Kuidas teadusuuringud on aidanud mõista depressiooni ravi

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Professor of Psychopharmacology, University of Tartu
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Current insights into antidepressant pharmacotherapy

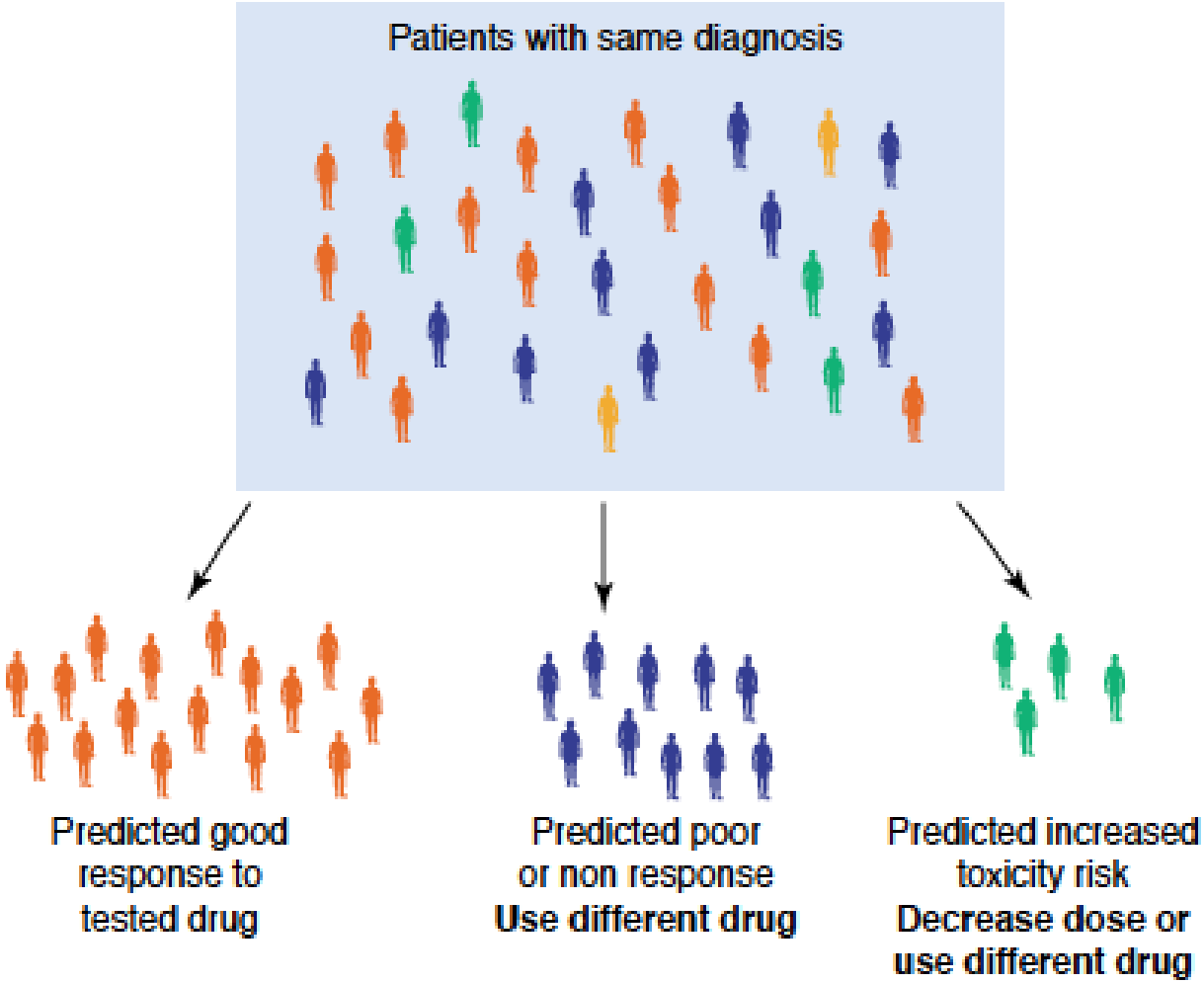
- *Pharmacological properties underlying treatment mechanisms*
- Factors underlying treatment response
  - sociodemographic
  - clinical, psychological
  - neurobiological
- Opportunities to improve treatment outcome

