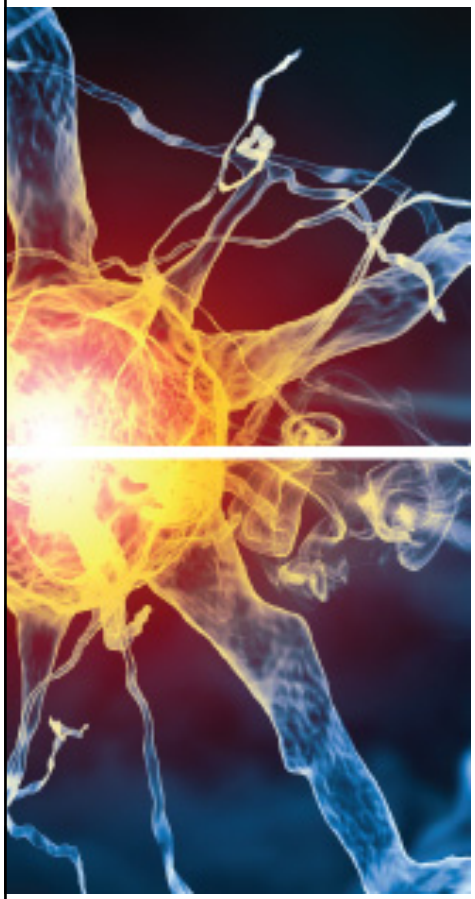
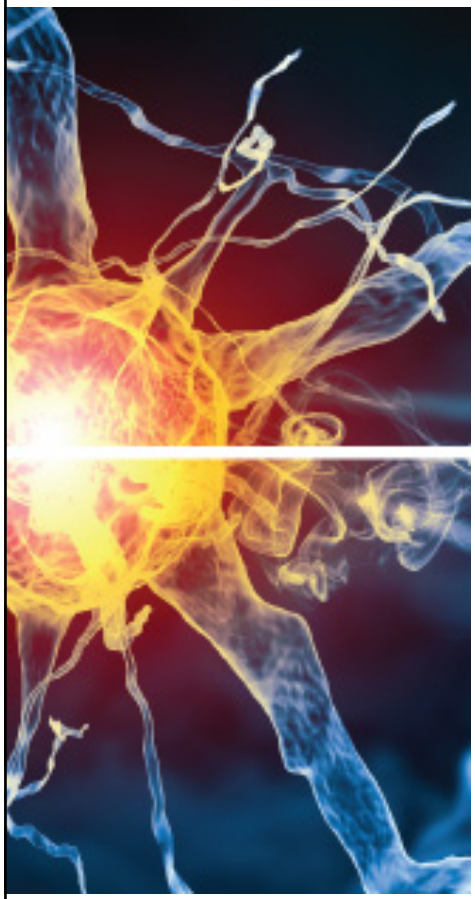


Neuroscience of Schizophrenia



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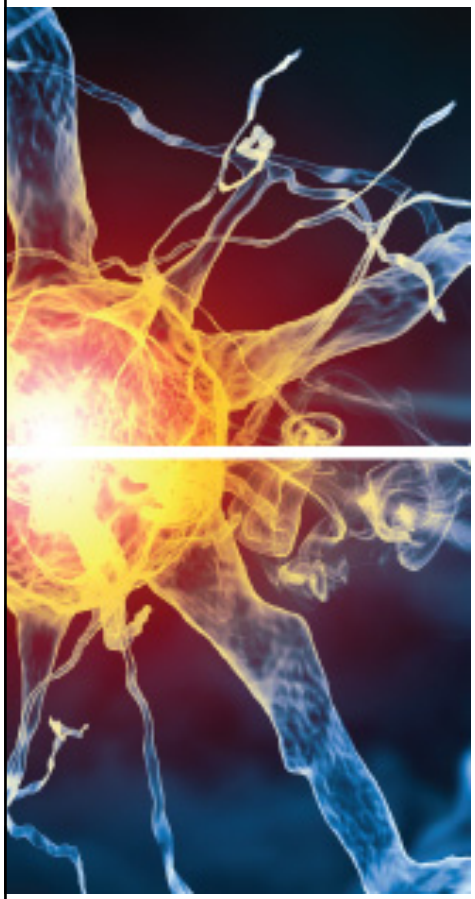
Instituto Nacional de Neurologia y Neurocirugia
Professor
Neurobiology of Schizophrenia Fellowship
Universidad Nacional Autonoma de Mexico
Mexico City, Mexico

Camilo de la Fuente-Sandoval, MD, PhD

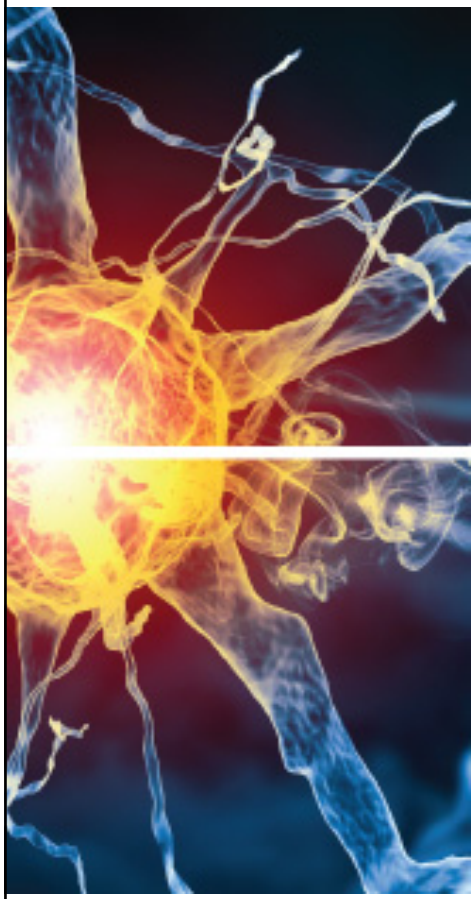
DIsclosures

- ***Consultant***: Janssen Pharmaceuticals, Inc. (Johnson & Johnson)



1 Learning Objective

Examine the biologic and genetic factors that influence the development and progression of schizophrenia.



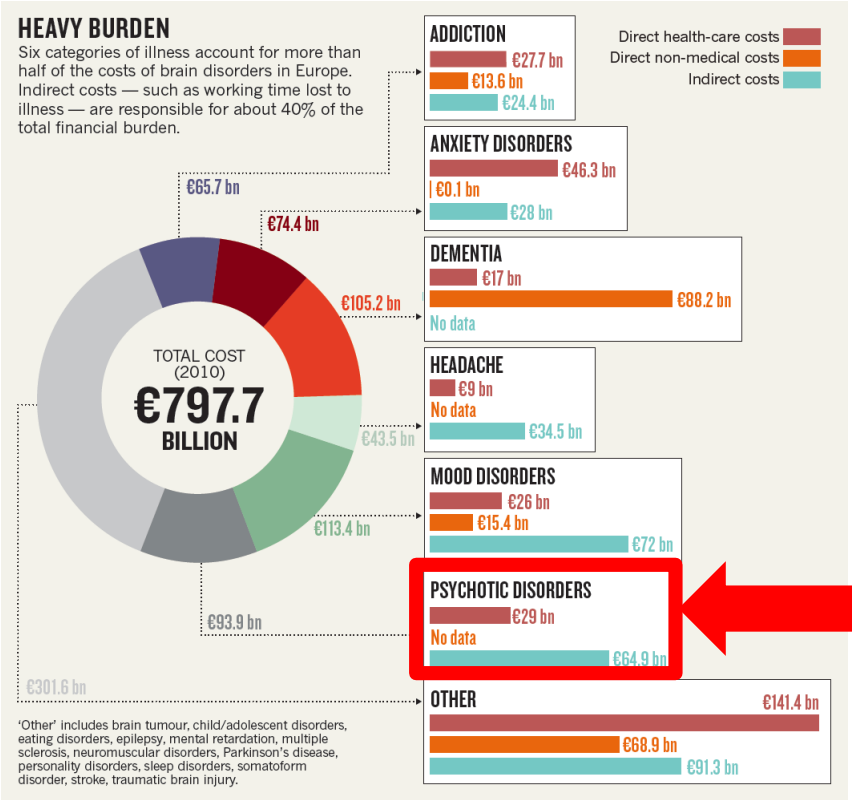
2 Learning Objective

Evaluate the role of glutamate receptors as treatment targets in schizophrenia.

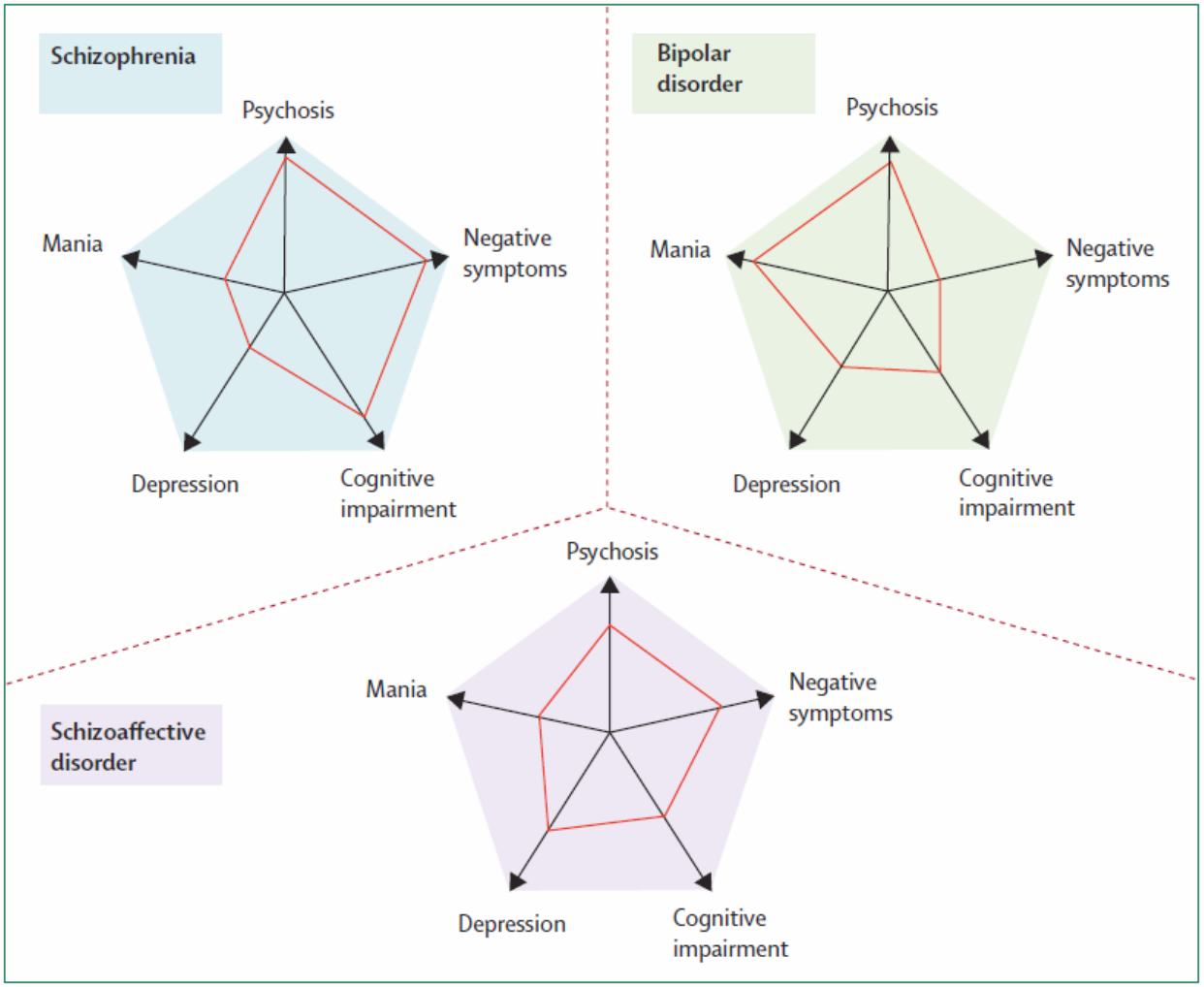
MENTAL HEALTH

Trillion-dollar brain drain

Enormous costs of mental health problems in Europe not matched by research investment.

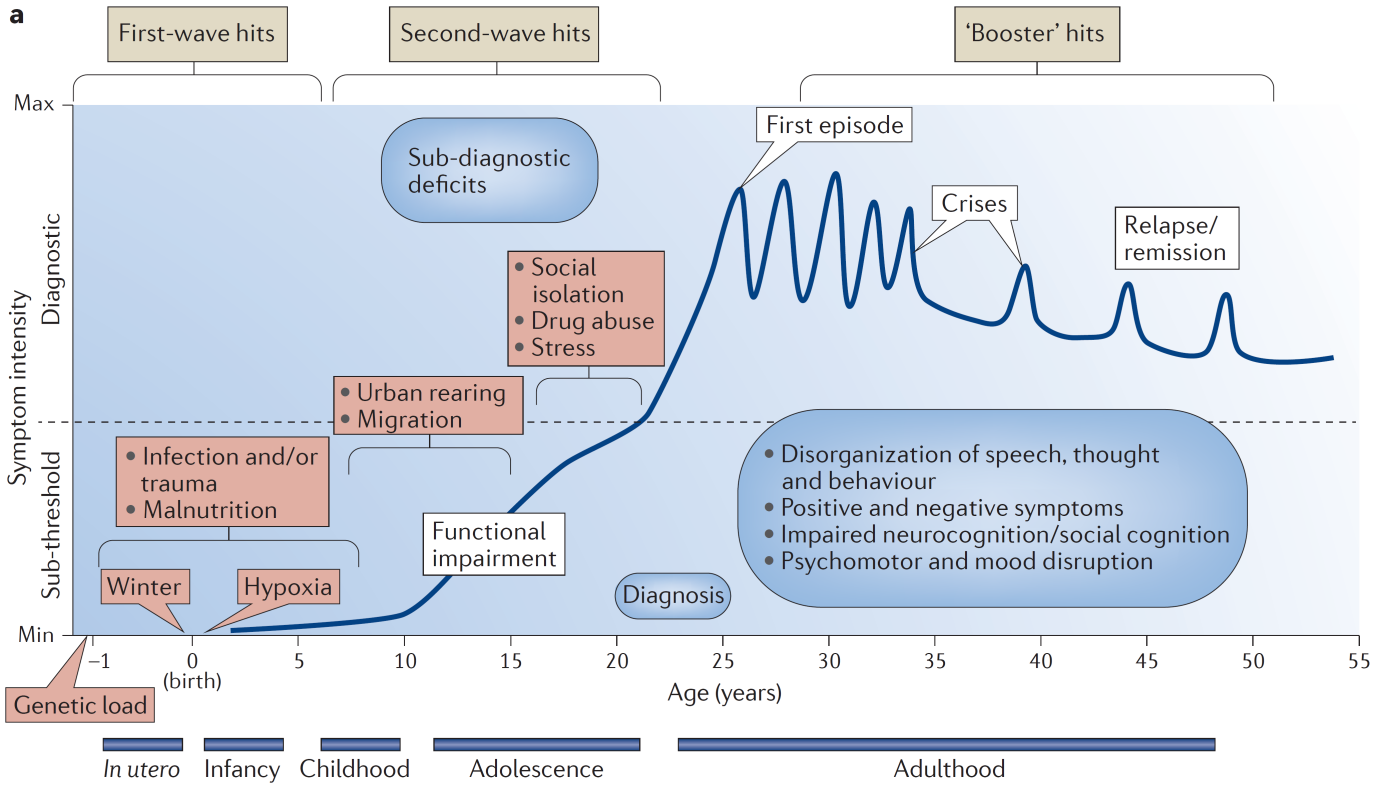


Smith K. *Nature*. 2011;478(7367):15.



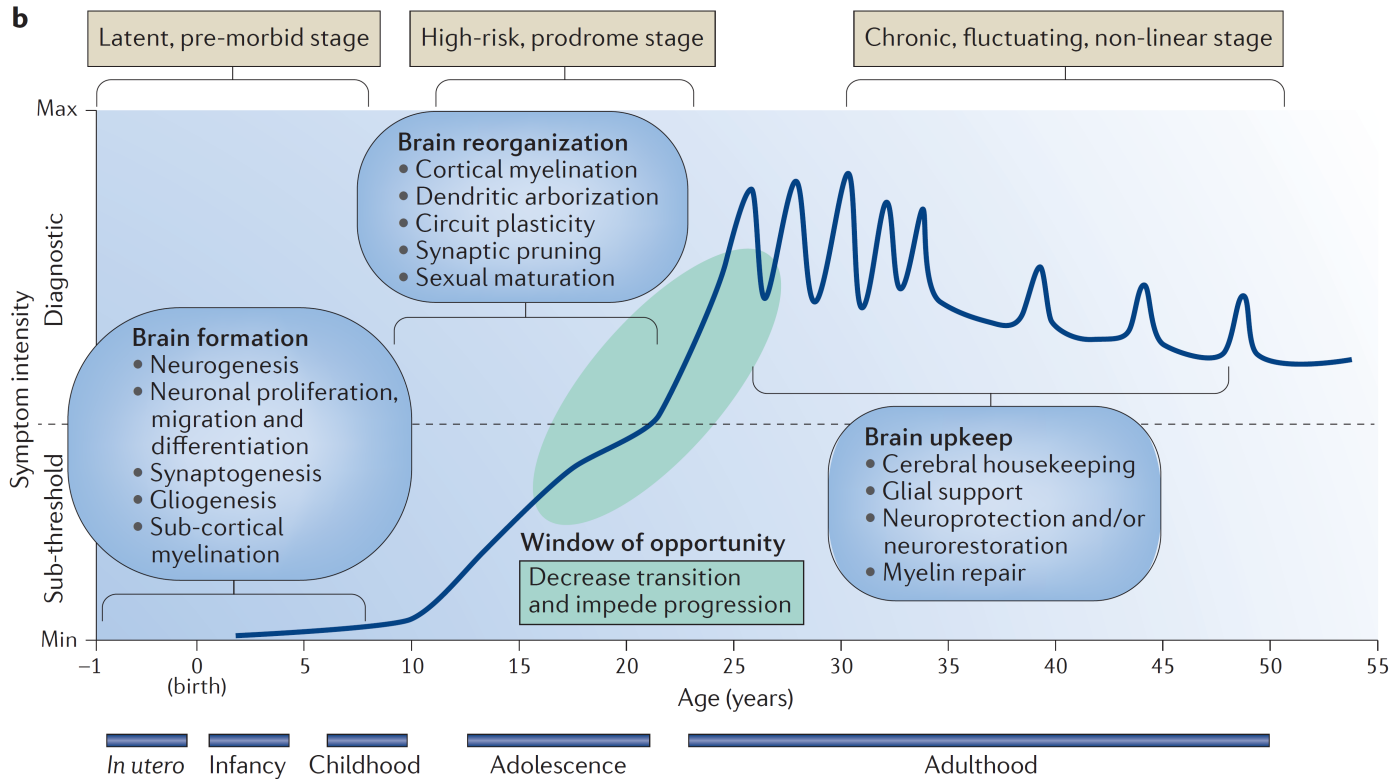
Van Os J, Kapur S. *Lancet* 2009;22;374(9690):635-45.

