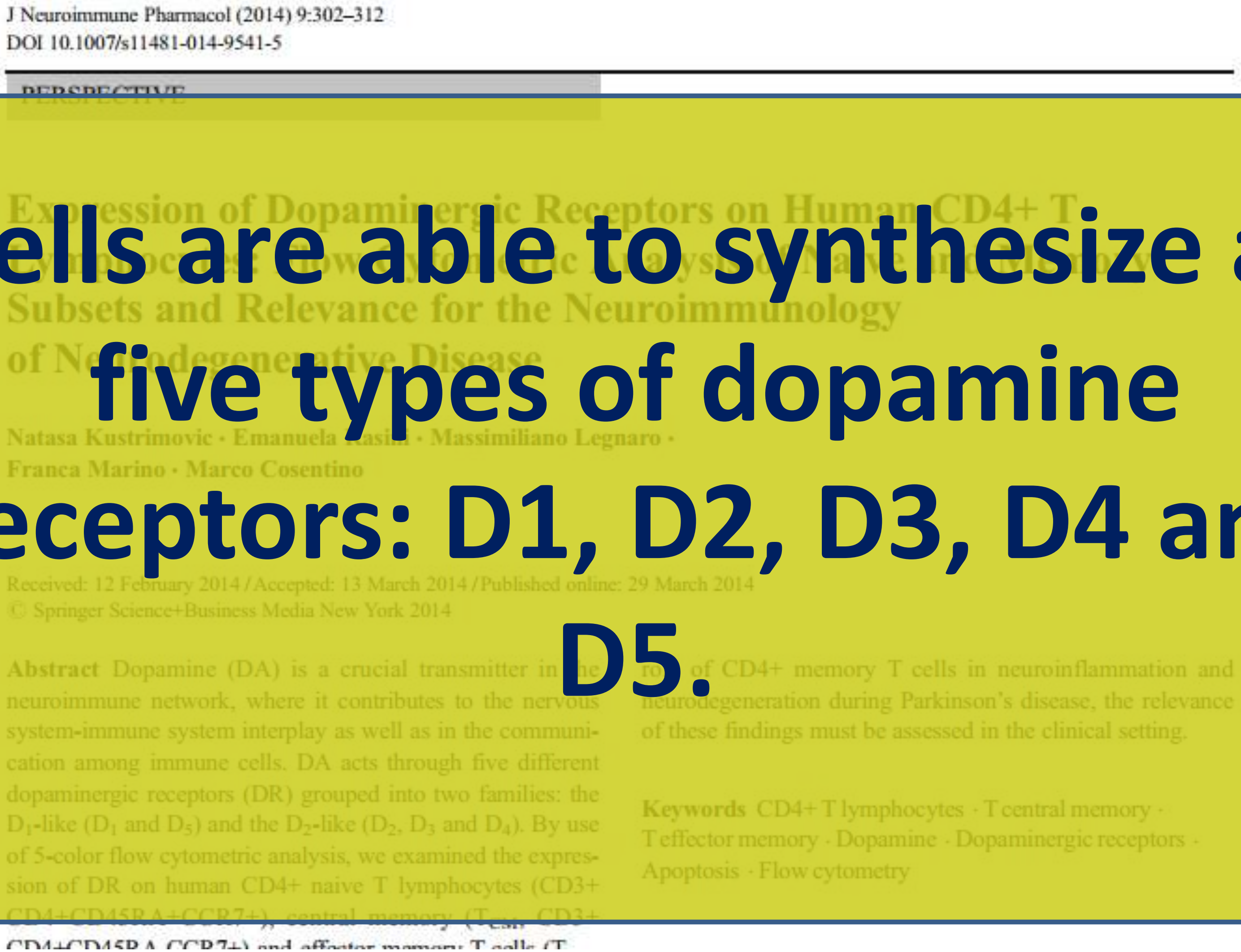
Abstract

The neurotransmitter dopamine on its own increased significantly TNFα and IL-10 secretion by resting normal-human T-cells, and induced ~5-fold elevation of the corresponding mRNA's, without affecting IFNγ and IL-4. Using seven highly selective dopamine-receptor (DR) agonists and antagonists we found that TNFα-upregulation, evident after 24 h, was mediated by D3R and D1/D5R while IL-10-upregulation, evident after 72 h, was mediated by D2R and D1/D5R. We confirmed the expression of D2R and D3R in these human T cells.

Dopamine's unique ability to trigger a selective secretion of either TNFα only (via D3R) or IL-10 only (via D2R) or both (via D1/D5R), differs from the robust and non-selective cytokine-secretion induced by 'classical' TCR-activation, and as such may have important beneficial or detrimental implications in various immunological and neurological diseases/injuries/cancers.

Keywords: Dopamine; T cells; Cytokines; TNFa; IL-10; Neuroimmunology; Schizophrenia; Parkinson; ADHD; Addiction



J Neuroimmune Pharmacol (2014) 9:302–312
DOI 10.1007/s11481-014-9541-5

PERSPECTIVE

Expression of Dopaminergic Receptors on Human CD4+ T Lymphocytes: Flow Cytometric Analysis of Naive and Memory Subsets and Relevance for the Neuroimmunology of Neurodegenerative Disease

Natasa Kustrimovic · Emanuela Rasini · Massimiliano Legnaro ·
Franca Marino · Marco Cosentino