Antidepressant efficacy in major depression

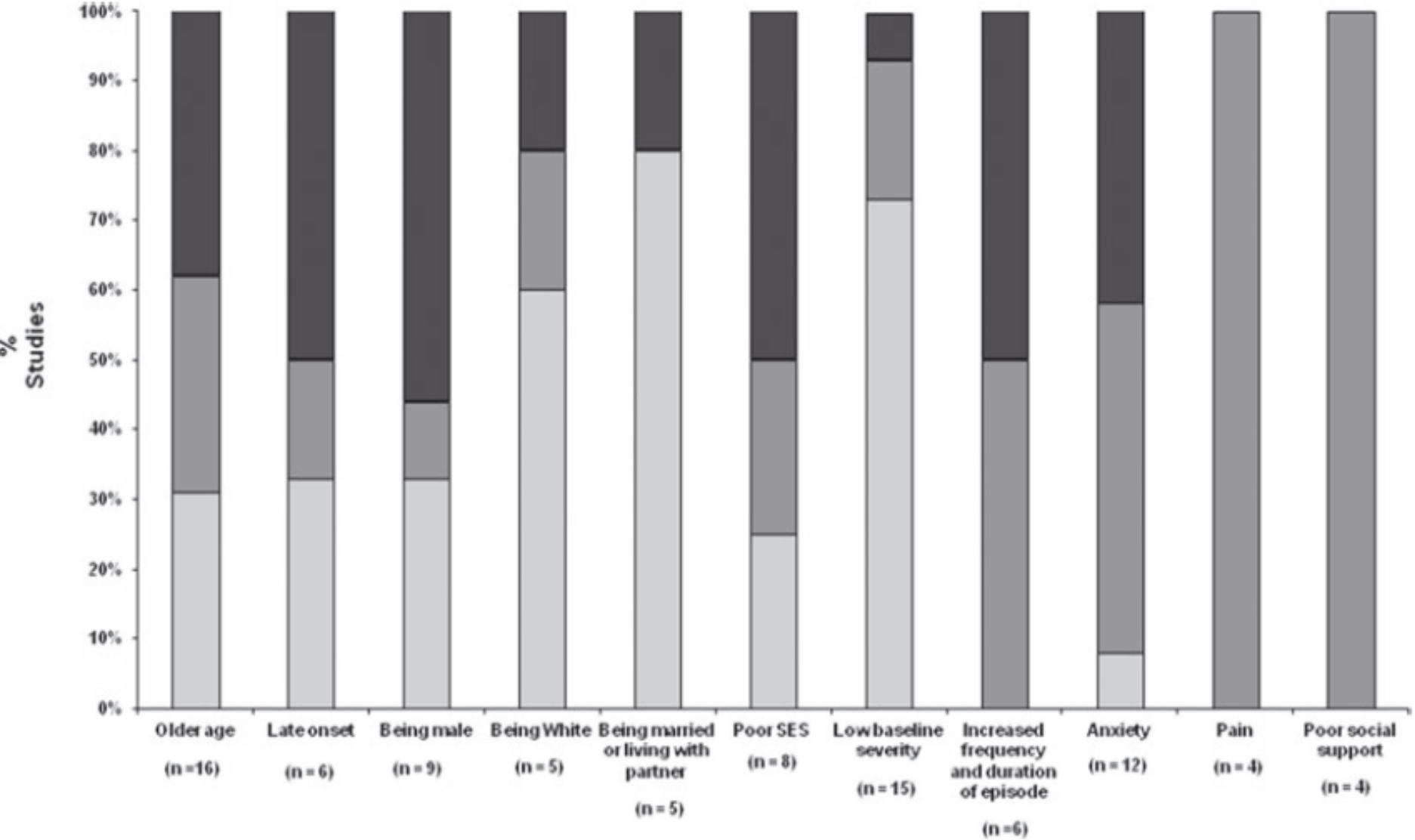
• Moderate efficacy	
– Response rate	50-60%
– Remission rate	< 50%
• No panacea	
– Across-Class difference of efficacy	< 15%