Onset and Progression of Schizophrenia – Risk Factors



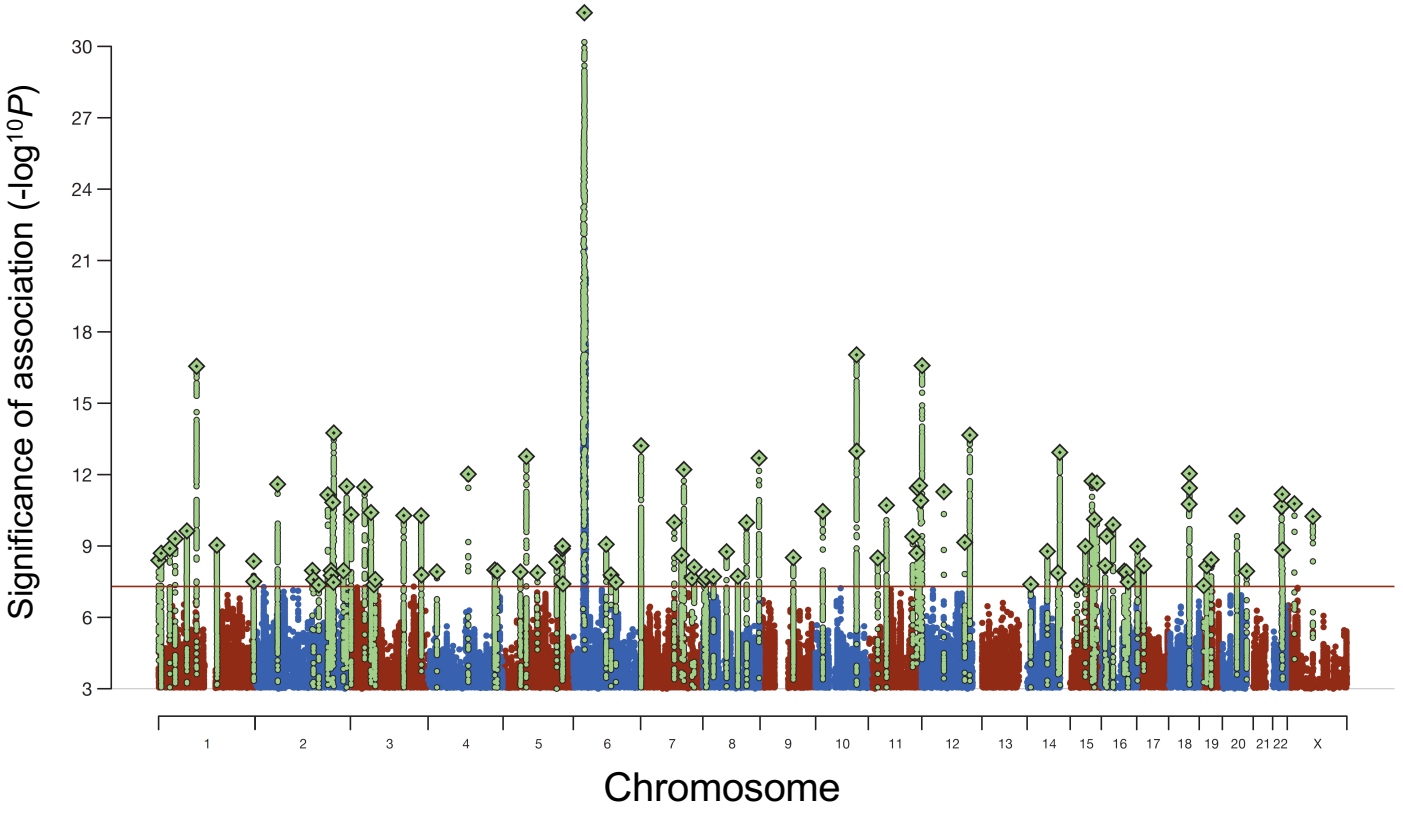
Millan MJ, et al. *Nat Rev Drug Discov.* 2016;15(7):485-515.

Onset and Progression of Schizophrenia – Developmental Processes



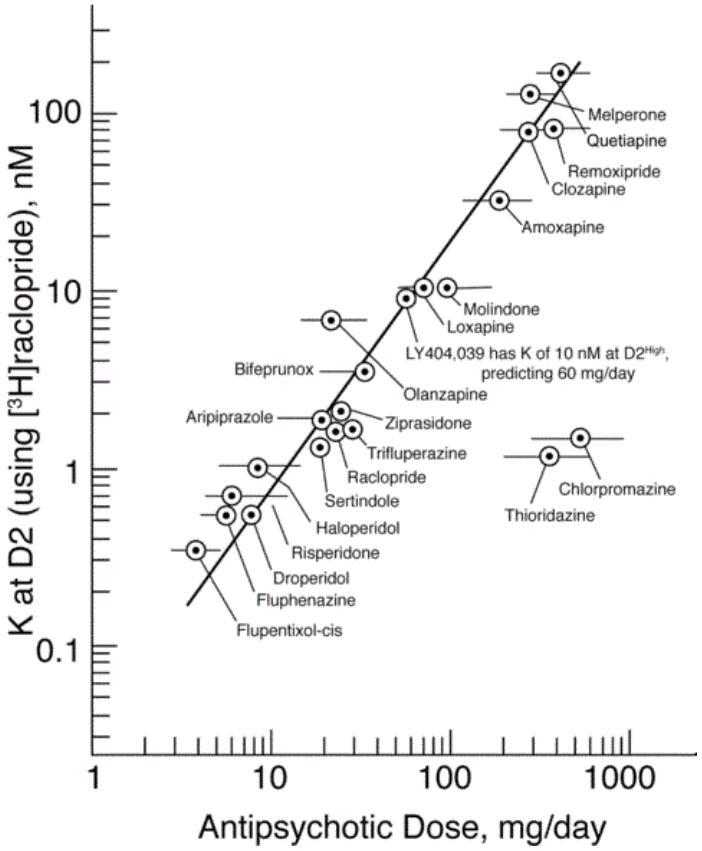
Millan MJ, et al. *Nat Rev Drug Discov*, 2016;15(7):485-515.

Genome-wide Association Meta-analysis



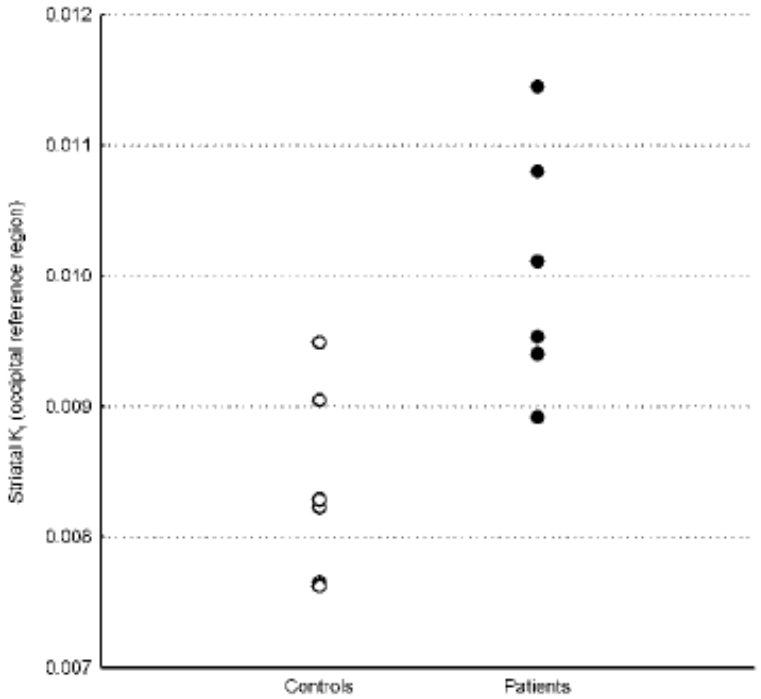
Schizophrenia WGP Genomics Consortium. *Nature*, 2014;511(7510):421-427.

Dopaminergic Hypothesis



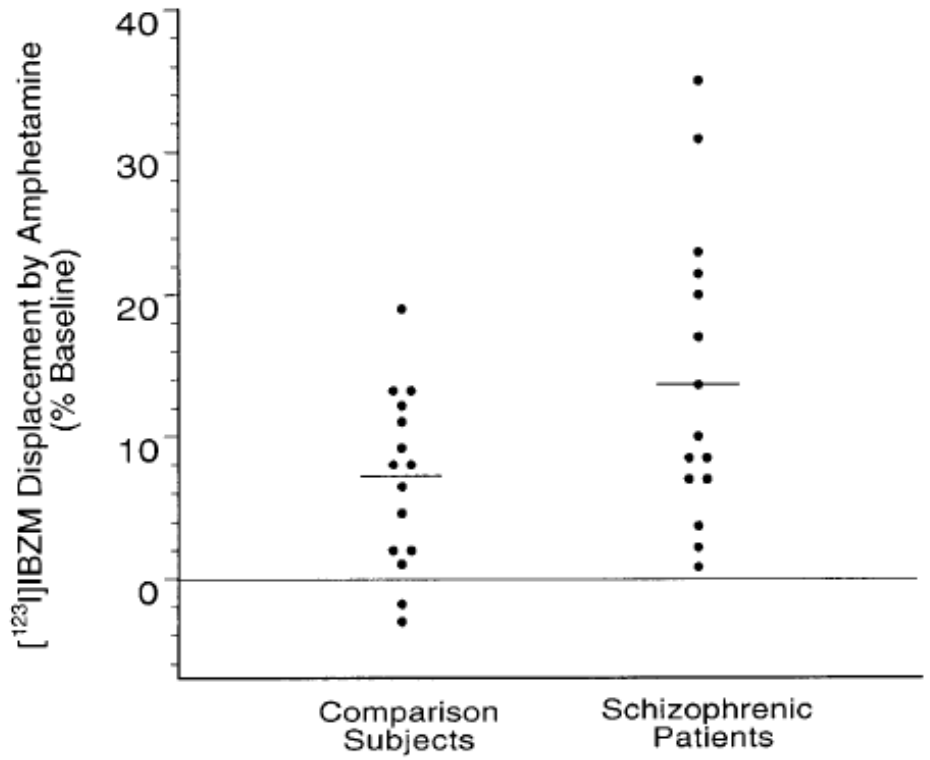
Seeman P. *CNS Neurosci Ther*, 2011;17(2):118-132.

Dopamine Synthesis



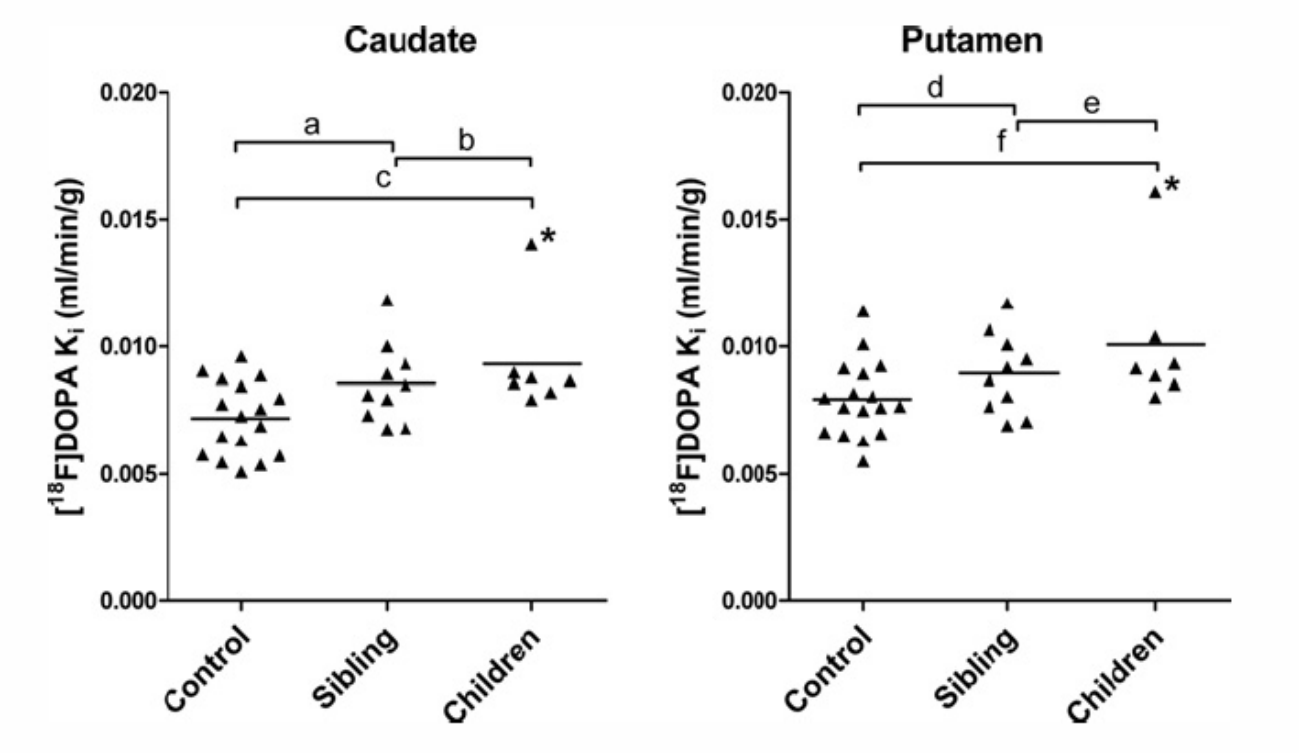
Meyer-Lindenberg A, et al. *Nat Neurosci*. 2002;5(3):267-271.

Dopamine Release



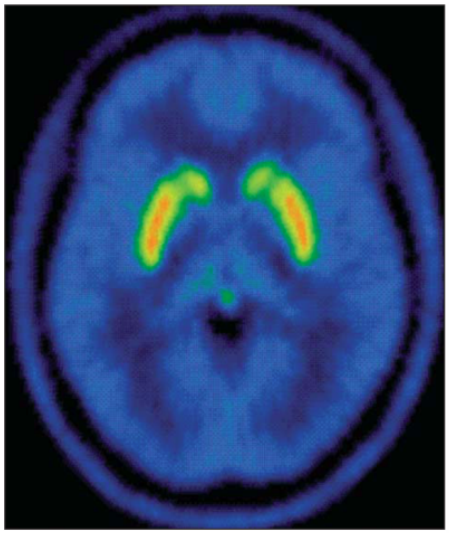
Abi-Darghami A, et al. *Am J Psychiatry*. 1998;155(6):761-767.

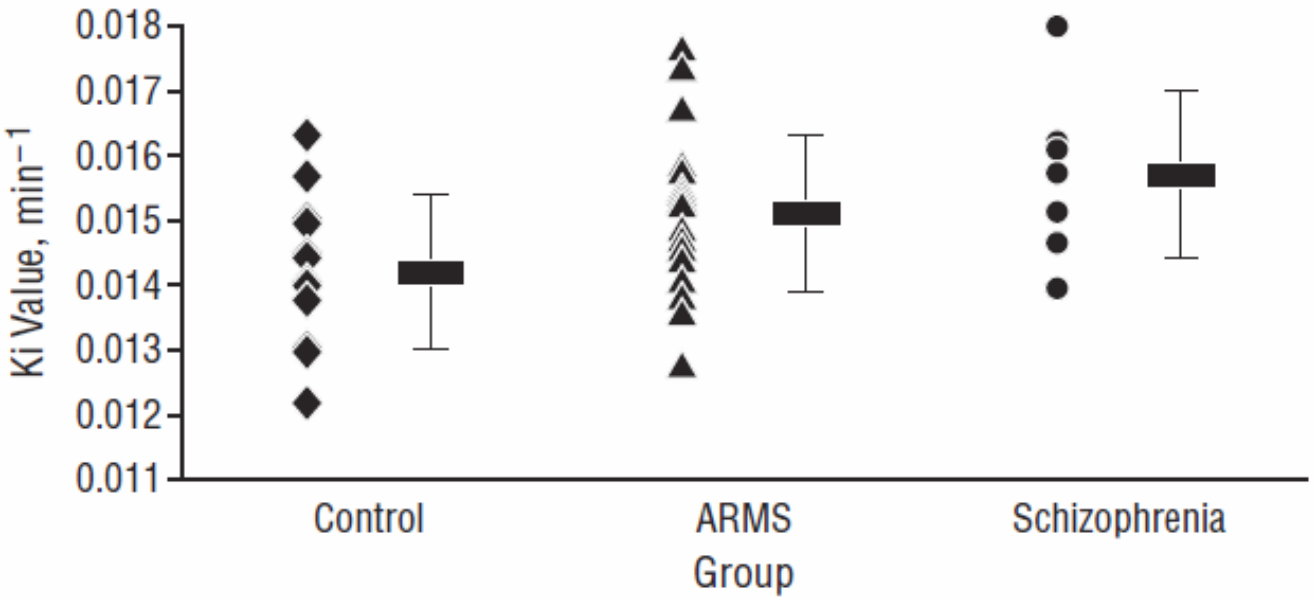
First-Degree Relatives



Hutunnen, J. et al. *Biol Psychiatry*, 2008;63(1):114-117.

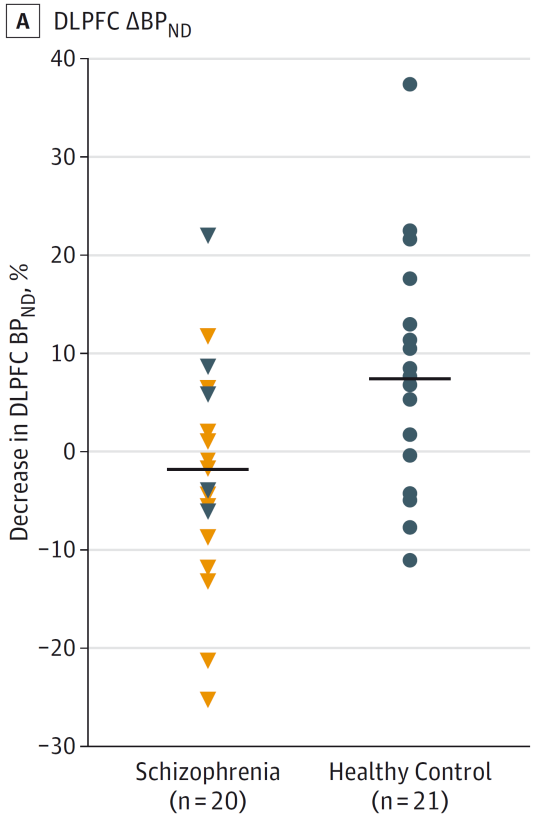
Clinical High-Risk Subjects





Howes OD, et al. *Arch Gen Psychiatry*. 2009;66(1):13-20.

Cortical Dopamine



Sliftein M, et al. *JAMA Psychiatry*. 2015;72(4):316-324.

Antipsychotic Response

- About 70-80% of patients with First-episode psychosis experience a remission in psychotic symptoms within the first year of treatment

Lieberman JA, et al. *Arch Gen Psychiatry*.1993;50(5):369-376.