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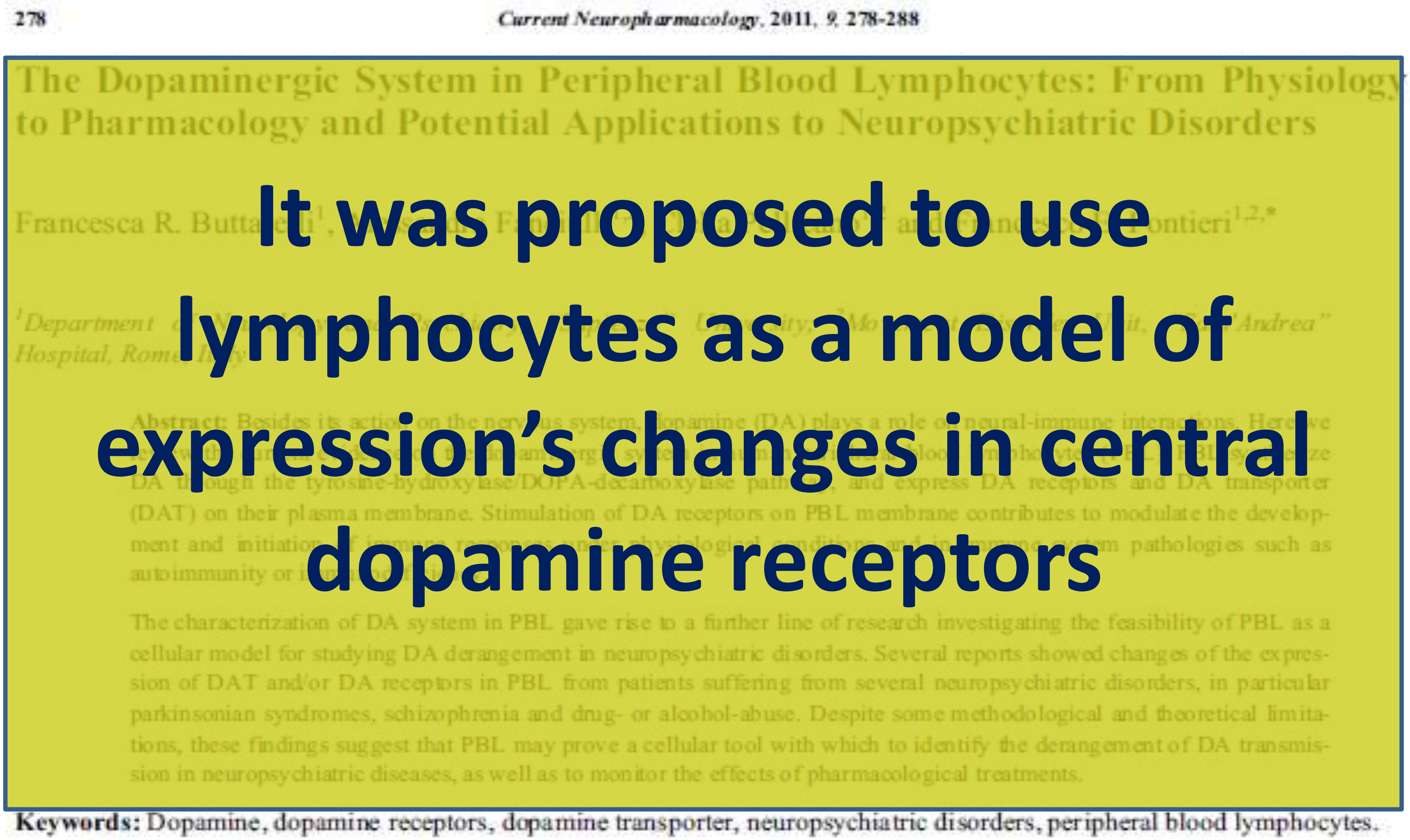
Abstract Dopamine (DA) is a crucial transmitter in the neuroimmune network, where it contributes to the nervous system-immune system interplay as well as in the communication among immune cells. DA acts through five different dopaminergic receptors (DR) grouped into two families: the D_1-like (D_1 and D_5) and the D_2-like (D_2, D_3 and D_4). By use of 5-color flow cytometric analysis, we examined the expression of DR on human CD4+ naive T lymphocytes (CD3+ CD4+CD45RA+CCR7+), central memory (T_{CM}: CD3+ CD4+CD45RA-CCR7+) and effector memory T cells (T

role of CD4+ memory T cells in neuroinflammation and neurodegeneration during Parkinson's disease, the relevance of these findings must be assessed in the clinical setting.

Keywords CD4+ T lymphocytes · T central memory · T effector memory · Dopamine · Dopaminergic receptors · Apoptosis · Flow cytometry

Cells are able to synthesize all five types of dopamine receptors: D1, D2, D3, D4 and D5.

It was proposed to use lymphocytes as a model of expression’s changes in central dopamine receptors



278 *Current Neuropharmacology*, 2011, *9*, 278-288

The Dopaminergic System in Peripheral Blood Lymphocytes: From Physiology to Pharmacology and Potential Applications to Neuropsychiatric Disorders

Francesca R. Butta[illegible][1], [illegible] Fa[illegible] [illegible] a[illegible]ontieri[1,2,*]

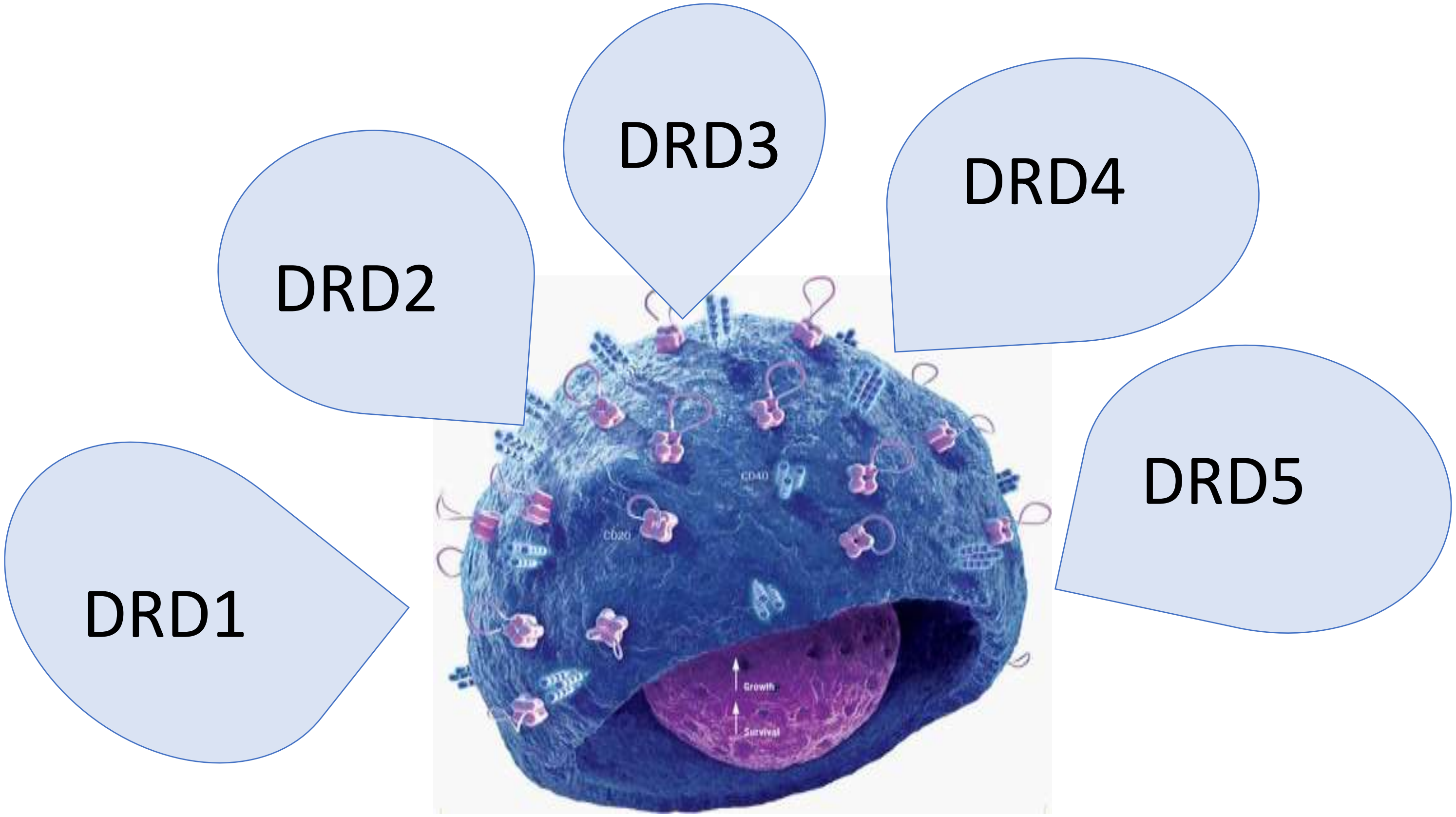
[1]Department [illegible] University, [2]Mo[illegible] Unit, [illegible] Andrea" Hospital, Rom[illegible]

Abstract: Besides its action on the nervous system, dopamine (DA) plays a role o[illegible] neural-immune interactions. Here [illegible] [illegible] synthesize DA through the tyrosine-hydroxylase/DOPA-decarboxylase path[illegible], and express DA receptors and DA transporter (DAT) on their plasma membrane. Stimulation of DA receptors on PBL membrane contributes to modulate the development and initiation [illegible] pathologies such as autoimmunity or i[illegible]

The characterization of DA system in PBL gave rise to a further line of research investigating the feasibility of PBL as a cellular model for studying DA derangement in neuropsychiatric disorders. Several reports showed changes of the expression of DAT and/or DA receptors in PBL from patients suffering from several neuropsychiatric disorders, in particular parkinsonian syndromes, schizophrenia and drug- or alcohol-abuse. Despite some methodological and theoretical limitations, these findings suggest that PBL may prove a cellular tool with which to identify the derangement of DA transmission in neuropsychiatric diseases, as well as to monitor the effects of pharmacological treatments.