Antipsychotic Response

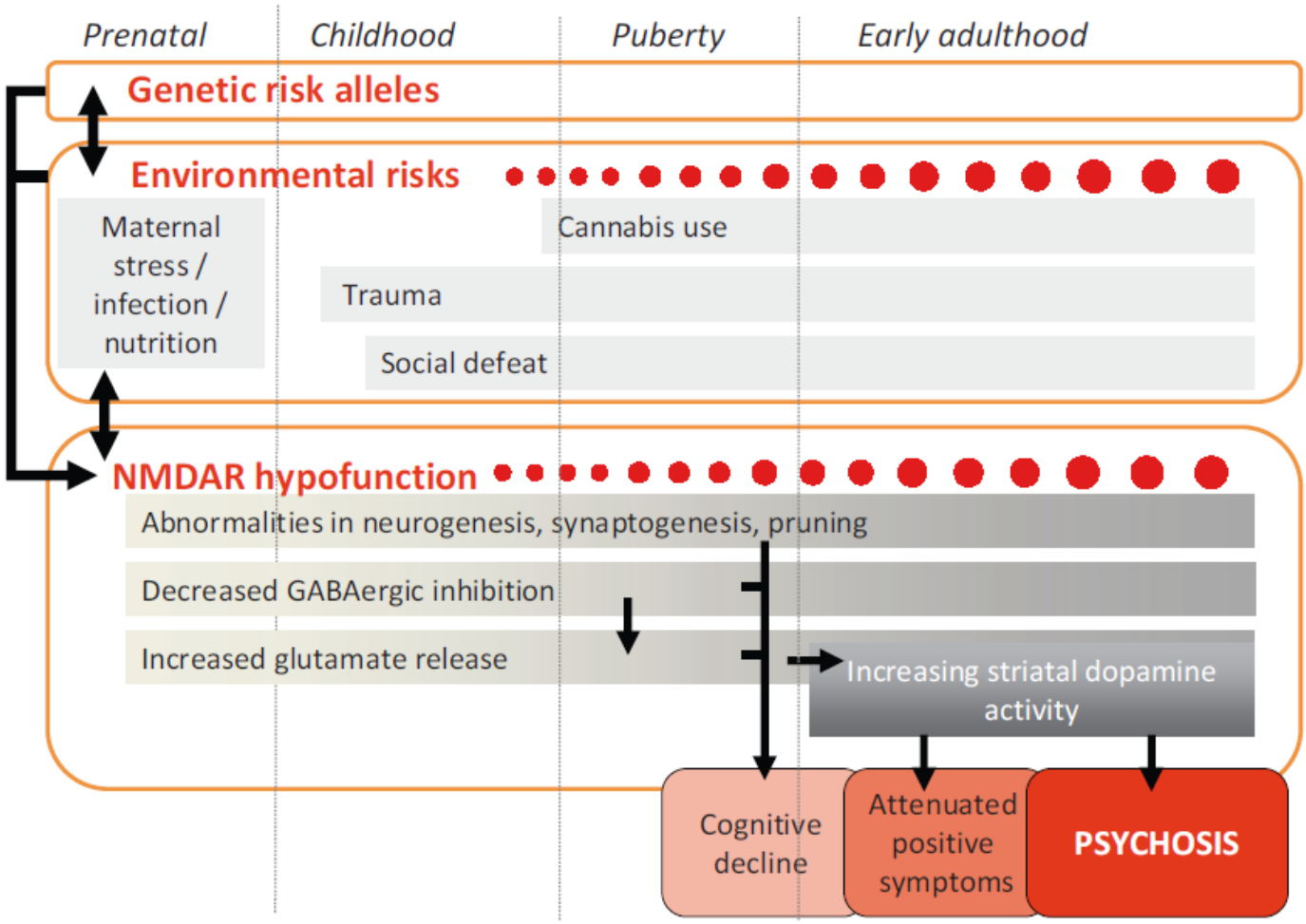
- About 70-80% of patients with First-episode psychosis experience a remission in psychotic symptoms within the first year of treatment
- One-year recurrence (weighted mean) 77% following discontinuation of antipsychotic medication
- Two-year - 90%

Lieberman JA, et al. *Arch Gen Psychiatry*.1993;50(5):369-376.
Zipursky RB, et al. *Schizophr Res*. 2014;152(2-3):408-414.

Antipsychotic Response

- About 70-80% of patients with First-episode psychosis experience a remission in psychotic symptoms within the first year of treatment
- One-year recurrence (weighted mean) 77% following discontinuation of antipsychotic medication
- Two-year - 90%
- Approximately, a third of patients with schizophrenia show limited if any response to first-line antipsychotic medications

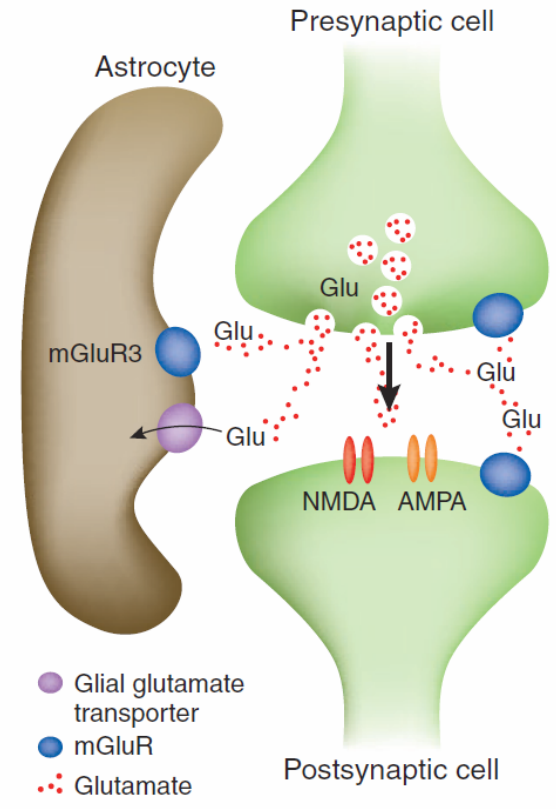
Lieberman JA, et al. *Arch Gen Psychiatry*.1993;50(5):369-376.
Zipursky RB, et al. *Schizophr Res*. 2014;152(2-3):408-414.
Lindenmayer JP. *Psychiatr Q*, 2000;71(4):373-384.



Egerton A, et al. *Curr Pharm Des*. 2012;18(4):466-478.

Glutamate

- Drug induced hypofunction of the NMDA receptor, induce both positive and negative symptoms



Javitt DC, et al. *Am J Psychiatry*. 1991;148(10):1301-1308.
Olney JW, Farber NB. *Arch Gen Psychia*try. 1995;52(12):998-1007.

LETTERS

nature medicine

Activation of mGlu2/3 receptors as a new approach to treat schizophrenia: a randomized Phase 2 clinical trial

Sandeep T Patil[1,13], Lu Zhang[1], Ferenc Martenyi[2], Stephen L Lowe[3], Kimberley A Jackson[4], Boris V Andreev[5], Alla S Avedisova[6], Leonid M Bardenstein[7], Issak Y Gurovich[8], Margarita A Morozova[9], Sergey N Mosolov[8], Nikolai G Neznanov[10], Alexander M Reznik[11], Anatoly B Smulevich[9], Vladimir A Tochilov[12], Bryan G Johnson[1], James A Monn[1] & Darryle D Schoepp[1,13]

Patil ST, et al. *Nat Med.* 2007;13(9):1102-1107.

Archival Report

Biological Psychiatry

Exploratory Analysis for a Targeted Patient Population Responsive to the Metabotropic Glutamate 2/3 Receptor Agonist Pomaglumetad Methionil in Schizophrenia

Bruce J. Kinon, Brian A. Millen, Lu Zhang, and David L. McKinzie

ABSTRACT

BACKGROUND: Accumulating evidence indicates that glutamatergic tone in schizophrenia may vary as a function of illness duration or medication history. We conducted an exploratory analysis of the existing clinical trial database of pomaglumetad methionil (pomaglumetad) to demonstrate treatment response in targeted patient populations.

METHODS: Results of the H8Y-MC-HBBM (HBBM) study and an integrated analysis based on five placebo-controlled trials were summarized. Patients with schizophrenia were randomly assigned to receive either pomaglumetad, 40 or 80 mg twice daily (BID), placebo, or risperidone, 2 mg BID, for up to 6 weeks. Patient subgroups were analyzed to determine the efficacy of pomaglumetad treatment in patients early-in-disease (≤3 years) and late-in-disease (≥10 years) (HBBM, 40 mg, $n = 206$, 80 mg, $n = 198$; integrated analysis, 40 mg, $n = 382$, 80 mg, $n = 381$) and in patients previously treated with central nervous system drugs with prominent serotonin 2A receptor antagonist activity (S2 group) or with predominant dopamine D2 receptor antagonist activity (D2 group; HBBM, 40 mg, $n = 275$, 80 mg, $n = 269$; integrated analysis, 40 mg, $n = 590$, 80 mg, $n = 506$).

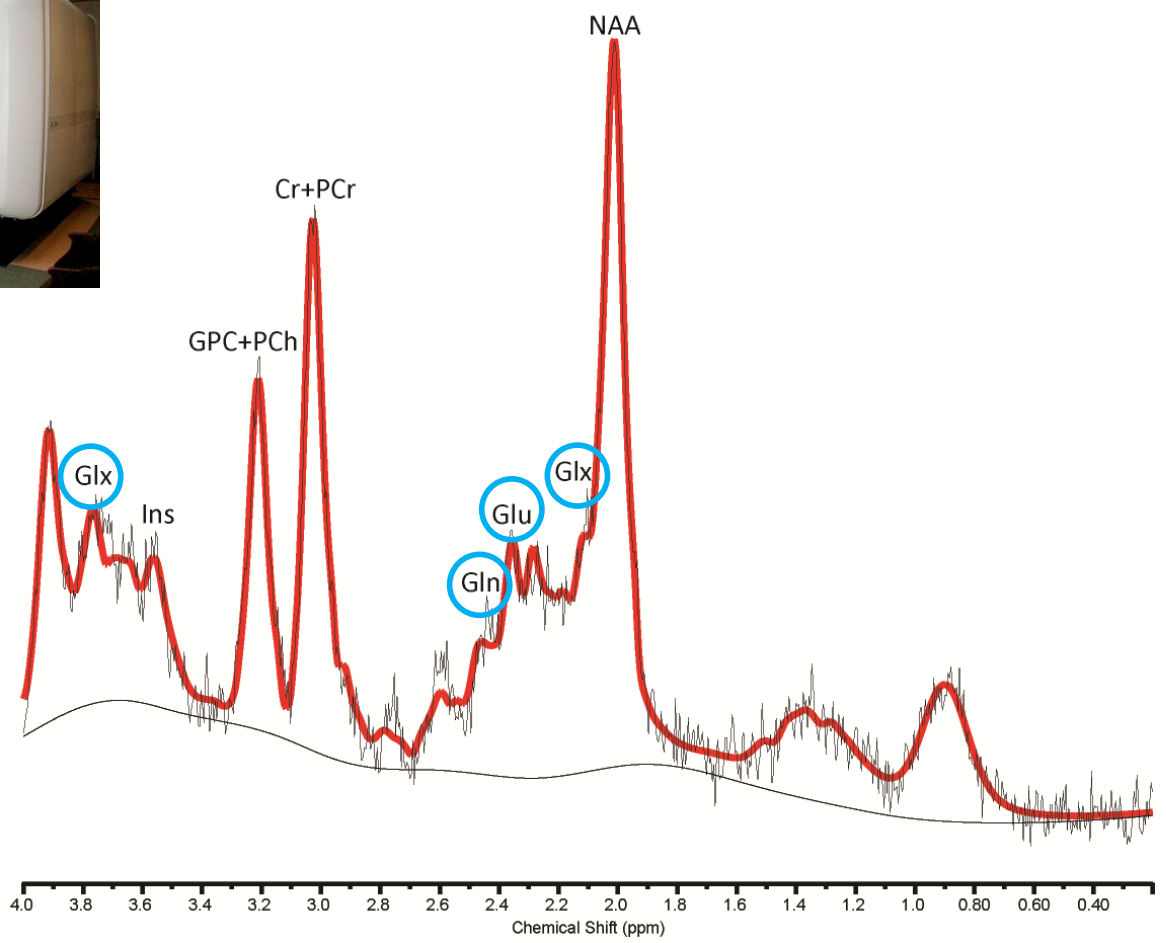
RESULTS: In the HBBM study and integrated analysis, only patients early-in-disease or previously treated with D2 drugs exhibited significantly greater improvement relative to those receiving placebo, when treated with pomaglumetad, 40 mg (but not 80 mg) BID. Treatment response to risperidone did not appear to depend upon these patient subgroups.

CONCLUSIONS: Demonstration of antipsychotic efficacy of a potential glutamate-based pharmacotherapy for schizophrenia may require the identification of appropriate patient subgroups whose treatment responsiveness may be fundamentally related to dysregulation of central nervous system glutamatergic tone.

Keywords: Epigenetic, Glutamate, Pomaglumetad, Risperidone, Schizophrenia, Treatment history

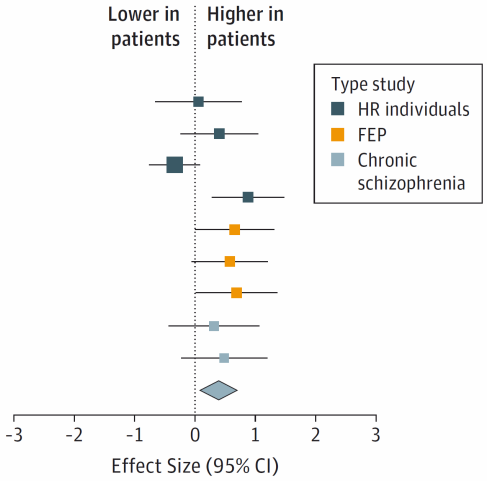
http://dx.doi.org/10.1016/j.biopsych.2015.03.016

Kinon BJ, et al. *Biol Psychiatry*. 2015;78(11):754-762.

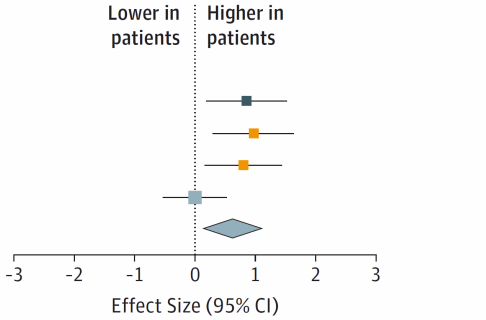

NAA
Cr+PCr
GPC+PCh
Glx
Ins
Glu
Glx
Gln
4.0
3.8
3.6
3.4
3.2
3.0
2.8
2.6
2.4
2.2
2.0
1.8
1.6
1.4
1.2
1.0
0.80
0.60
0.40
Chemical Shift (ppm)

Study Effect Sizes in Brain Regions Showing Significant Glutamatergic Differences Between Cases and Controls

Source	Hedges *g*
Basal ganglia: Glx	
Block et al,[31] 2000	0.06
de la Fuente-Sandoval et al,[18] 2011	0.40
Keshavan et al,[37] 2009	-0.34
Tandon et al,[25] 2013	0.88
de la Fuente-Sandoval et al,[18] 2011	0.66
de la Fuente-Sandoval et al,[17] 2013	0.63
Goto et al,[19] 2012	0.69
Block et al,[31] 2000	0.31
Yamasue et al,[50] 2003	0.49
Summary: $g = 0.39$ (95% CI, 0.09-0.70); $I^2 = 52\%$	



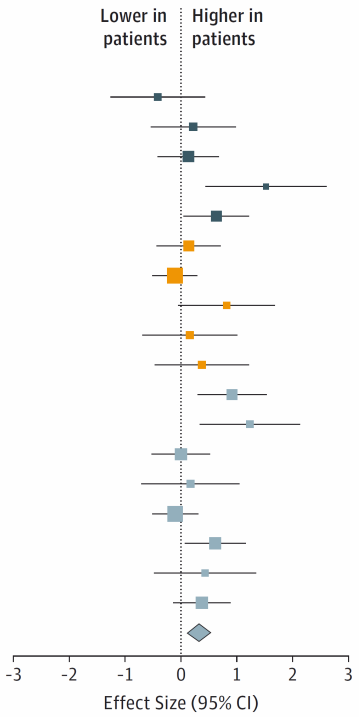
Source	Hedges *g*
Basal ganglia: glutamate	
de la Fuente-Sandoval et al,[18] 2011	0.86
de la Fuente-Sandoval et al,[18] 2011	0.97
de la Fuente-Sandoval et al,[17] 2013	0.80
Tayoshi et al,[55] 2009	0.00
Summary: $g = 0.63$ (95% CI, 0.15-1.11); $I^2 = 57\%$	



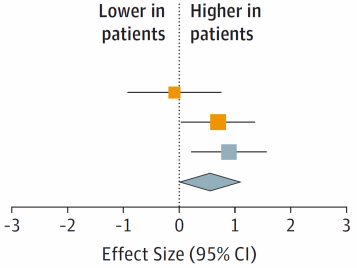
Merrit K, et al. *JAMA Psychiatry*. 2016;73(7):665-674.

Study Effect Sizes in Brain Regions Showing Significant Glutamatergic Differences Between Cases and Controls, cont.

Source	Hedges *g*
Medial temporal lobe: Glx	
Capizzano et al,[75] 2011	-0.42
Capizzano et al,[75] 2011	0.22
Stone et al,[62] 2009	0.13
Wood et al,[49] 2010	1.52
Wood et al,[49] 2010	0.63
Galińska et al,[30] 2009	0.14
Hasan et al,[33] 2014	-0.11
Szulc et al,[24] 2004	0.82
Wood et al,[48] 2008	0.16
Wood et al,[48] 2008	0.38
Chang et al,[14] 2007	0.92
da Silva Alves et al,[16] 2011	1.23
Hutcheson et al,[34] 2012	0.00
Kegeles et al,[36] 2000	0.17
Kraguljac et al,[38] 2012	-0.10
Kraguljac et al,[21] 2013	0.61
Szulc et al,[24] 2004	0.43
Szulc et al,[43] 2011	0.37
Summary: $g = 0.32$ (95% CI, 0.12-0.52); $I^2 = 42\%$	



Source	Hedges *g*
Thalamus: glutamine	
Bustillo et al,[76] 2010	-0.08
Théberge et al,[9] 2002	0.70
Théberge et al,[54] 2003	0.89
Summary: $g = 0.56$ (95% CI, 0.02-1.09); $I^2 = 41\%$	



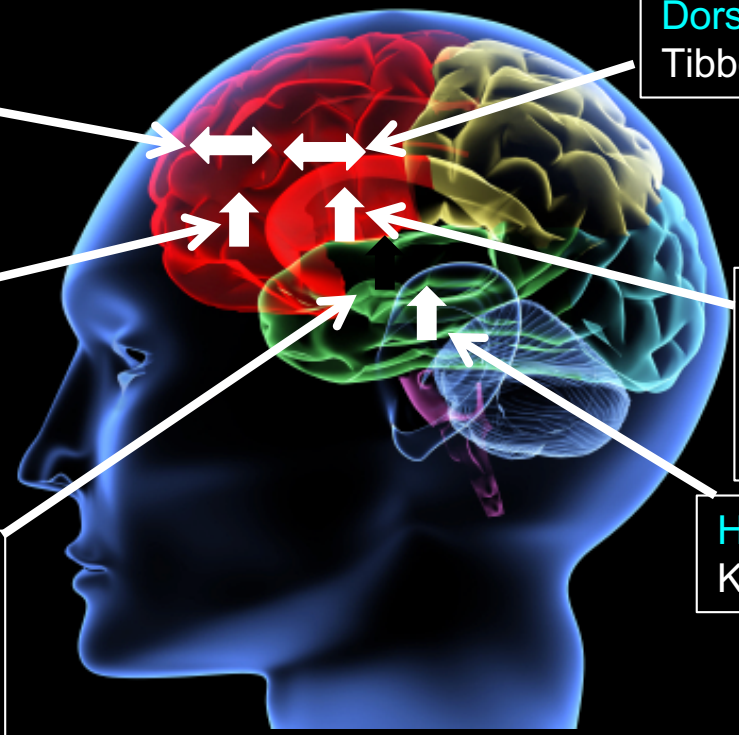
Merrit K, et al. *JAMA Psychiatry*. 2016;73(7):665-674.