Keywords: Dopamine, dopamine receptors, dopamine transporter, neuropsychiatric disorders, peripheral blood lymphocytes.

Thus lymphocytes in peripheral blood can be considered as a biological model of dopaminergic transmission in central nervous system.



DRD3

DRD4

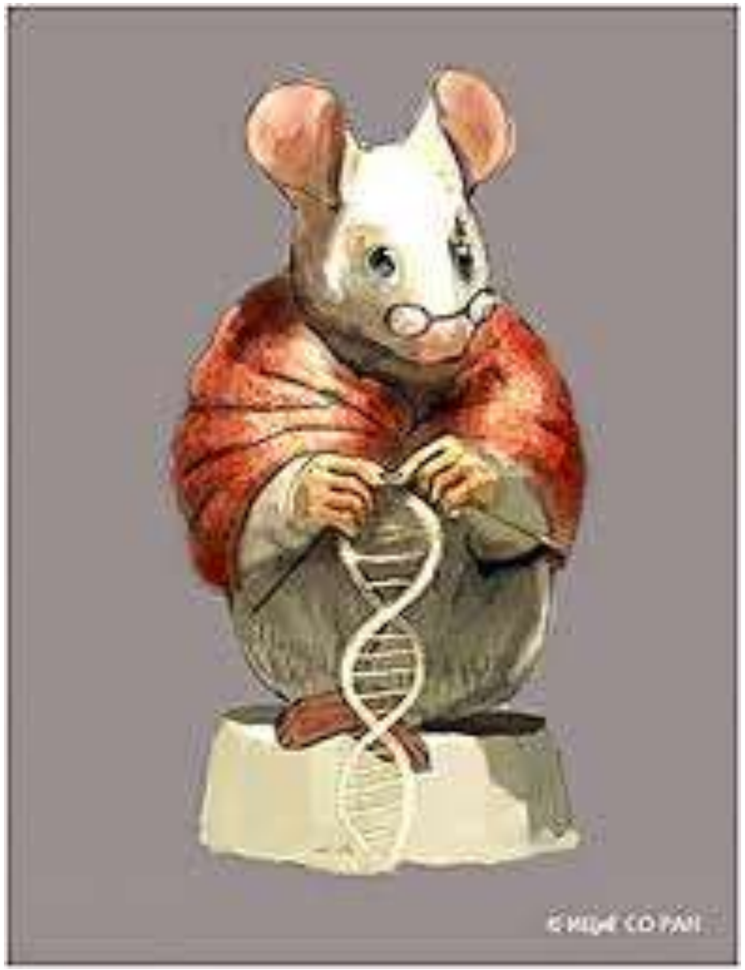
DRD2

DRD5

DRD1

Kustrimovic N. et al., 2014; Buttarelli F. et al., 2011; Bergquist et al., 1998

PURPOSE



To evaluate associations between dopamine receptors' expression level and antipsychotics' efficacy in patients treated by monotherapy

INCLUSION CRITERIA

Male

Caucasian

Age from 18 to 55 years old

Patients which did not receive antipsychotics at least for 3 months before inclusion

NON-INCLUSION CRITERIA

Female

Asian / black

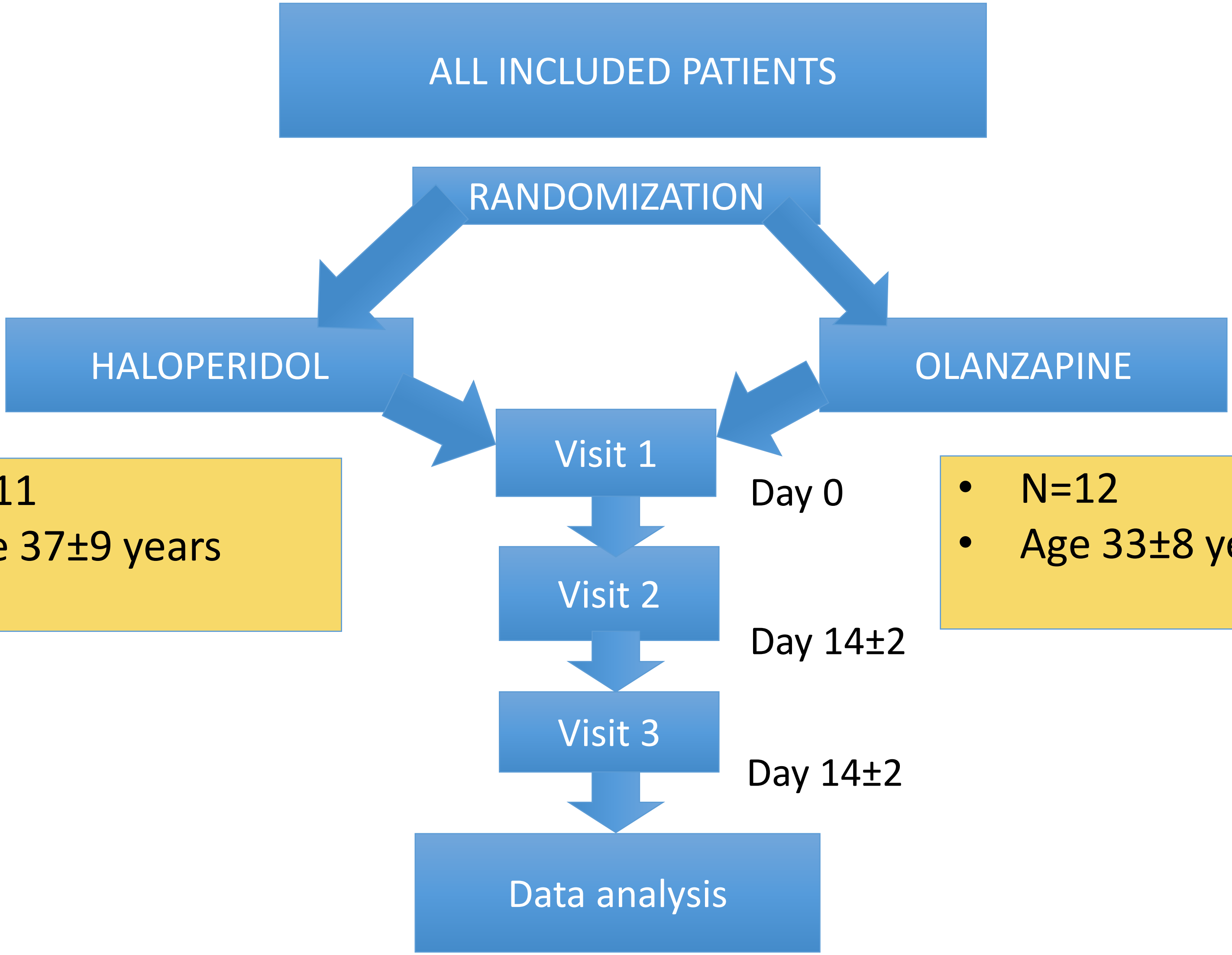
Younger than 18 and older than 55 years

Somatic disorders in decompensated state

Another central nervous system disorder

Drug abuse

STUDY FLOW



ALL INCLUDED PATIENTS

RANDOMIZATION

HALOPERIDOL

OLANZAPINE

- N=11
- Age 37±9 years

Visit 1

Day 0

Visit 2

Day 14±2

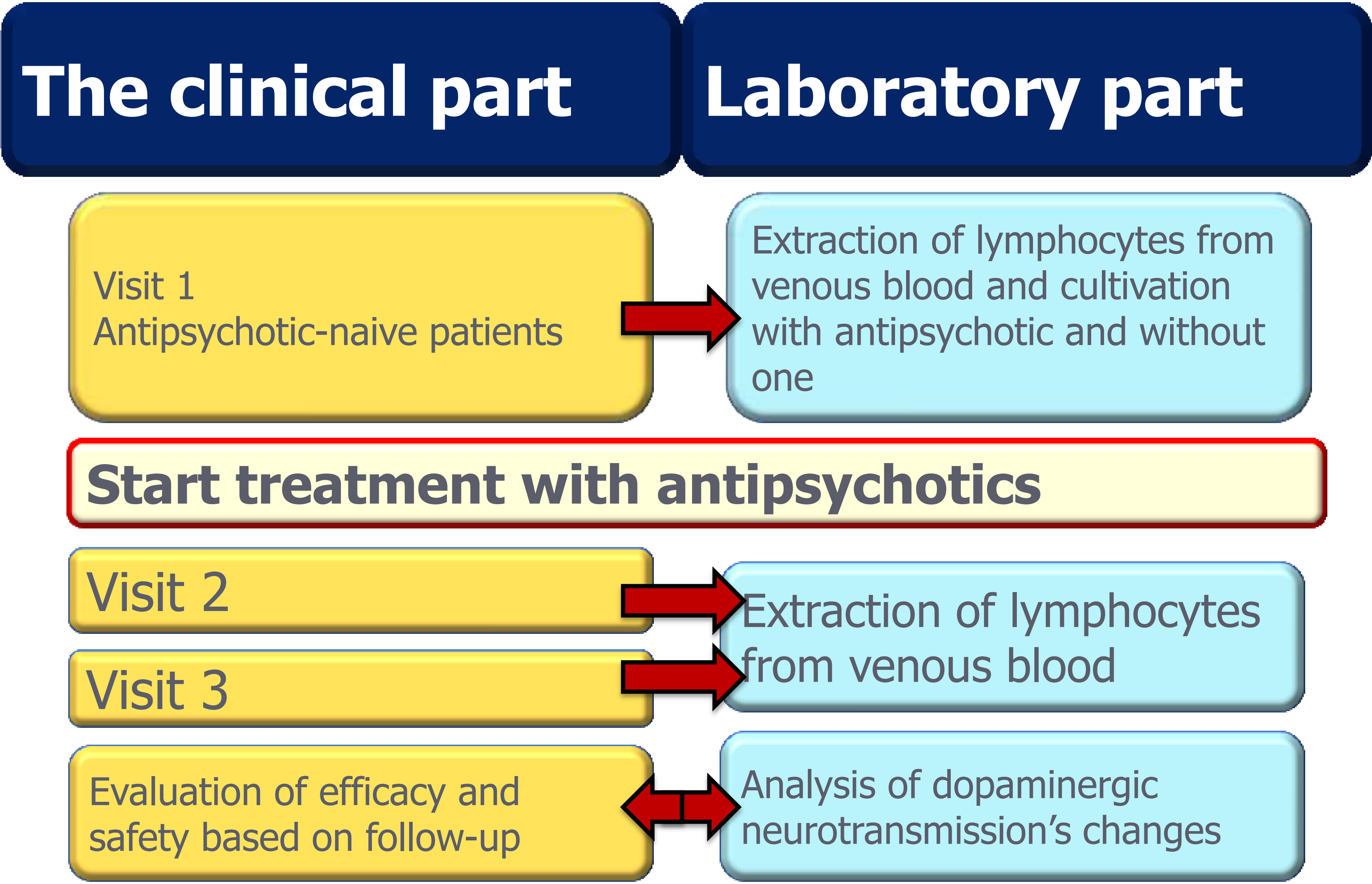
Visit 3

Day 14±2

Data analysis

- N=12
- Age 33±8 years

Study design



The clinical part

Laboratory part

Visit 1
Antipsychotic-naive patients

Extraction of lymphocytes from venous blood and cultivation with antipsychotic and without one