Glu Abnormalities in Unmedicated Patients with Schizophrenia: Other Brain Regions

DLPFC:
Stanley et al, 1996
Ohrmann et al, 2007
Kegeles et al, 2012

MPFC:
Bartha et al, 1997
Théberge et al, 2002
Théberge et al, 2007
Aoyama et al, 2011
Kegeles et al, 2012

Thalamus:
Théberge et al, 2002
Théberge et al, 2007
Aoyama et al, 2011

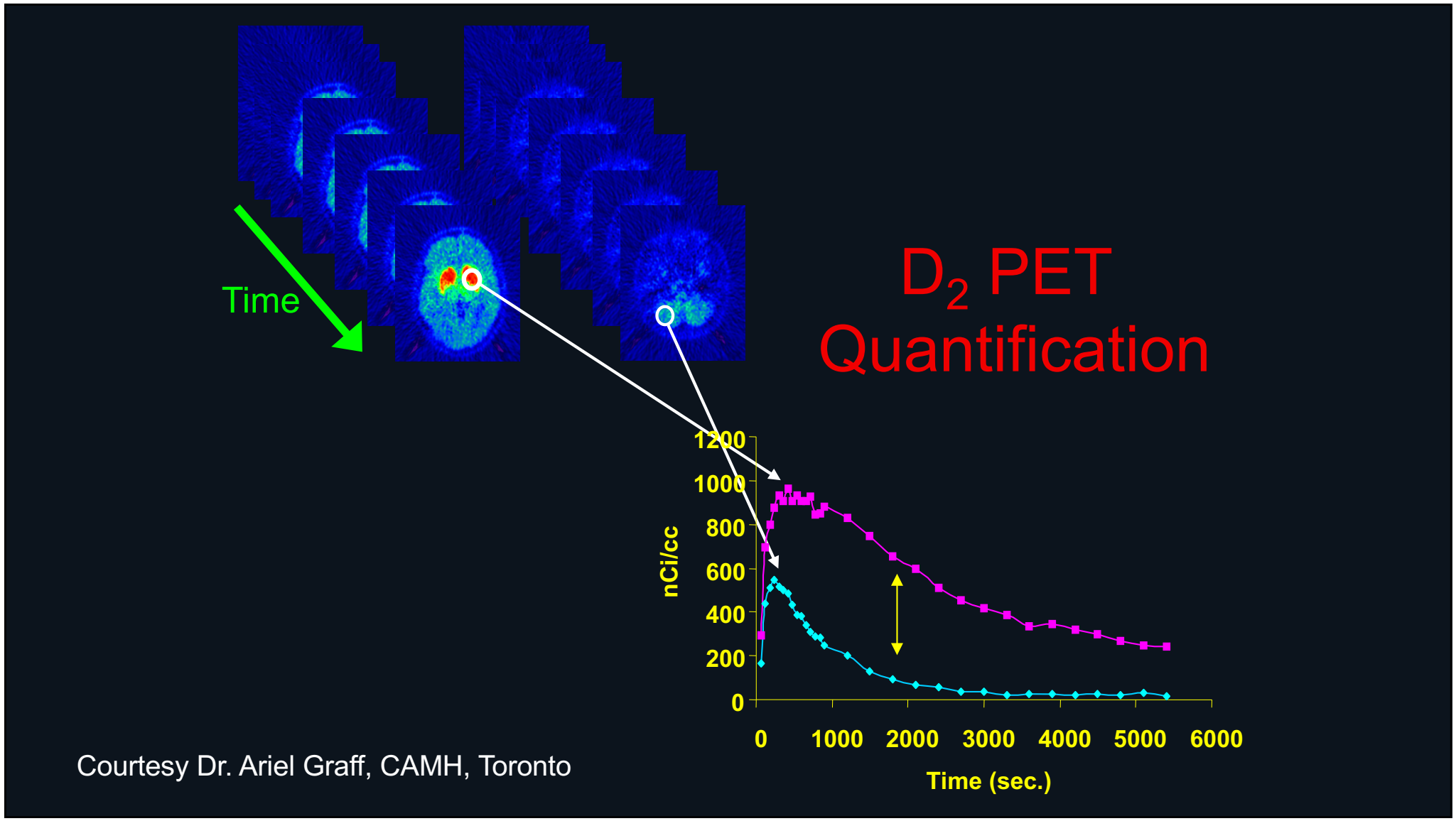


Dorsal ACC:
Tibbo et al, 2013

Head of caudate:
de la Fuente et al, 2011
de la Fuente et al, 2013
Plitman et al, 2016

Hippocampus:
Kraguljac et al, 2013

Courtesy Dr. Lawrence Kegeles, Columbia University


Time
D2 PET
Quantification
1200
1000
800
600
400
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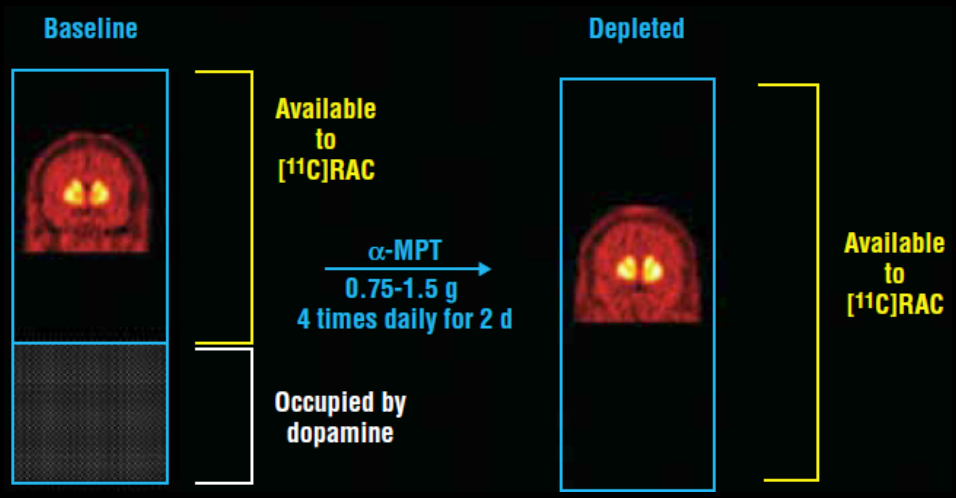
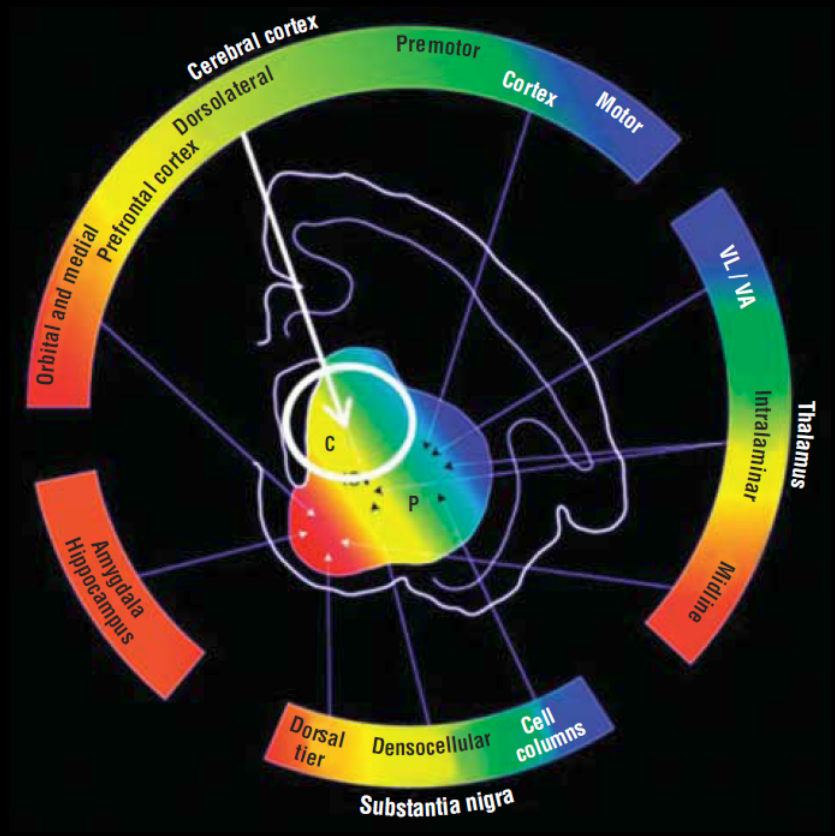
0
nCi/cc
0
1000
2000
3000
4000
5000
6000
Time (sec.)
Courtesy Dr. Ariel Graff, CAMH, Toronto





Abi-Dargham A, et al. *Proc Natl Acad Sci U S A*. 2000;97(14):8104-9.
Mawlawi O, et al. *J Cereb Blood Flow Metab*. 2001;21(9):1034-57.
Kegeles LS, et al. *Arch Gen Psychiatry*. 2010;67(3):231-9.

Neuropsychopharmacology (2011) 36, 1781–1791

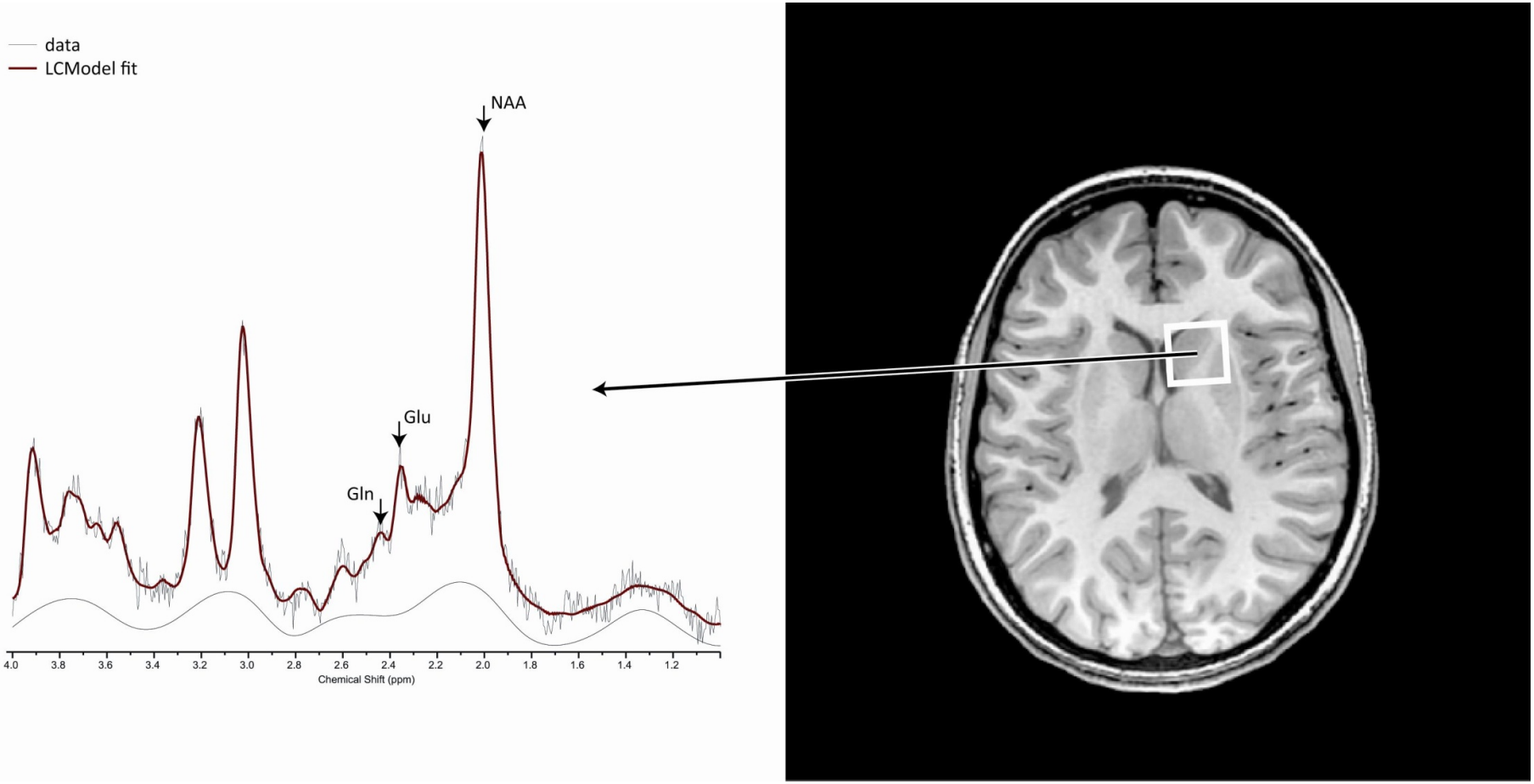
www.neuropsychopharmacology.org

Higher Levels of Glutamate in the Associative-Striatum of Subjects with Prodromal Symptoms of Schizophrenia and Patients with First-Episode Psychosis

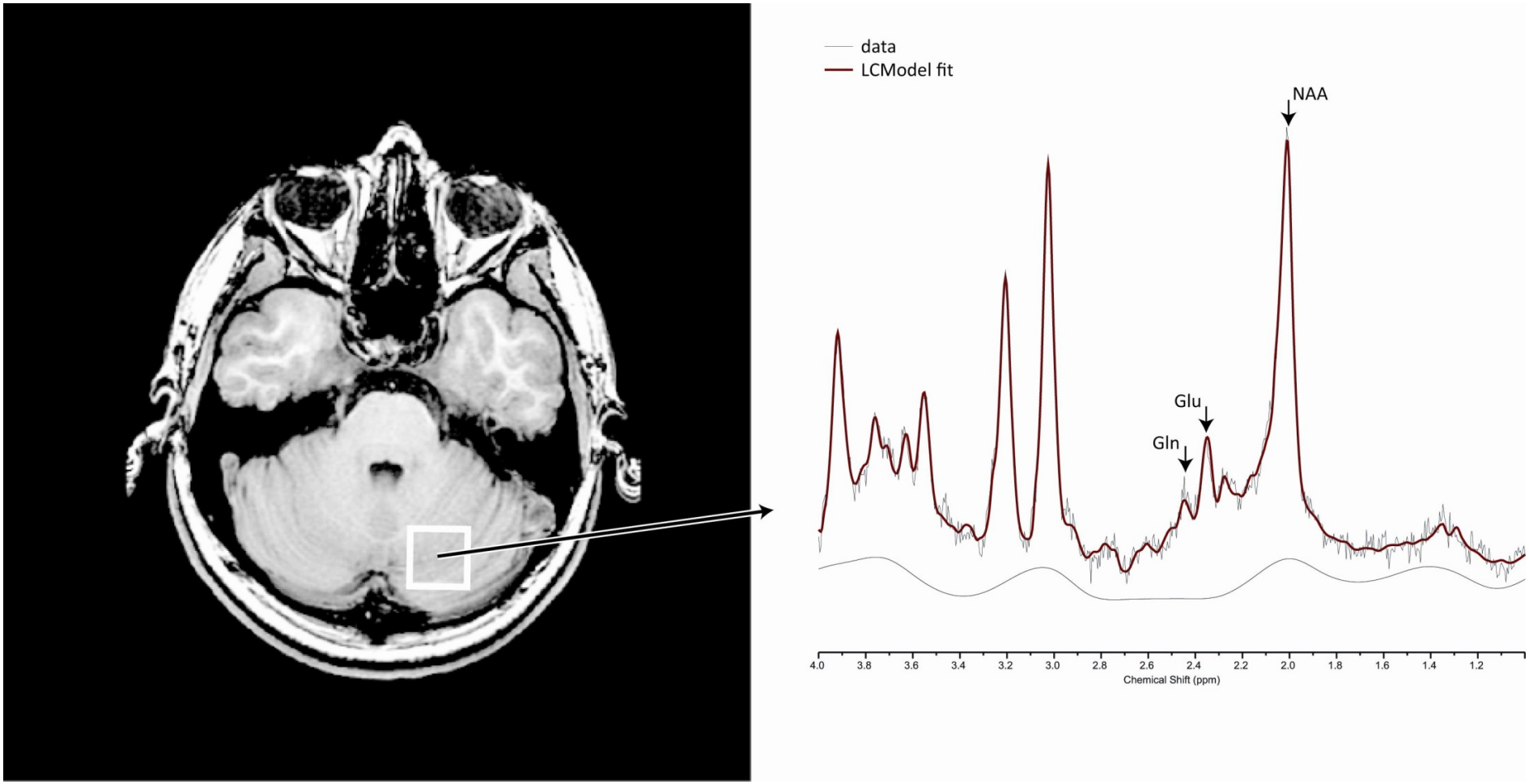
Camilo de la Fuente-Sandoval[1,2], Pablo León-Ortiz[2], Rafael Favila[3], Sylvana Stephano[2], David Mamo[4], Jesús Ramírez-Bermúdez[2] and Ariel Graff-Guerrero*[,4]

[1]Experimental Psychiatry Laboratory, Instituto Nacional de Neurología y Neurocirugía, Mexico City, Mexico; [2]Neuropsychiatry Department, Instituto Nacional de Neurología y Neurocirugía, Mexico City, Mexico; [3]MR Advanced Applications, GE Healthcare, Mexico City, Mexico; [4]Multimodal Neuroimaging Schizophrenia Group, PET Centre, Centre for Addiction and Mental Health & Department of Psychiatry, University of Toronto, Toronto, ON, Canada

de la Fuente-Sandoval C, et al. *Neuropyschopharmacology.* 2011;36(9):1781-1791.



de la Fuente-Sandoval C, et al. *Neuropyschopharmacology*. 2011;36(9):1781-1791.



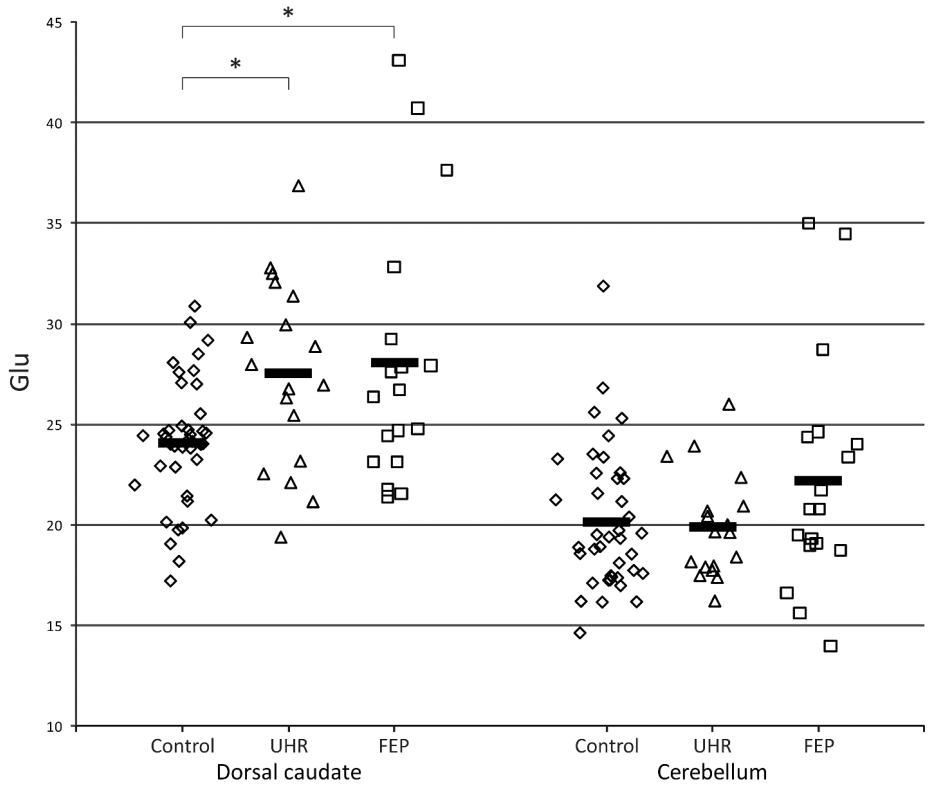
de la Fuente-Sandoval C, et al. *Neuropyschopharmacology*. 2011;36(9):1781-1791.