Start treatment with antipsychotics

Visit 2

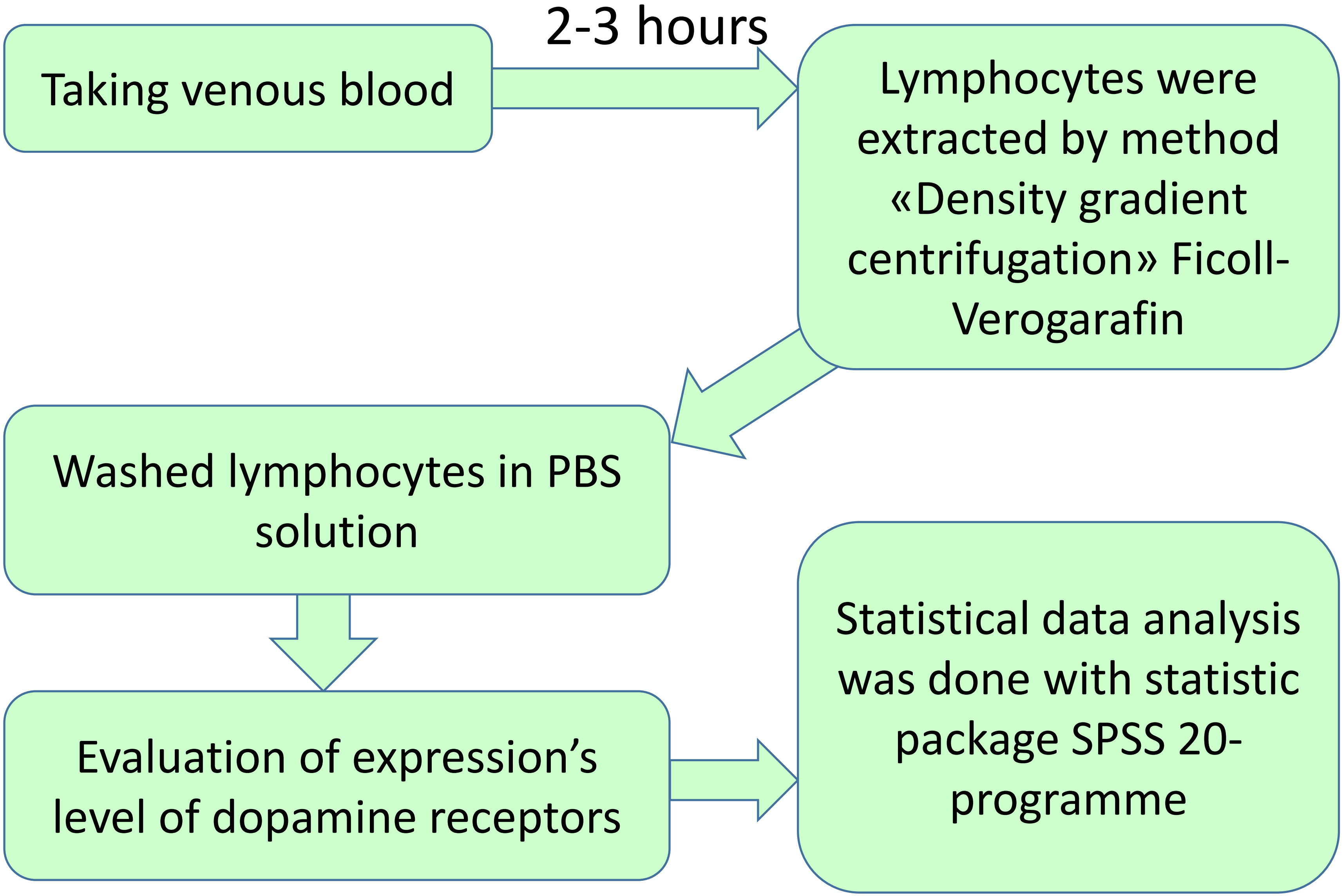
Visit 3

Extraction of lymphocytes from venous blood

Evaluation of efficacy and safety based on follow-up

Analysis of dopaminergic neurotransmission’s changes

MATERIALS AND METHODS



Taking venous blood

2-3 hours

Lymphocytes were extracted by method «Density gradient centrifugation» Ficoll-Verogarafin

Washed lymphocytes in PBS solution

Evaluation of expression's level of dopamine receptors

Statistical data analysis was done with statistic package SPSS 20-programme

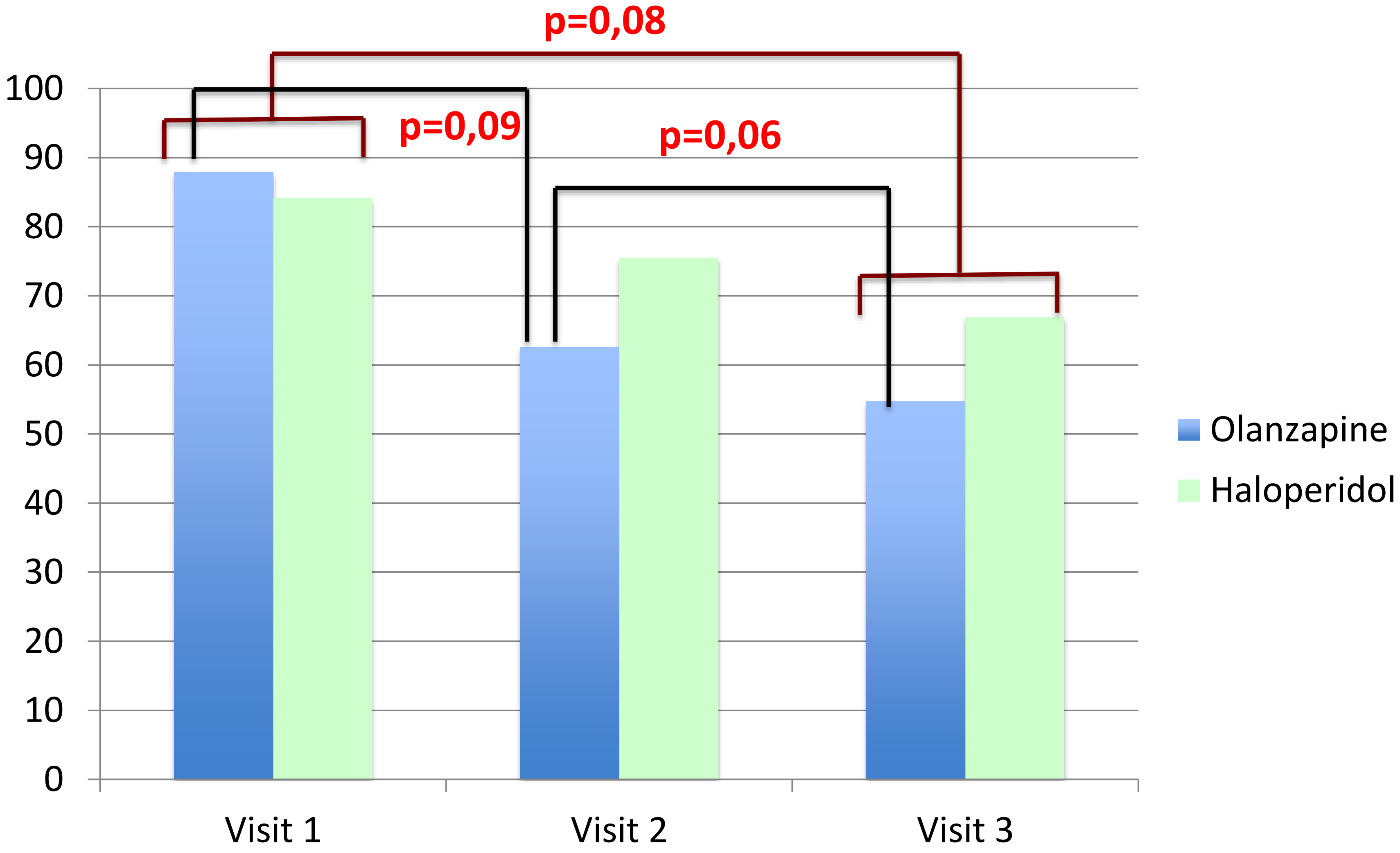
Initial mental state of patients

Antipsychotic	PANSS	CGI-S
Haloperidol	**84,17±16,96**	**5,17±0,72**
Olanzapine	**87,90±13,64**	**4,8±0,79**

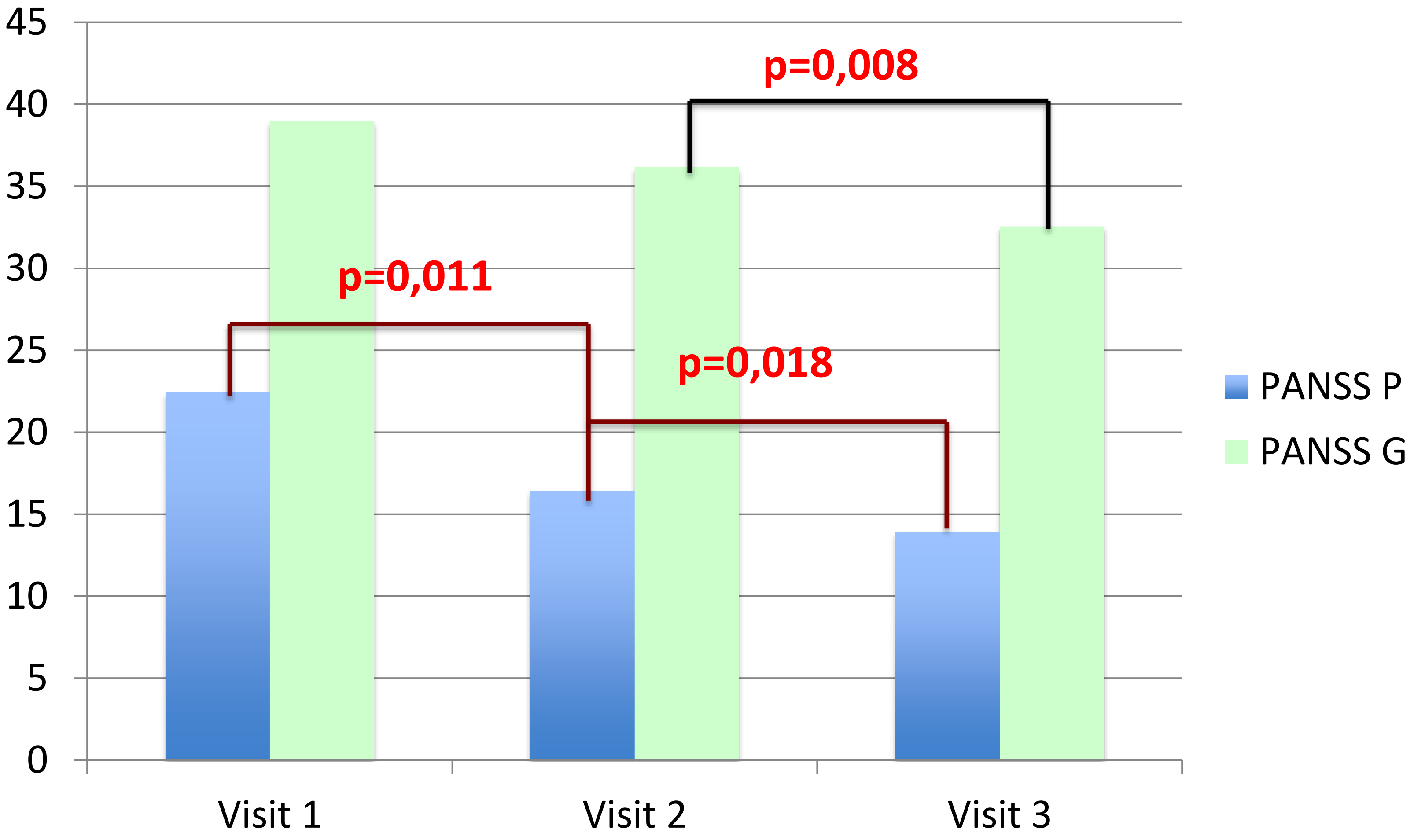
p=0,355

p=0,257

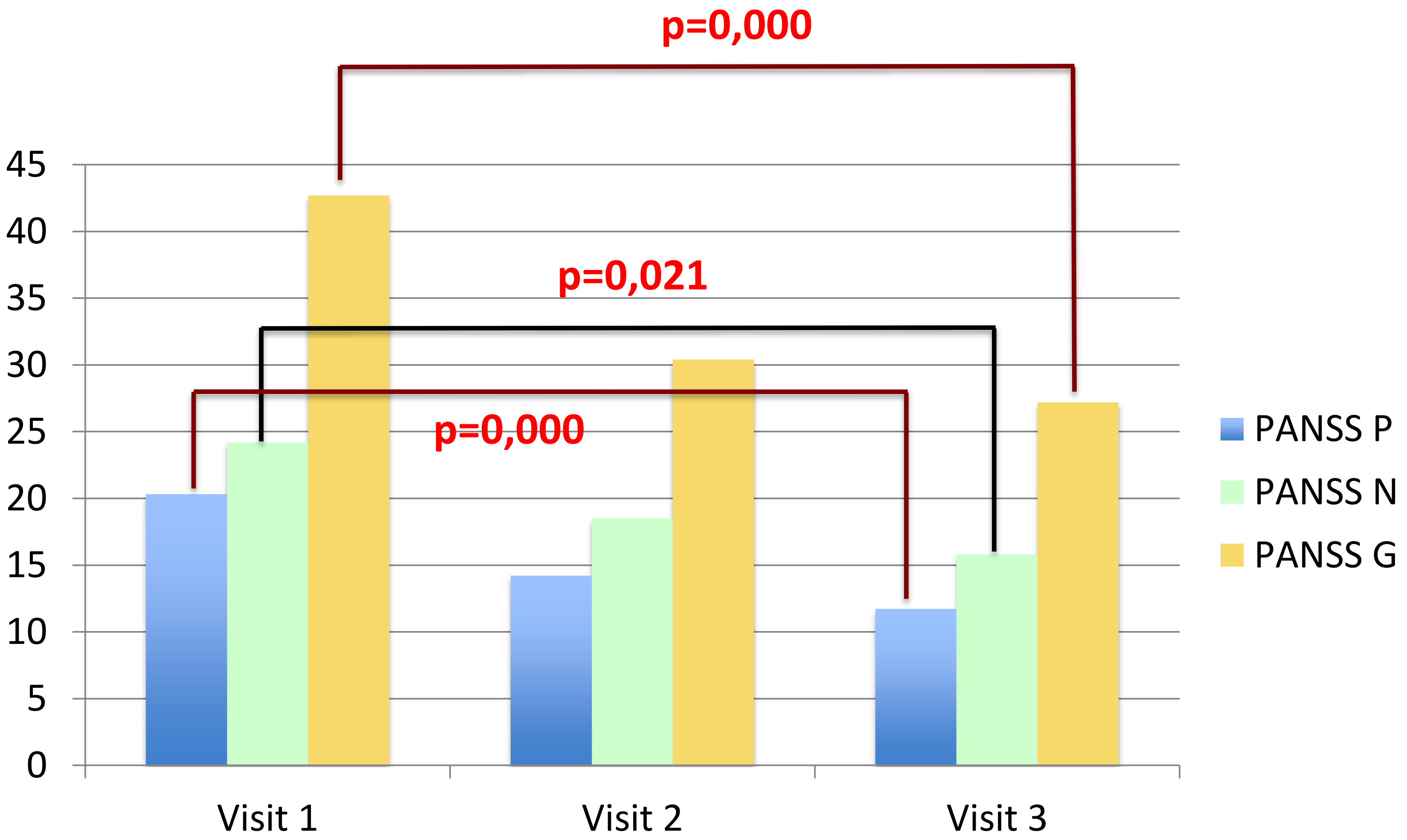
Psychotic symptoms' changes during follow-up (by PANSS overall score)