Demographics of the Sample

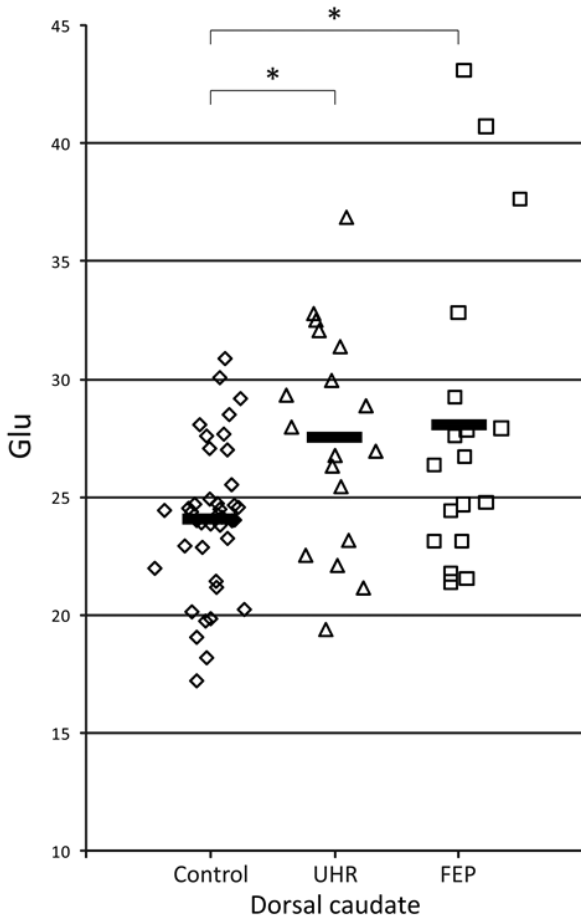
	Control Subjects	UHR	FEP	Statistic
Age (±SD) years	21.83 ± 4.47	19.56 ± 3.46	23.44 ± 4.93 [b]	F[2,73] = 3.60, *p* = .03
Gender (male/female)	28/12	14/4	10/8	Fisher's = 2.09 NS
Education (±SD)years	14.47 ± 3.32	10.67 ± 2.61 [a]	12.11 ± 3.51 [a]	F[2,73] = 9.60, *p* < .001
Handedness (right/left)	40/0	18/0	18/0	NS
Length of illness (±SD) weeks	NA	16.56 ± 12.28	18.72 ± 18.14	NS
Tobacco (Ever Used)	9/40	1/18	6/18	Fisher's = 4.32 NS
Cannabis (Ever Used)	0/40	1/18	2/18	Fisher's = 6.12 *p* = .03
Use of antipsychotic treatment	0/18	0/18	0/18	NS
Use of SSRIs	0/18	4/18	0/18	Fisher's = 9.26 *p* =.005

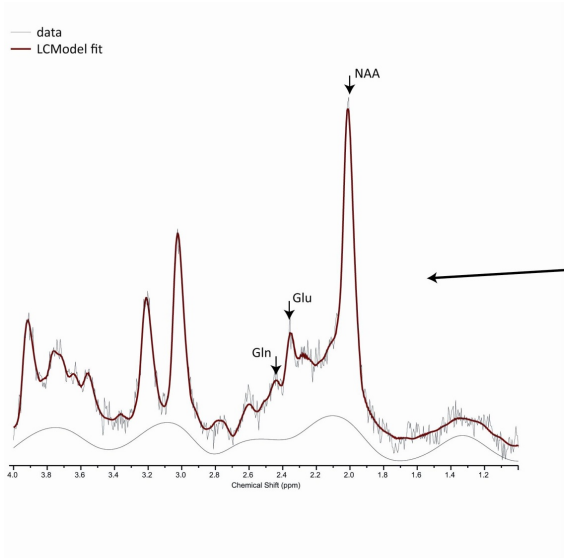
de la Fuente-Sandoval C, et al. *Neuropyschopharmacology*. 2011;36(9):1781-1791.

Results

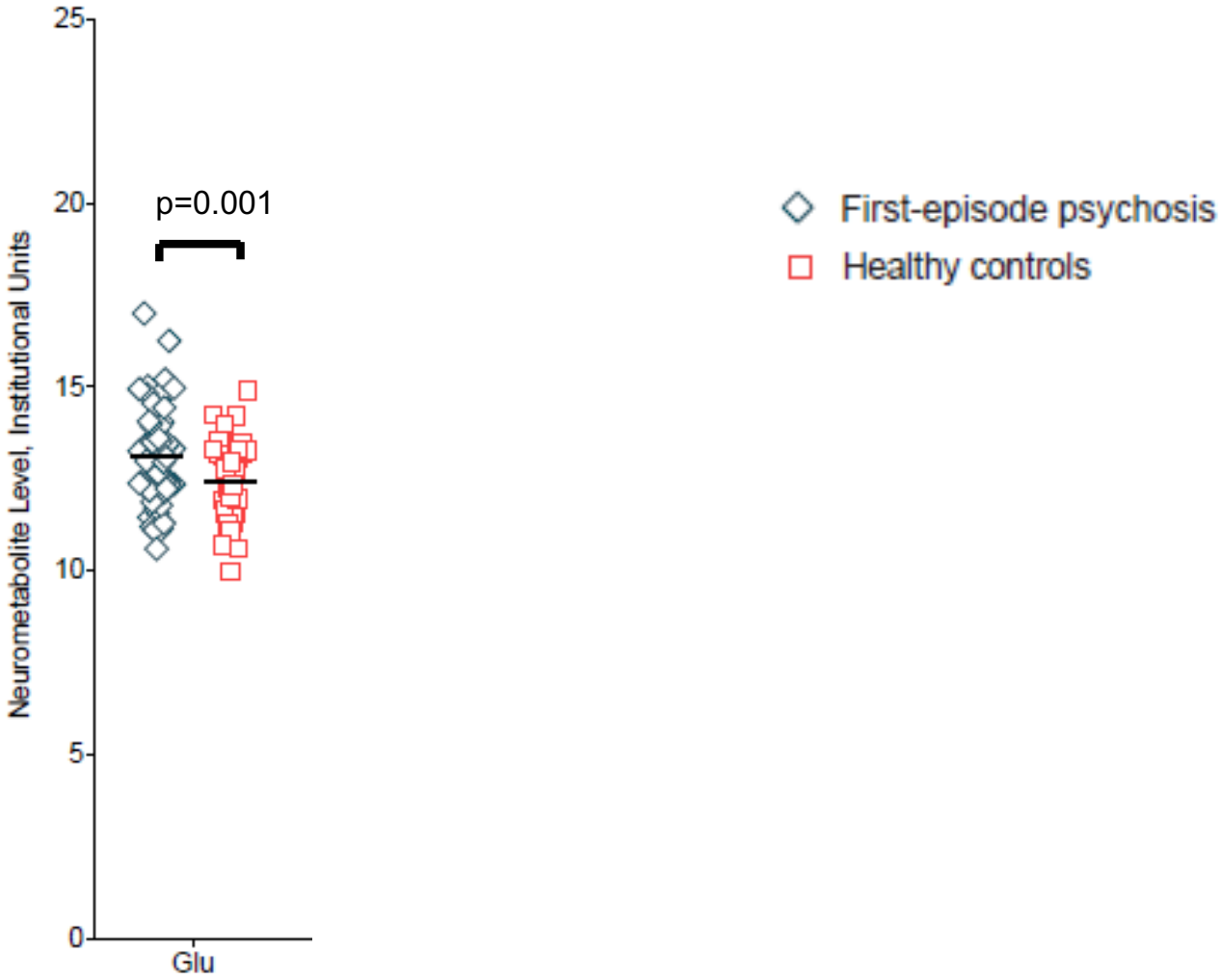


de la Fuente-Sandoval C, et al. *Neuropyschopharmacology*. 2011;36(9):1781-1791.

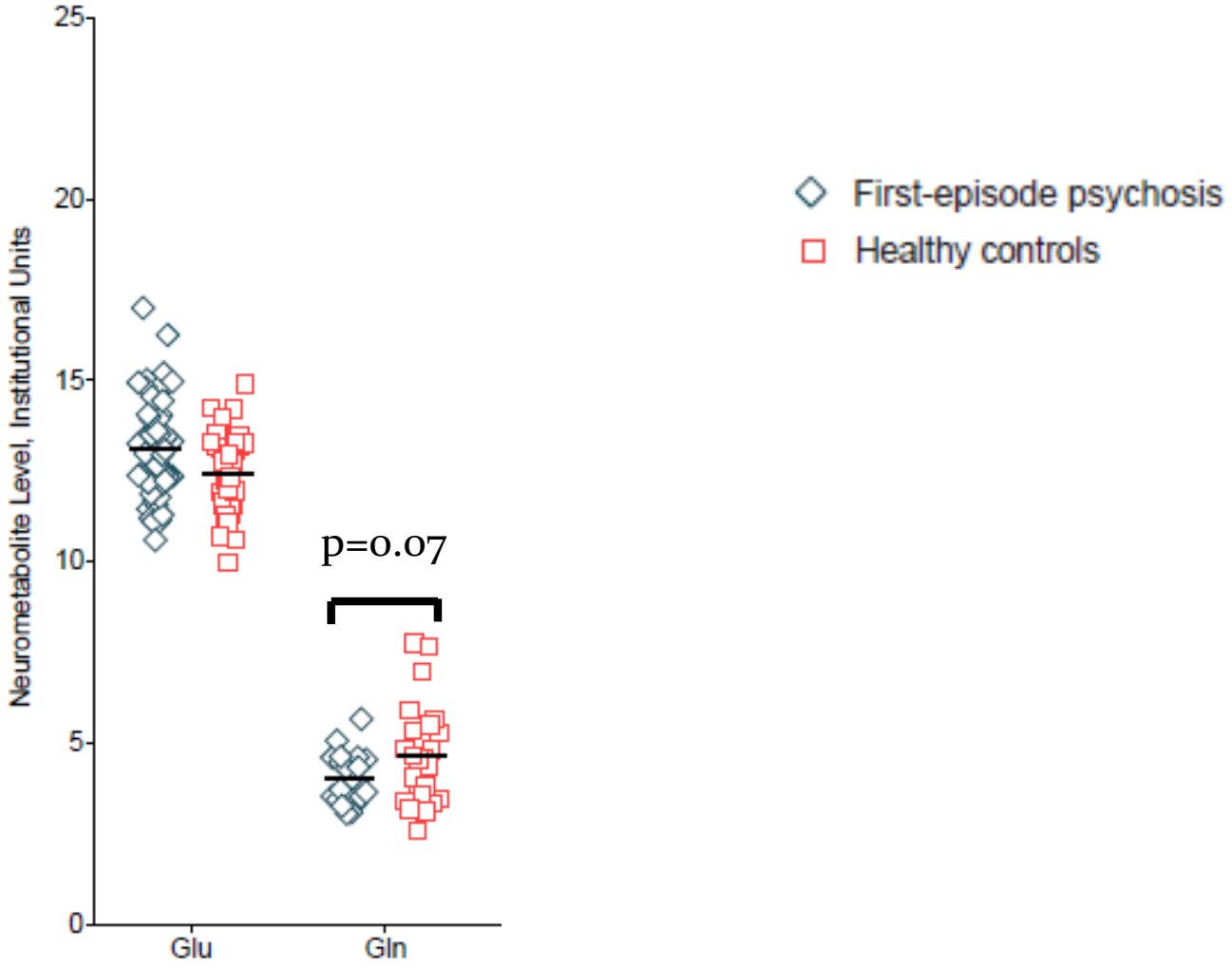




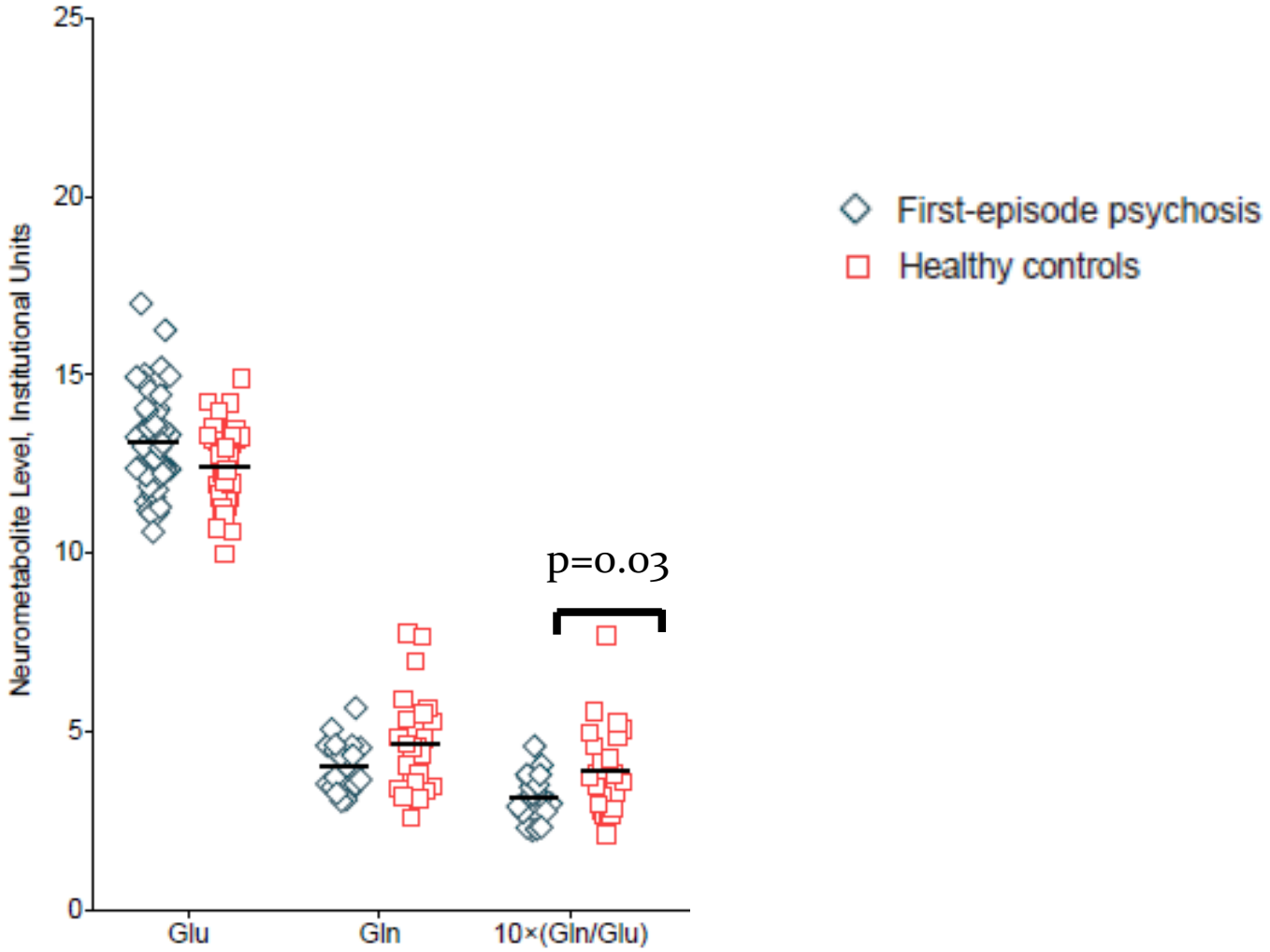
de la Fuente-Sandoval C, et al. *Neuropyschopharmacology*. 2011;36(9):1781-1791.



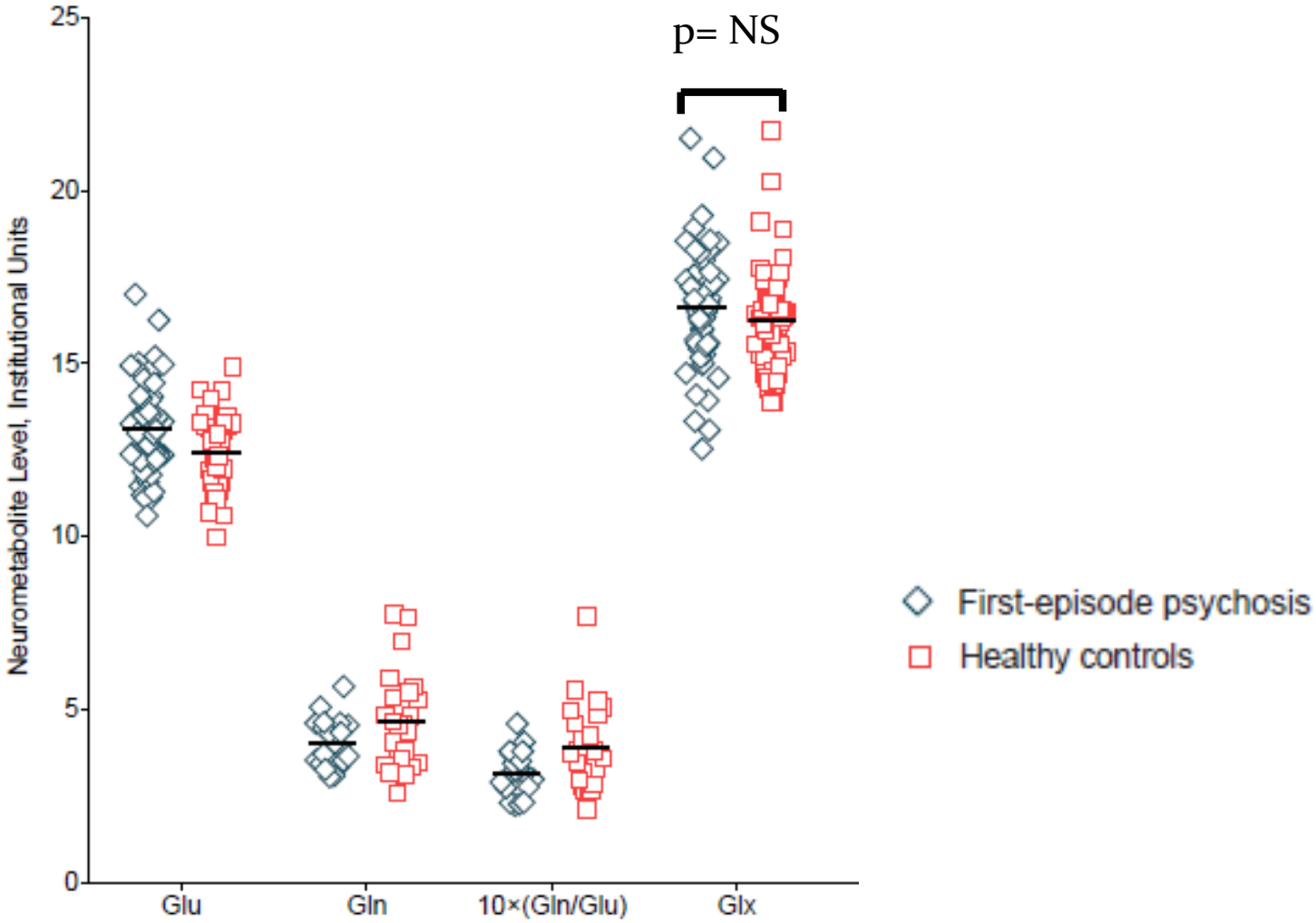
Plitman E, et al. *Schizophr Bull*. 2016;42(2):415-24.



Plitman E, et al. *Schizophr Bull*. 2016;42(2):415-24.



Plitman E, et al. *Schizophr Bull*. 2016;42(2):415-24.



Plitman E, et al. *Schizophr Bull*. 2016;42(2):415-24.

Treatment Effect on Glutamate

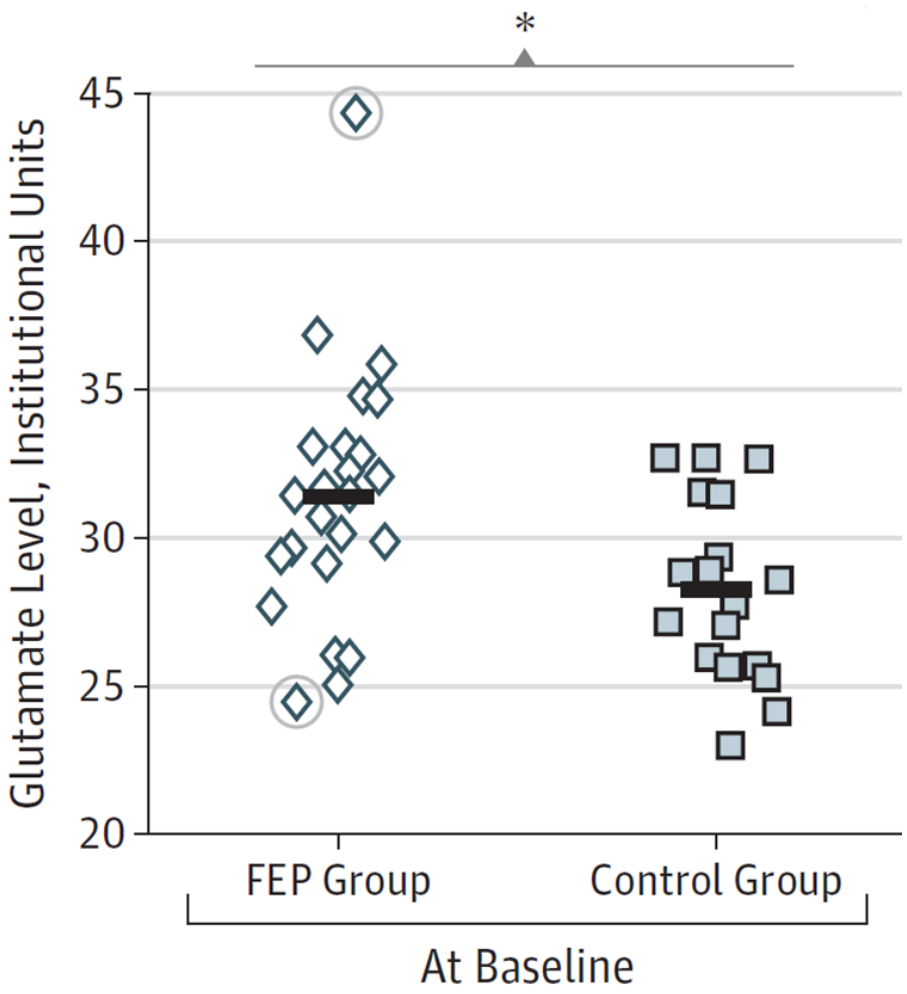
- Compare glutamate levels, using ^{1}H-MRS, in:
  - 24 First-Episode Psychosis patients
    Antipsychotic-naïve
  - 18 age-and-sex matched controls
  - Two ^{1}H-MRS studies
    - FEP – before and after treatment with risperidone (Responders)
    - Control – baseline and at 4 weeks

de la Fuente-Sandoval et al. *JAMA Psychiatry*. 2013;70(10):1057-1066.

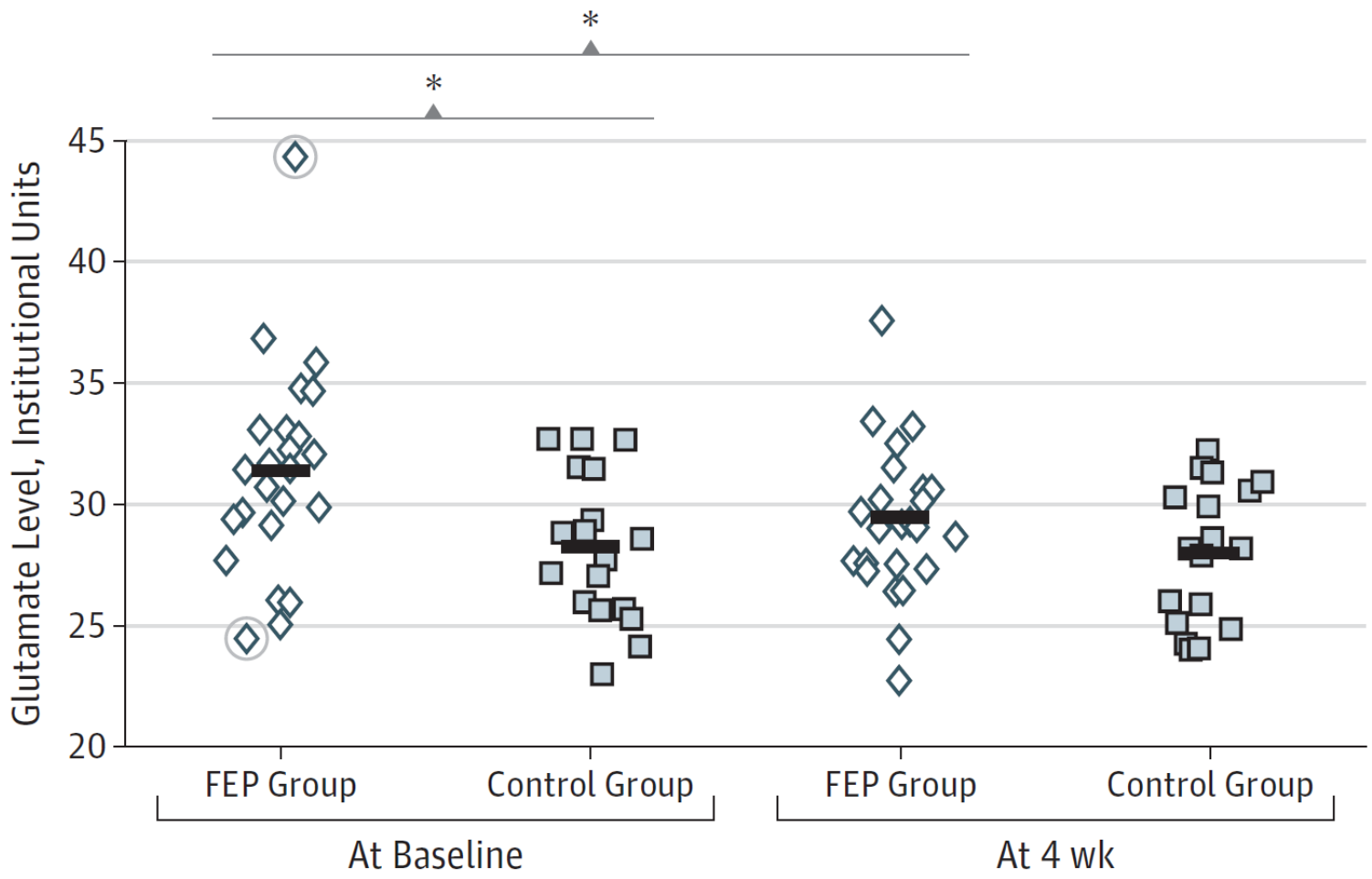
Results

	FEP	Healthy Controls
Age (±SD) years	26.58 ± 8.49 (range 18-47)	24.56 ± 5.07 (range 18-35)
Education (±SD) years	10.96 ± 3.44	15.61 ± 2.99 *
Gender (male/female)	13/11	8/10
Handedness (right/left)	24/0	18/0
Tobacco (Ever Used)	8/24	2/18
Cannabis (Ever Used)	3/24	0/18
Duration of untreated psychosis (±SD) weeks	20.33 ± 25.84	N/A
PANSS Positive Symptoms	23.33 ± 4.99	N/A
PANSS Negative Symptoms	24.08 ± 6.03	N/A
PANSS General Symptoms	47.92 ± 8.75	N/A

de la Fuente-Sandoval et al. *JAMA Psychiatry*. 2013;70(10):1057-1066.

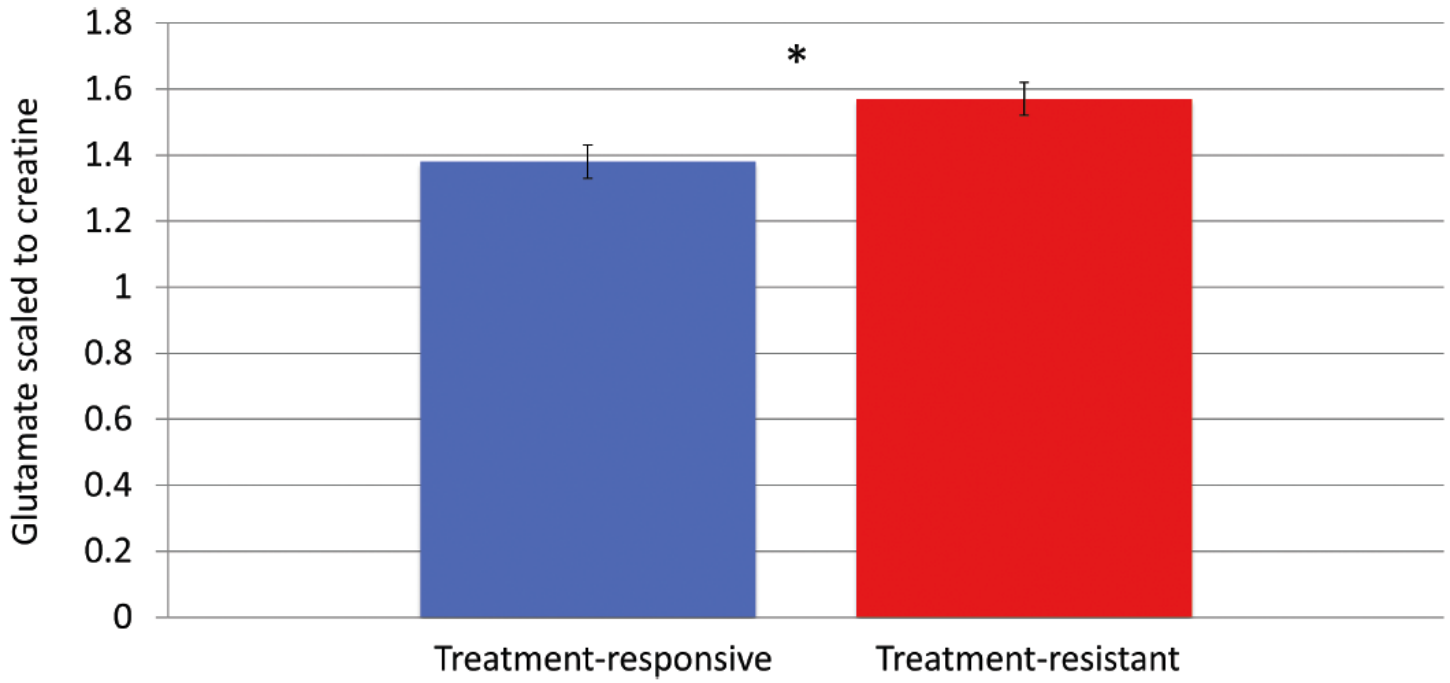


de la Fuente-Sandoval et al. *JAMA Psychiatry*. 2013;70(10):1057-1066.



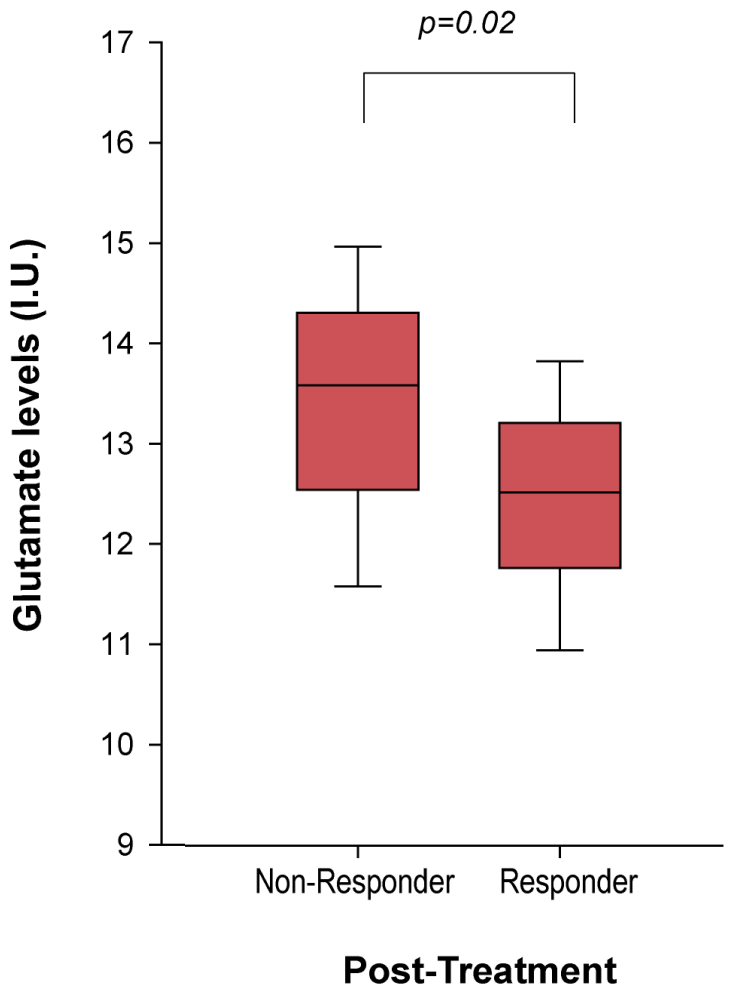
de la Fuente-Sandoval et al. *JAMA Psychiatry*. 2013;70(10):1057-1066.

Anterior Cingulate ^{1}H-MRS

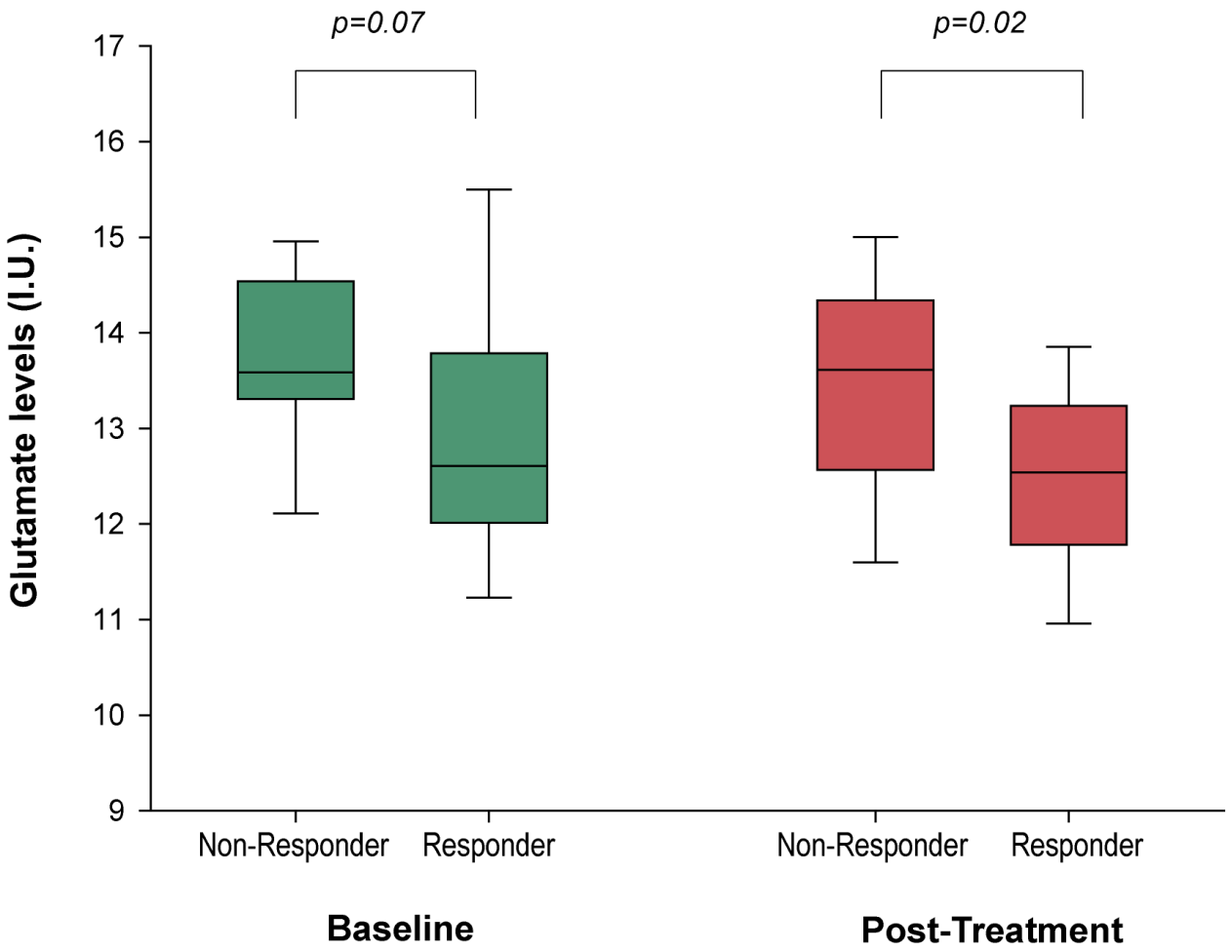


** = Resistant patients had significantly higher levels, t(35) = 2.34, P = .025, 2-tailed. Error bars represent SE of the mean.

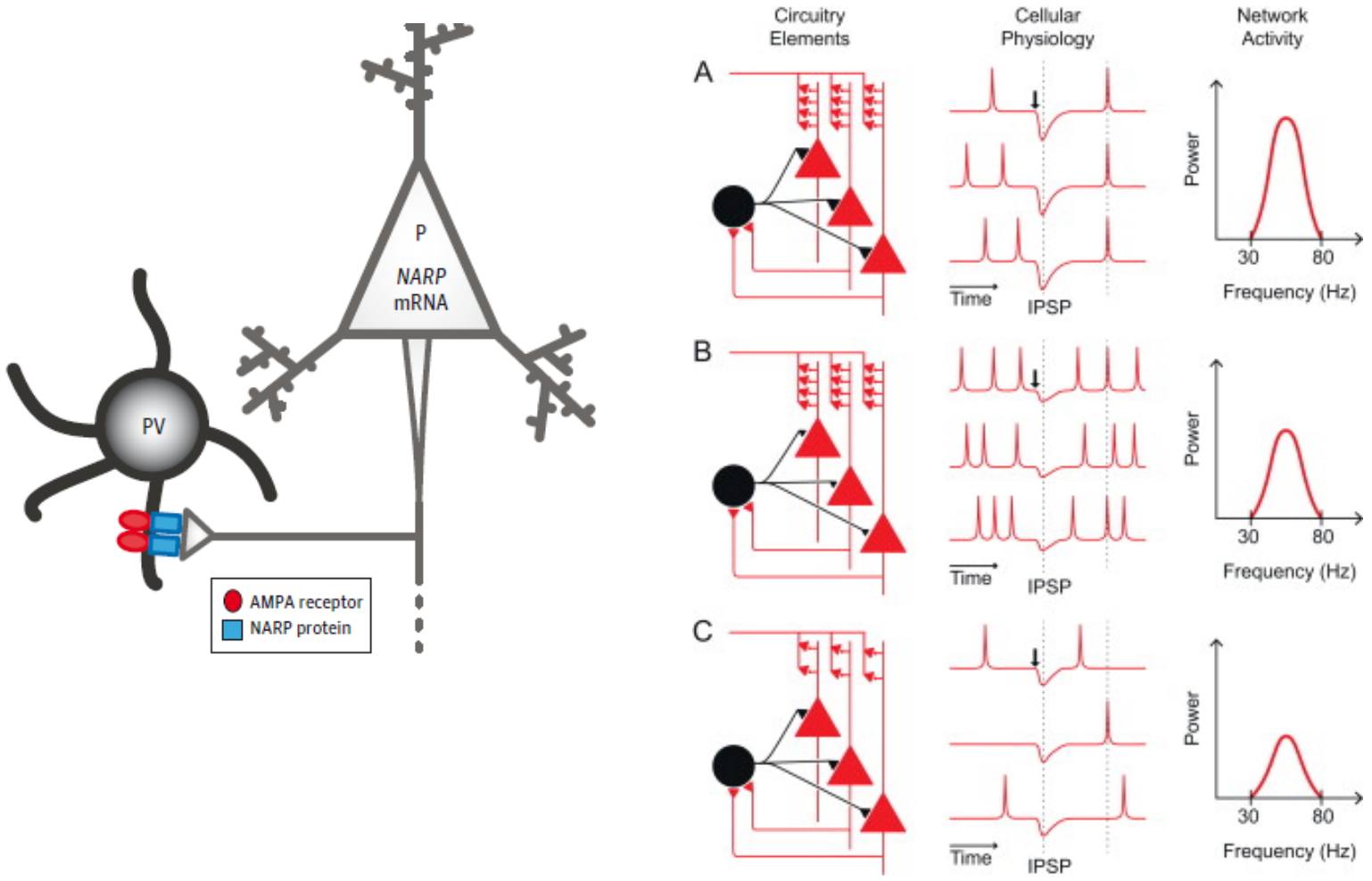
Mouchlianitis E, et al. *Schizophr Bull*. 2016;42(3):744-52.