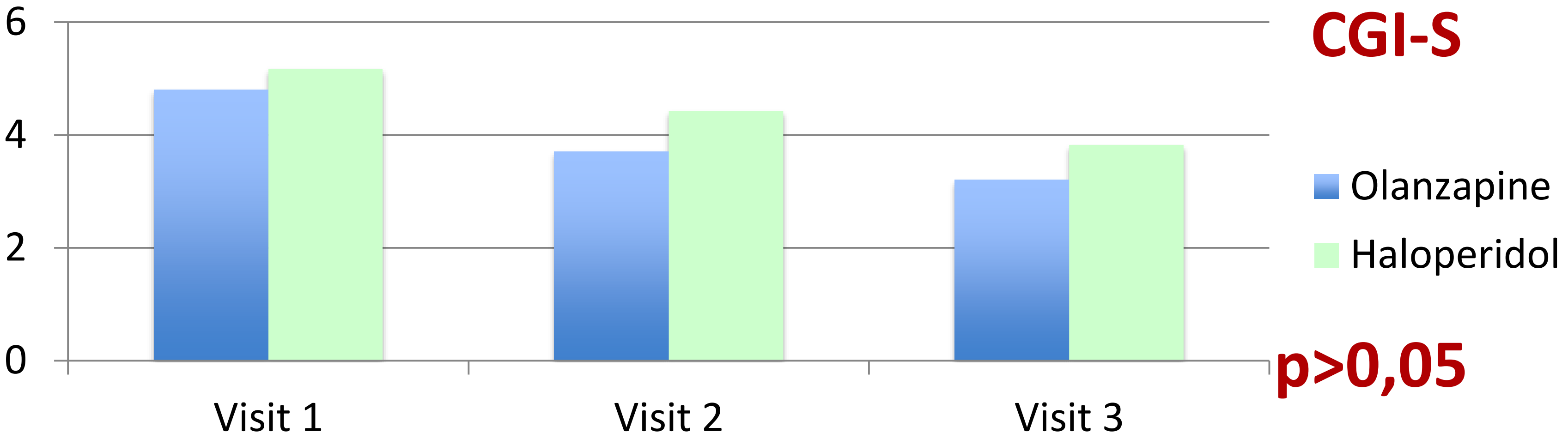
Clinical global impression scale (CGI-S) Changes between visits in patients received haloperidol



Psychiatric symptoms changes by PANSS subscales in patients received olanzapine

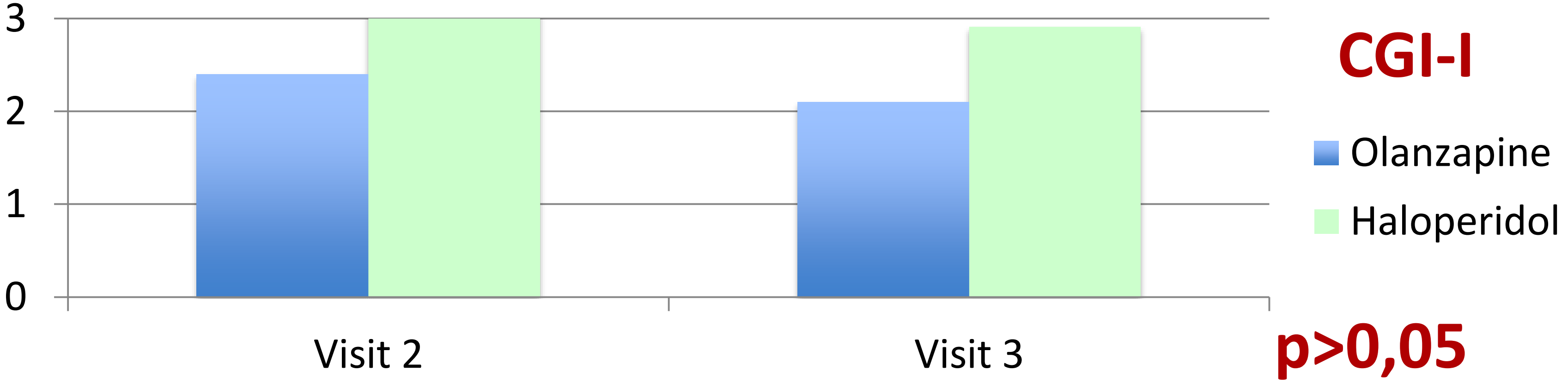


Changes in CGI-S and CGI-I scores



CGI-S

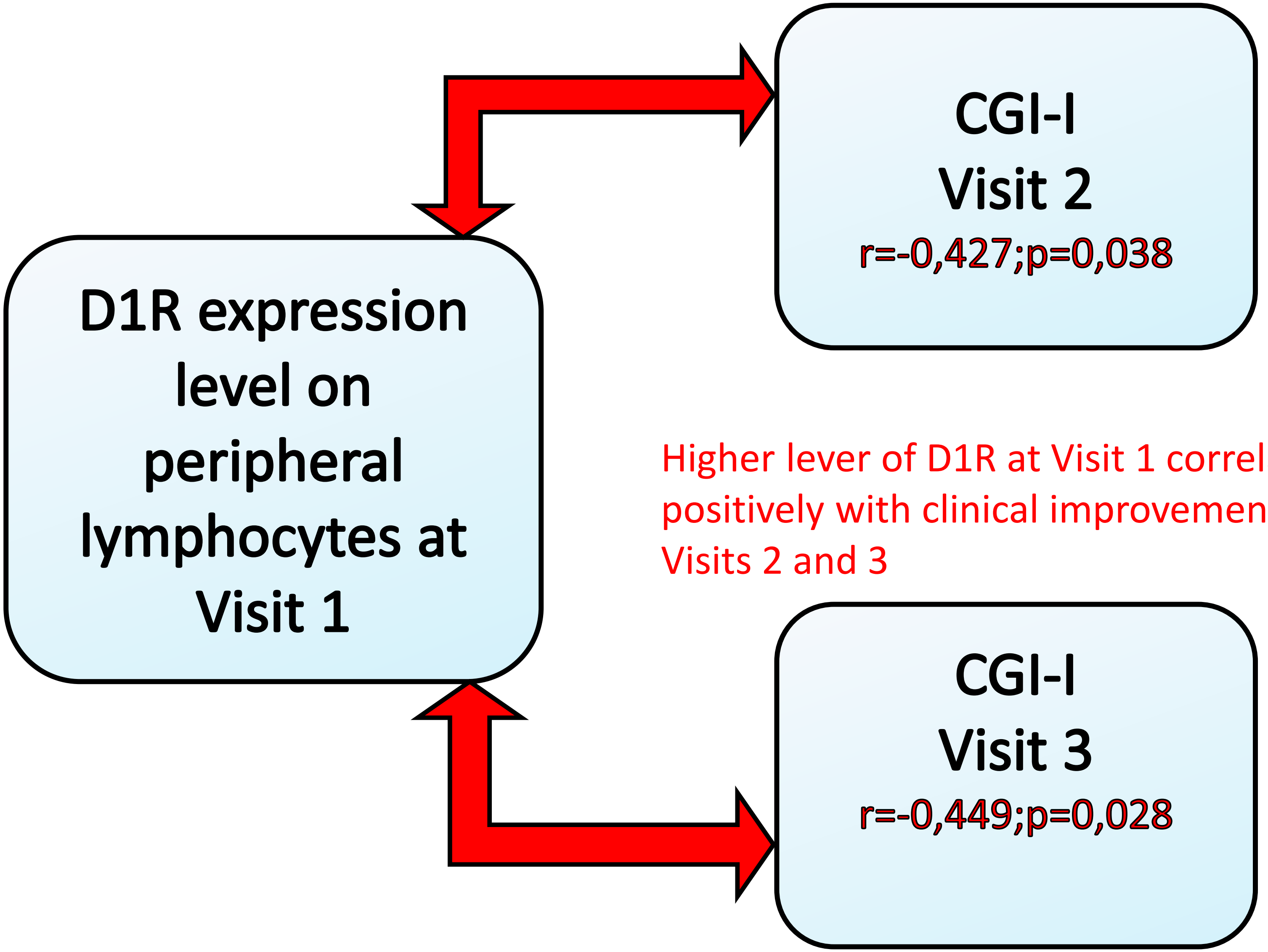
p>0,05



CGI-I

p>0,05

CORRELATIONS



D1R expression level on peripheral lymphocytes at Visit 1

CGI-I
Visit 2
r=-0,427;p=0,038

CGI-I
Visit 3
r=-0,449;p=0,028

Higher lever of D1R at Visit 1 correlated positively with clinical improvement at Visits 2 and 3