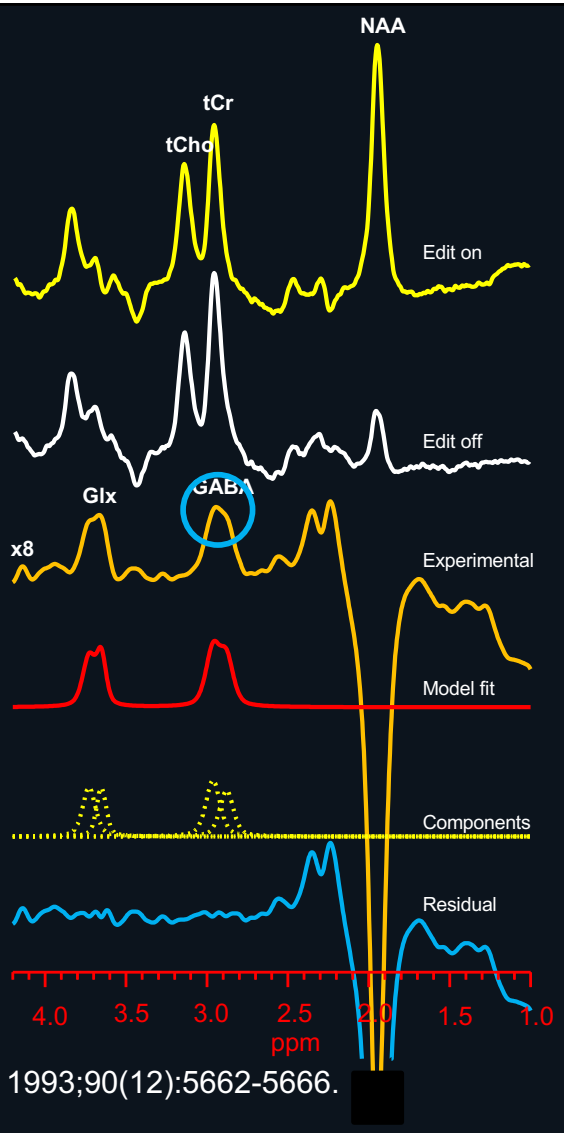
Presented at the International Congress on Schizophrenia Research, San Diego, 2017.



Presented at the International Congress on Schizophrenia Research, San Diego, 2017.

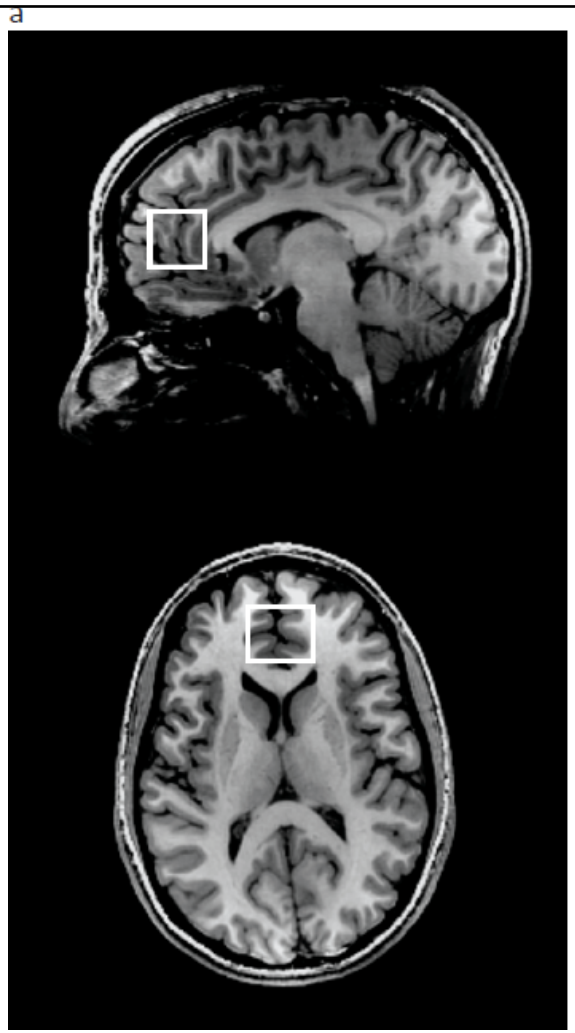


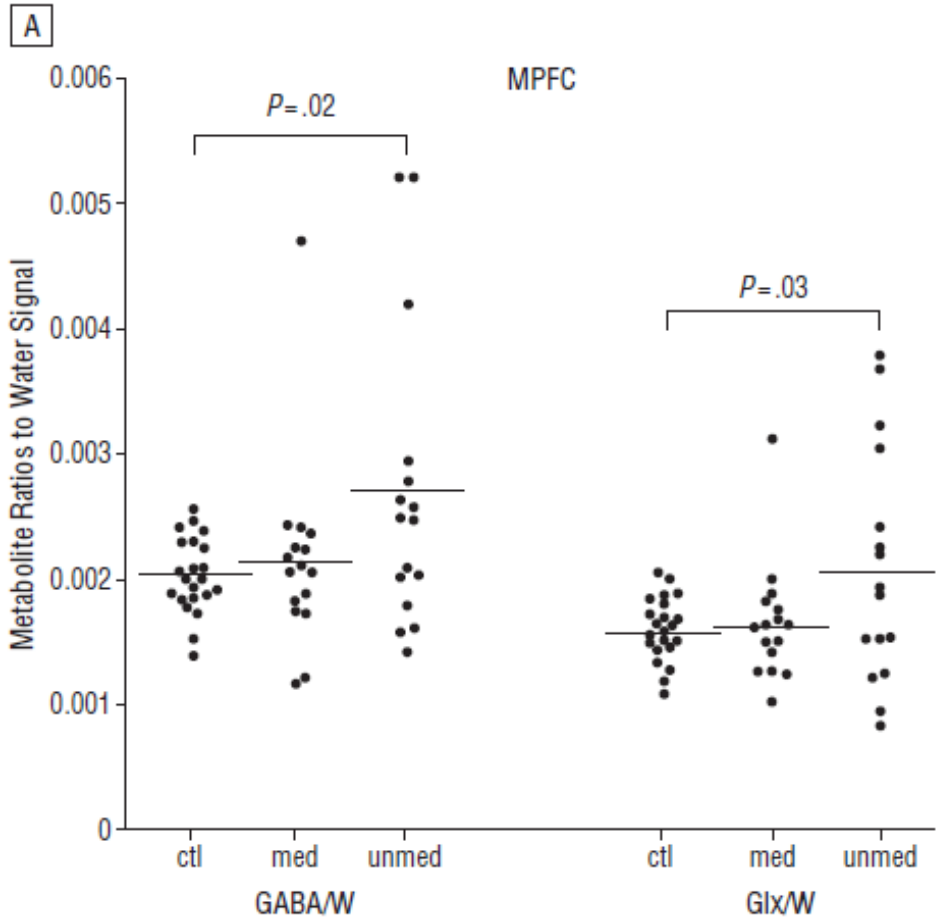
Gonzalez-Burgos G, et al. *Biol Psychiatry*. 2015;77(12):1031-1040.
Kimoto S, et al. *JAMA Psychiatry*. 2015;72(8):747-756.



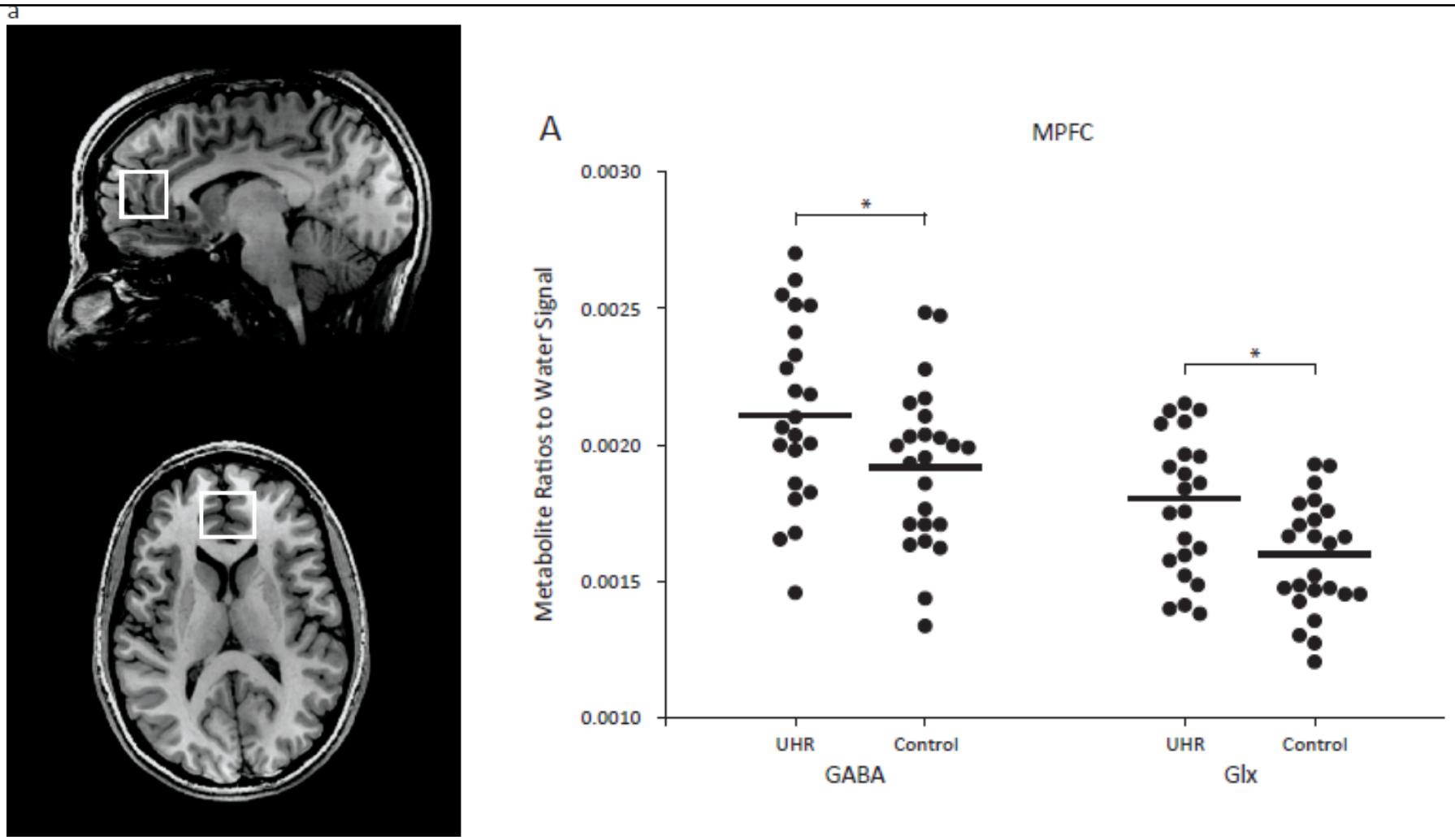
Rothman DL, et al. *Proc Natl Acad Sci U S A*. 1993;90(12):5662-5666.

Author (year)	Tesla	Studied group	Medication status	Brain Region	GABA Results
Goto et al, 2009	3	Schizophrenia	antipsychotic treated	basal ganglia	↓
Yoon et al, 2010	3	Schizophrenia	antipsychotic treated	occipital cortex	↓
Tayoshi et al, 2010	3	Schizophrenia	antipsychotic treated	basal ganglia	↓
Ongur et al, 2010	4	Schizophrenia	antipsychotic / anticonvulsants treated	anterior cingulate cortex/parieto-occipital cortex	⇧/ No differences
Rowland et al, 2012	3	Schizophrenia	antipsychotic treated	medial prefrontal cortex	No differences
Kegeles et al, 2012	3	First-episode schizophrenia	unmedicated	medial prefrontal cortex	⇧
Rowland et al 2016	3	Schizophrenia	medicated	medial prefrontal cortex	↓

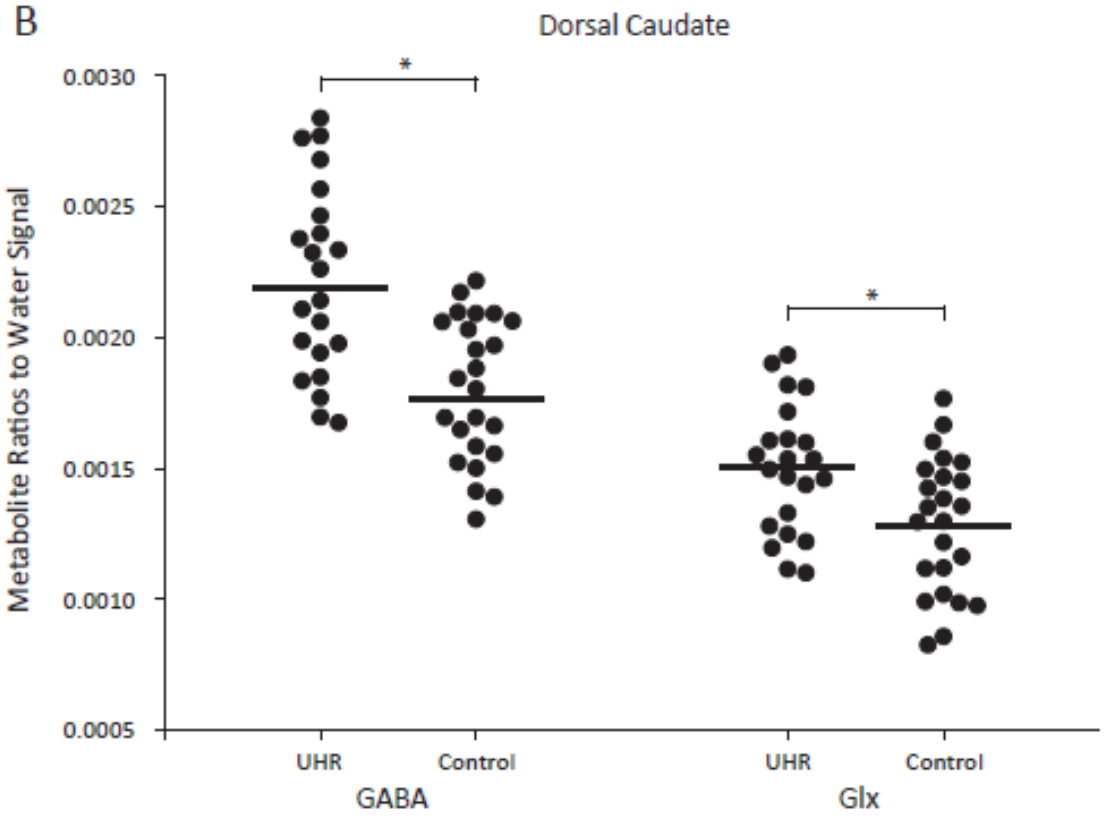


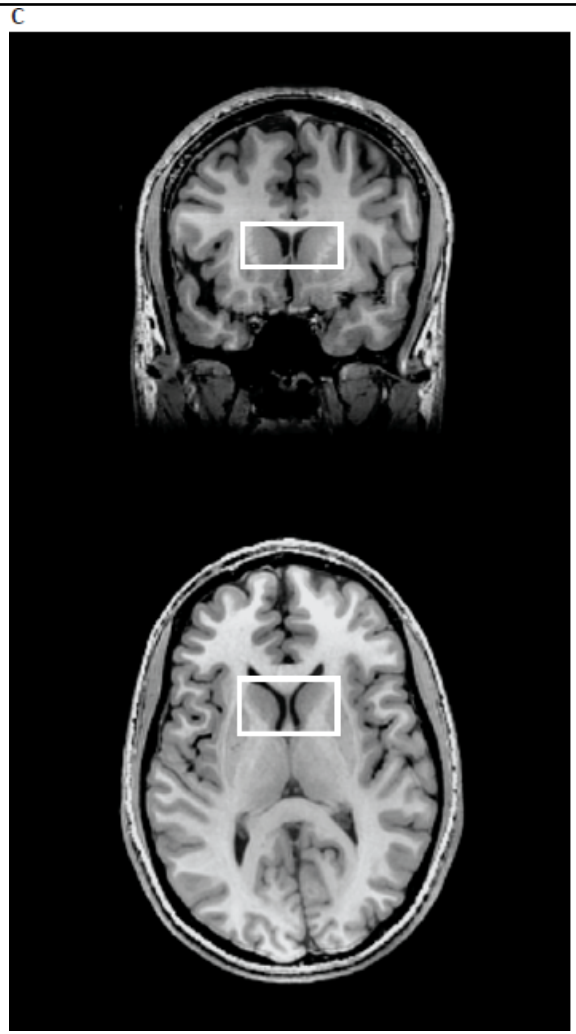


Kegeles LS, et al. *Arch Gen Psychiatry*. 2012;69(5):449-59.



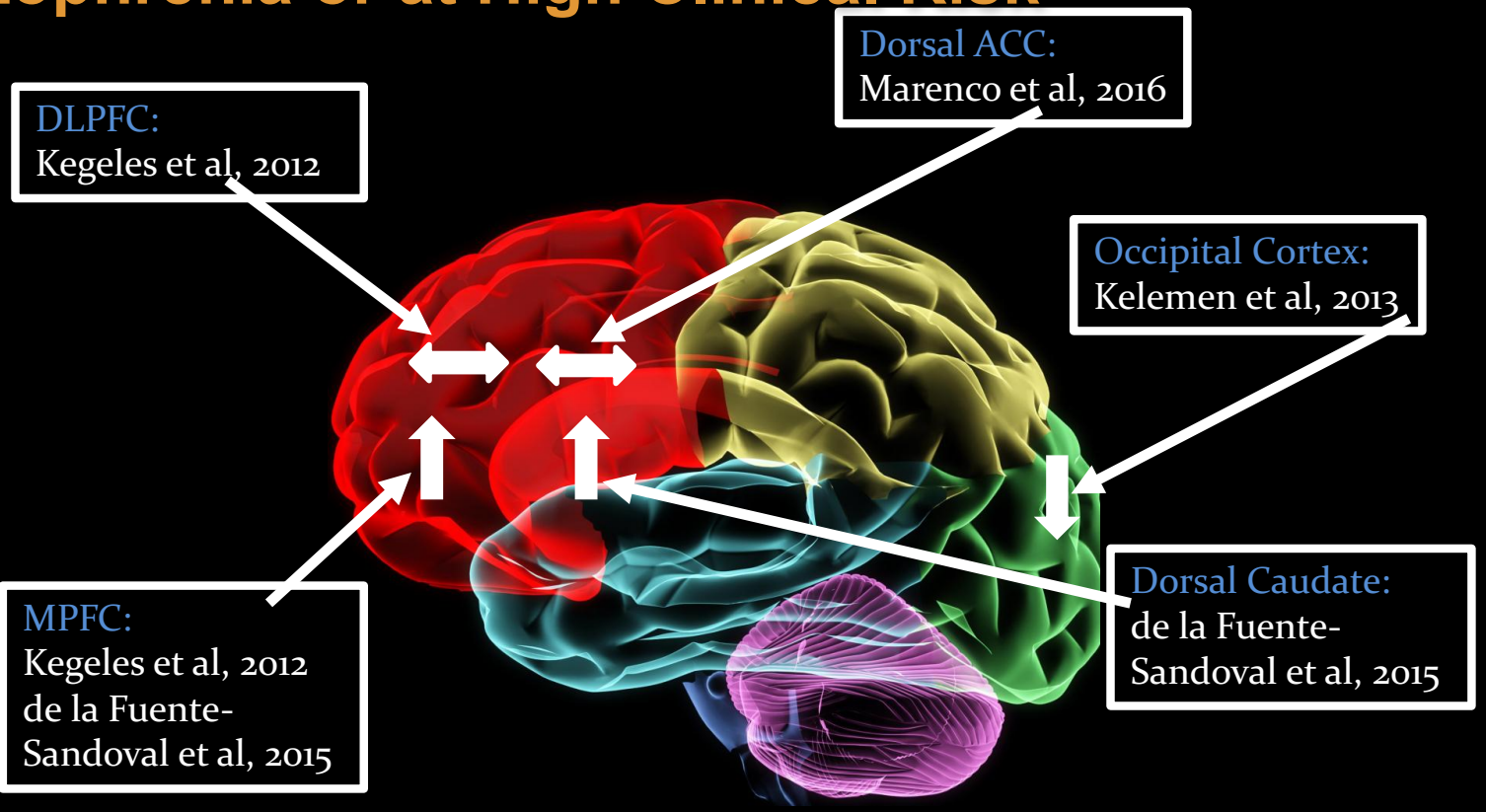
de la Fuente-Sandoval C, et al .*Int J Neuropsychopharmacol*. 2015;19(3):pyv105.





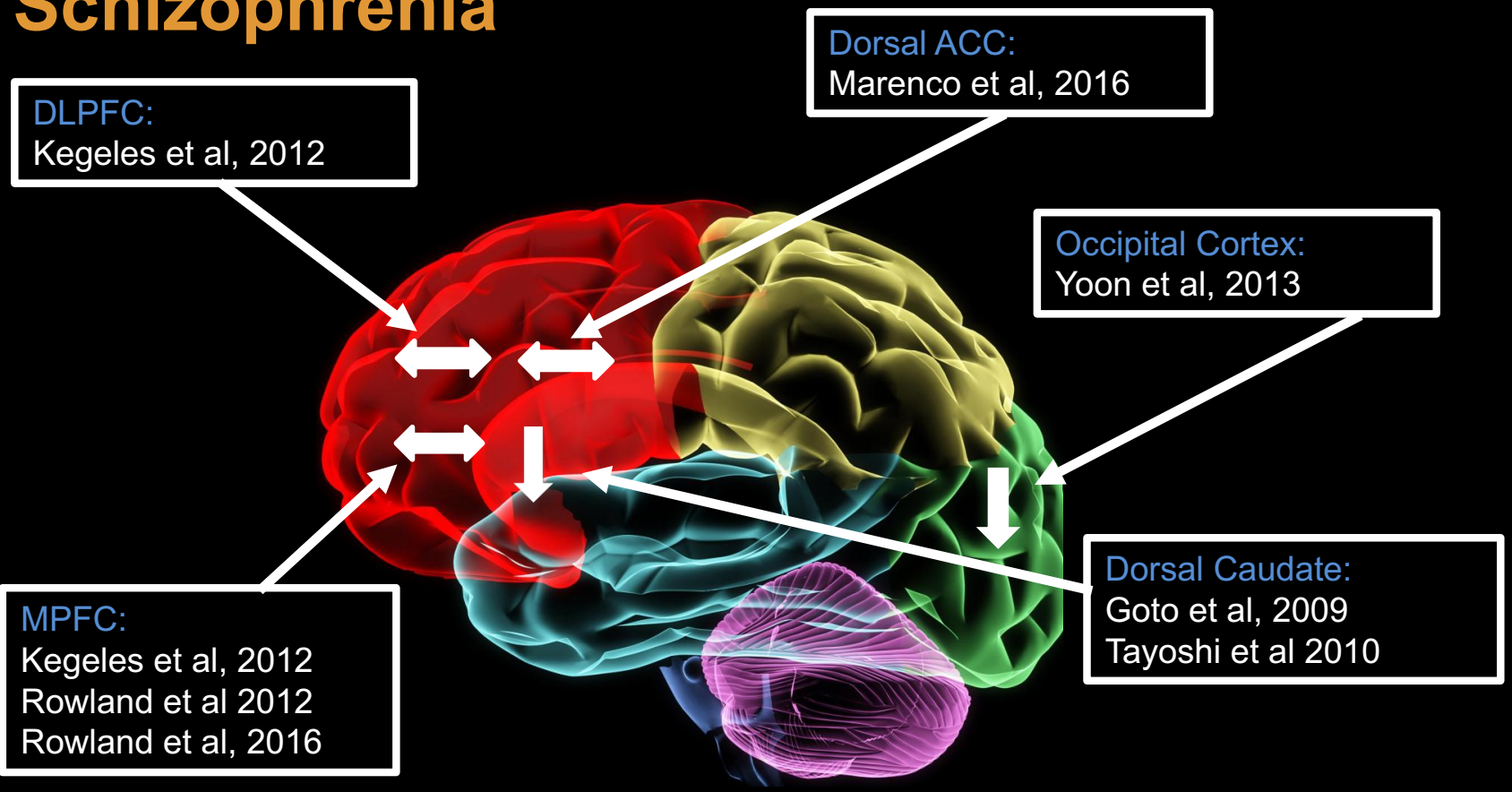
de la Fuente-Sandoval C, et al .*Int J Neuropsychopharmacol*. 2015;19(3):pyv105.

GABA Abnormalities in Unmedicated Patients with Schizophrenia or at High Clinical Risk

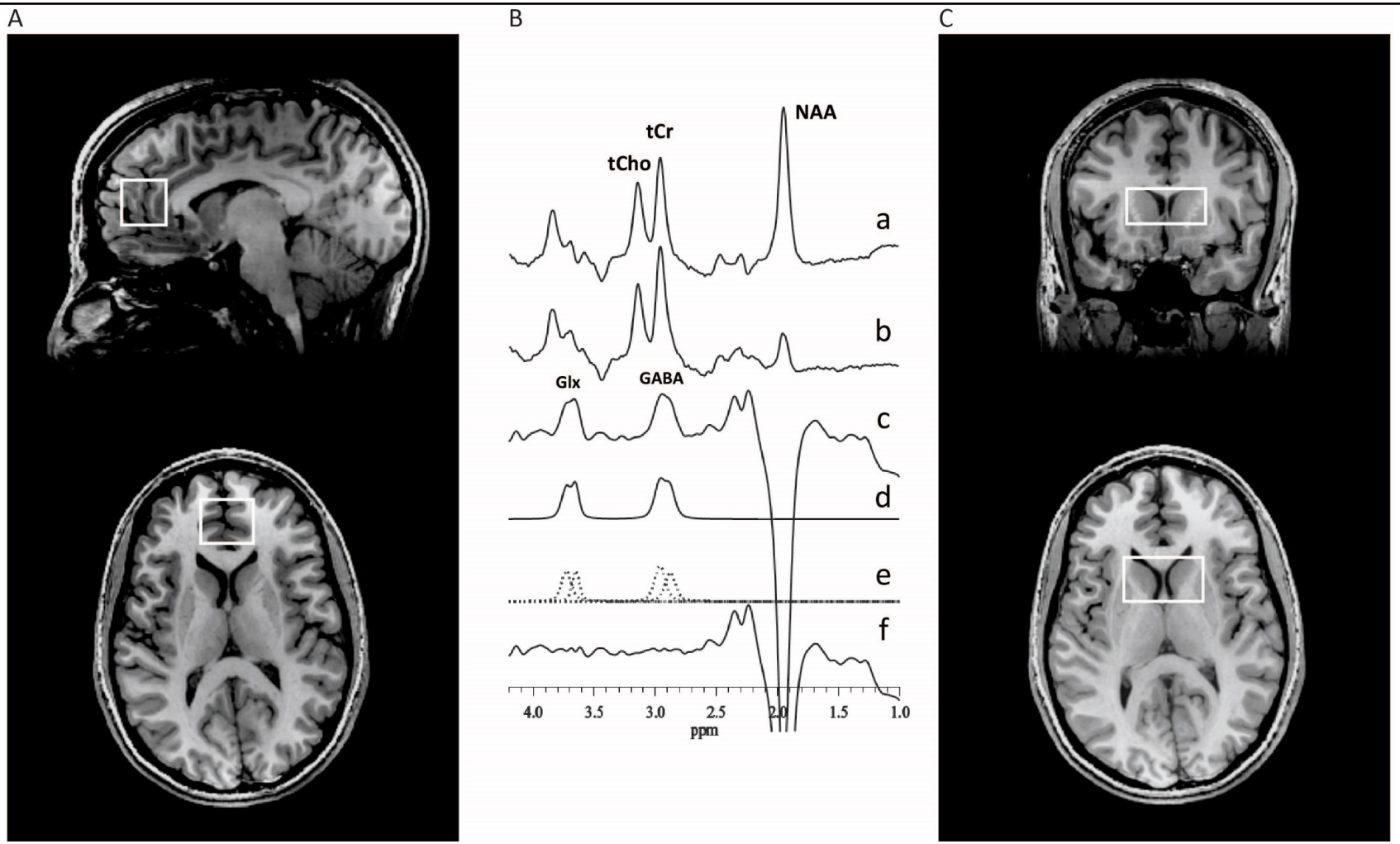


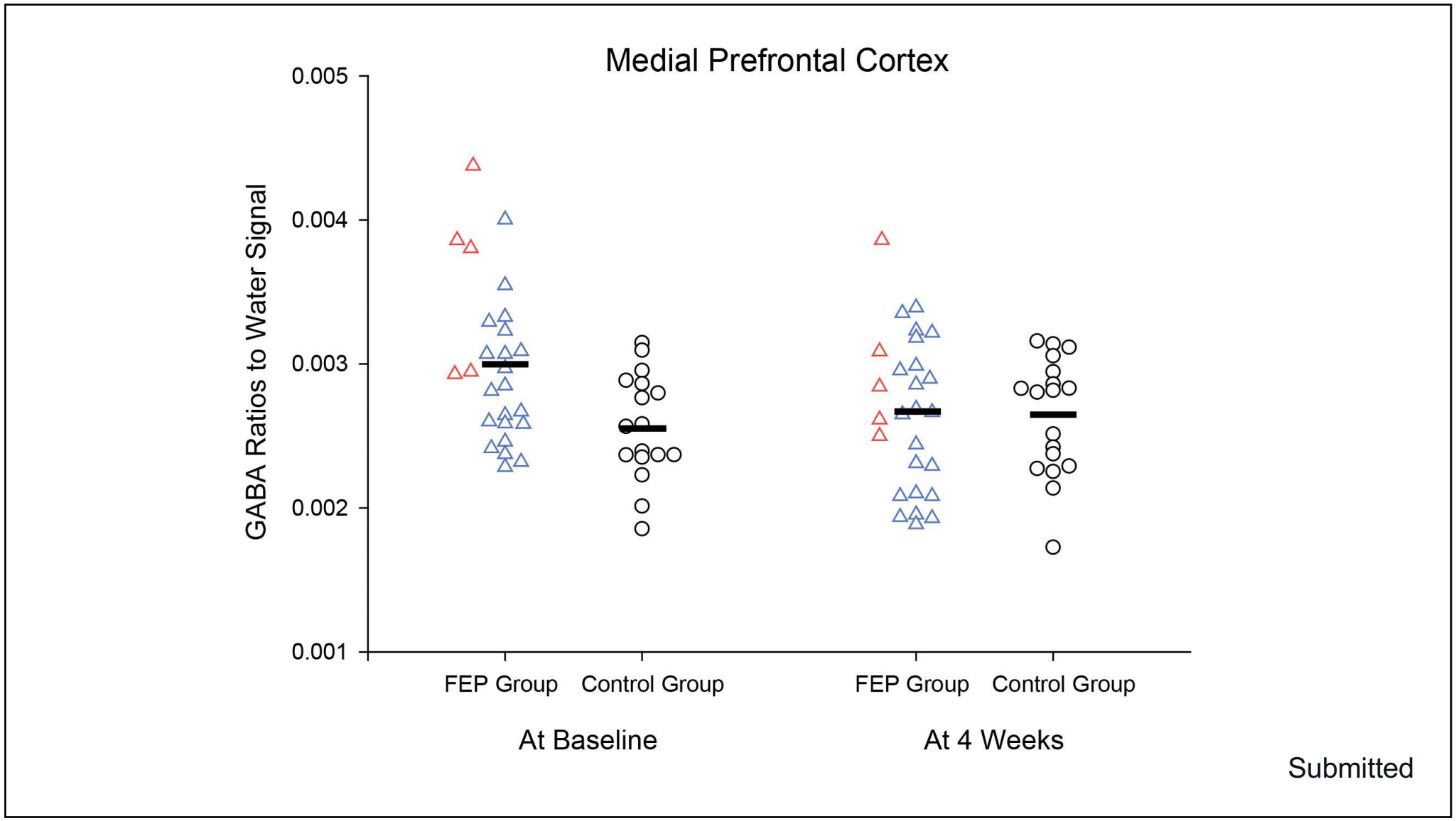
de la Fuente-Sandoval. *Am J Psychiatry.* 2016;173(7):734.

GABA Abnormalities in MEDICATED Patients with Schizophrenia

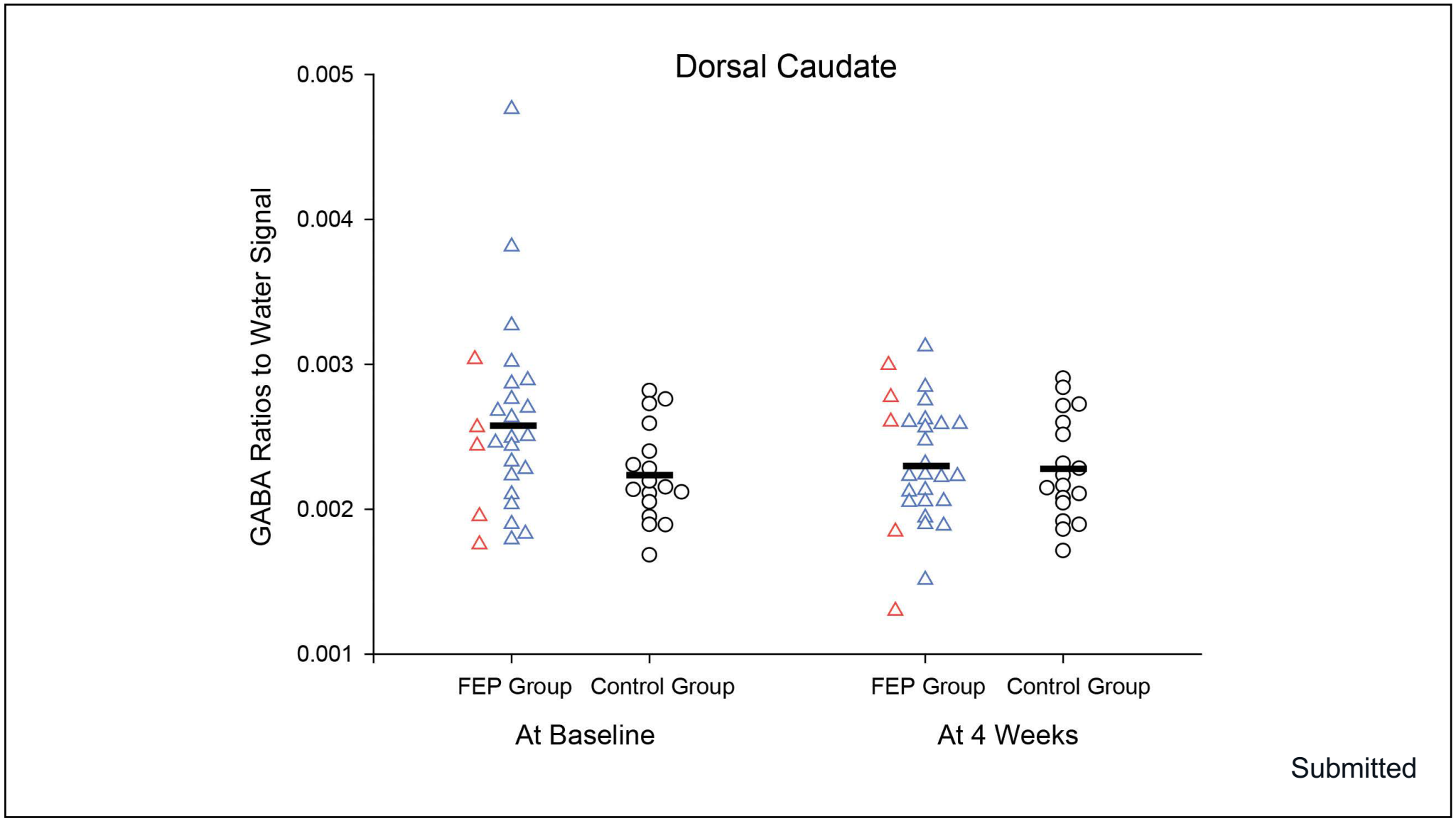


de la Fuente-Sandoval. *Am J Psychiatry*. 2016;173(7):734.


A
B
C
NAA
tCr
tCho
a
b
Glx
GABA
c
d
e
f
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm

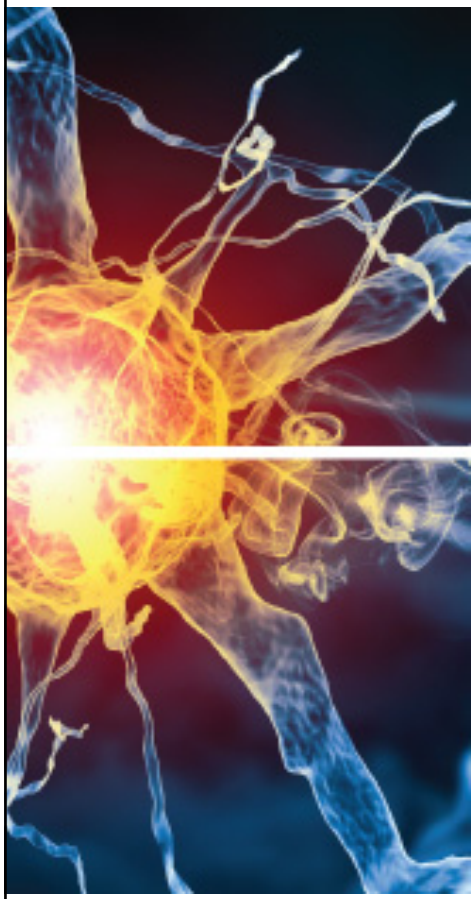

Medial Prefrontal Cortex
GABA Ratios to Water Signal
0.005
0.004
0.003
0.002
0.001
FEP Group
Control Group
FEP Group
Control Group
At Baseline
At 4 Weeks

Submitted


Dorsal Caudate
GABA Ratios to Water Signal
0.005
0.004
0.003
0.002
0.001
FEP Group
Control Group
FEP Group
Control Group
At Baseline
At 4 Weeks
Submitted

Conclusions

- Higher Glutamate in the dorsal caudate of FEP and CHR
- Higher GABA in the MPFC and caudate of FEP and CHR
- Normalize with clinical response to treatment?
- Predictors of Response?
- Other potential (glutamate agents?) treatments in the FEP



Questions & Answers