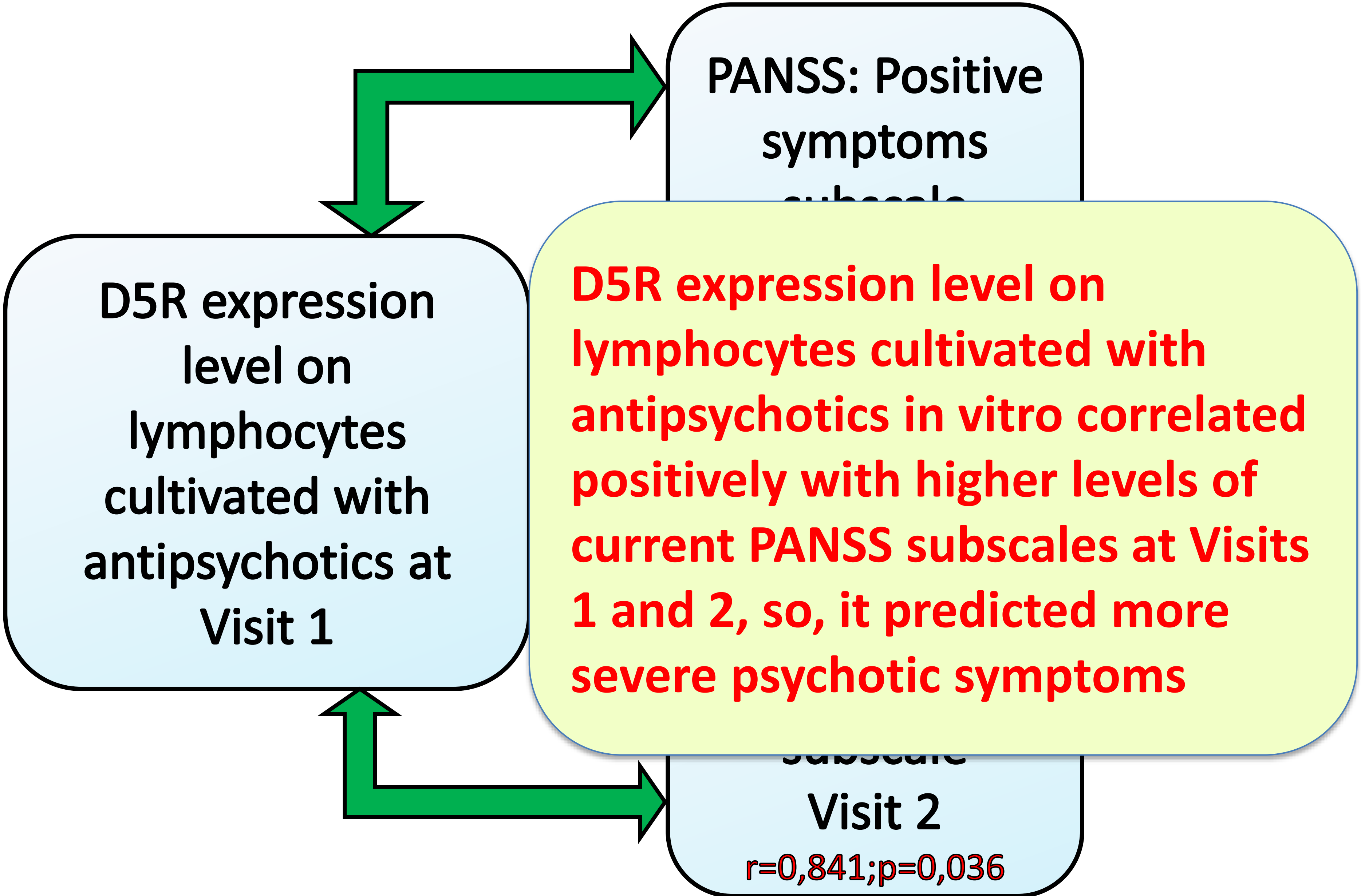
CORRELATIONS

D5R expression level on peripheral lymphocytes at Visit 1

CGI-I
Visit 3
r=-0,828;p=0,042

Higher lever of D5R at Visit 1 correlated positively with clinical improvement at Visit 3

CORRELATIONS



PANSS: Positive symptoms

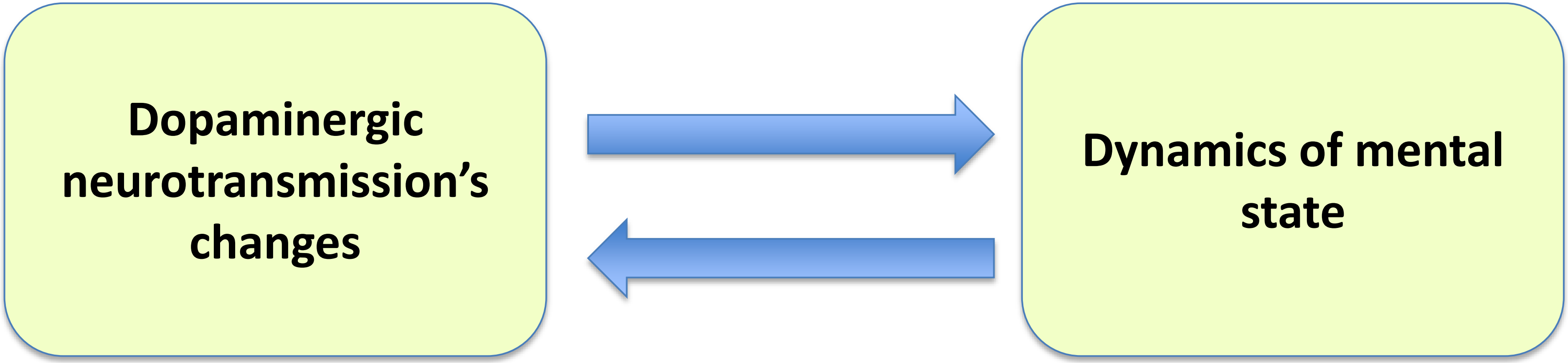
D5R expression level on lymphocytes cultivated with antipsychotics at Visit 1

Visit 2

r=0,841;p=0,036

D5R expression level on lymphocytes cultivated with antipsychotics in vitro correlated positively with higher levels of current PANSS subscales at Visits 1 and 2, so, it predicted more severe psychotic symptoms

CONCLUSION



Dopaminergic neurotransmission's changes

Dynamics of mental state

It is going to develop personalized approach to diagnostics and treatment of mental disorders based on phenotype: parameters of dopaminergic neurotransmission on peripheral blood lymphocytes

The study is funded by grant №14-15-00904 of Russian Science Foundation

«Antipsychotics: the development of personalized approaches to therapy based on the individual characteristics of the receptor neurotransmission lymphocytes»

THANK YOU