Papakostas et al 2008; Zisook et al 2006; Trivedi et al 2006

Prediction of treatment outcome in depression



Sociodemographic, clinical and psychological factors



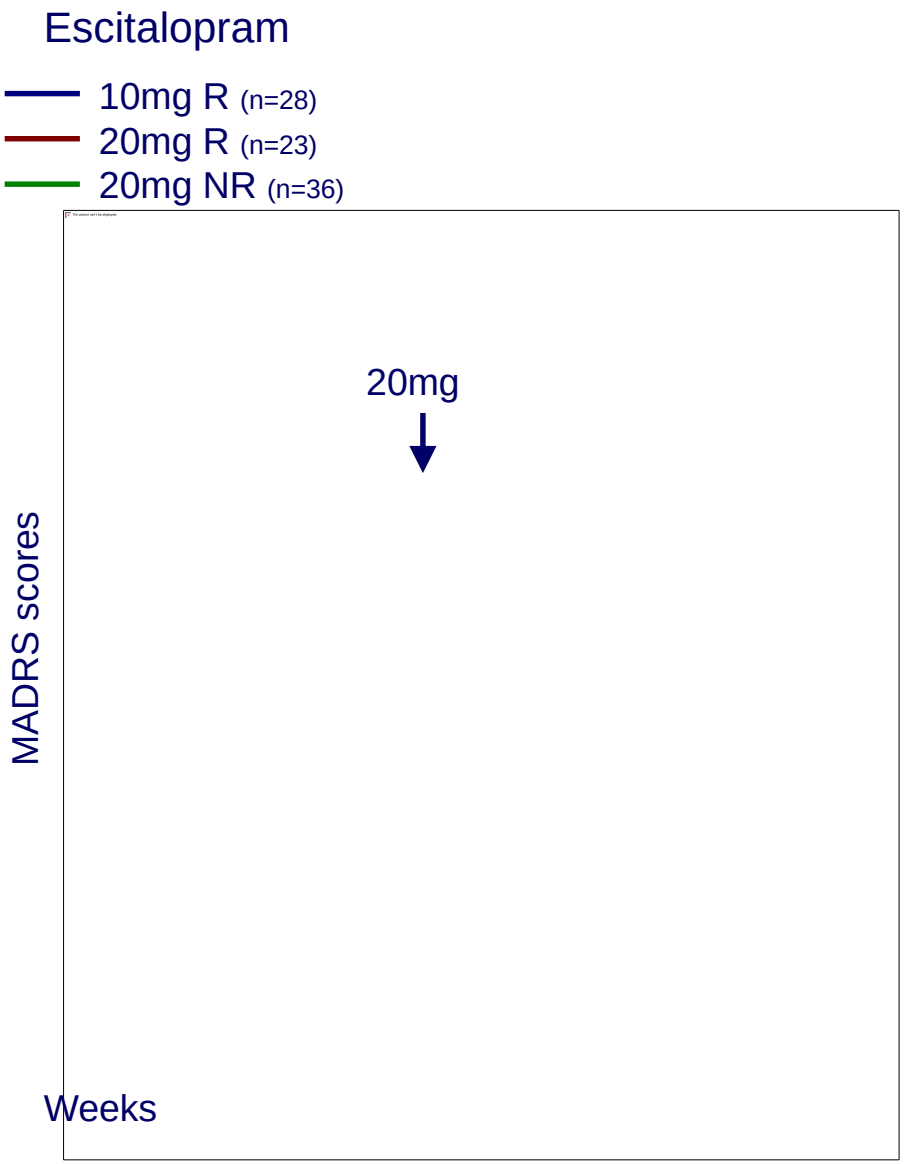
DEPRESSION AND ANXIETY 29:340–354 (201

Review

COMPREHENSIVE REVIEW OF FACTORS IMPLICATED IN THE HETEROGENEITY OF RESPONSE IN DEPRESSION

Gebra Cuyún Carter, Ph.D., M.P.H.,[1] Ronald A Cantrell, Ph.D.,[1] Victoria Zarotsky, Pharm.D.,[2*] Virginia S Haynes, Ph.D.,[1] Glenn Phillips, Ph.D.,[1] Carlos I Alatorre, Ph.D., M.B.A.,[1] Iris Goetz, M.D., M.Sc.,[1] Rosirene Paczkowski, M.P.H.,[1] and Lauren B Marangell, M.D.[1]

Severity and treatment response in depression



Pettai et al 2016

NORDIC JOURNAL OF PSYCHIATRY
2018, VOL. 72, NO. 5, 354–360
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ORIGINAL ARTICLE

Personality traits and escitalopram treatment outcome in major depression

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ABSTRACT

Background: Selective serotonin re-uptake inhibitors (SSRI) have proven to be effective in treatment of depression. Still, treatment efficacy varies significantly from patient to patient and about 40% of patients do not respond to initial treatment. Personality traits have been considered one source of variability in treatment outcome.

Aim: Current study aimed at identifying specific personality traits that could be predictive of treatment response and/or the dynamics of symptom change in depressive patients.

Method: In a sample of 132 outpatients with major depressive disorder (MDD) treated with an SSRI-group antidepressant escitalopram, the Swedish universities Scales of Personality (SSP) were used in order to find predictive personality traits. For the assessment of the severity of depressive symptoms and the improvement rates, the Hamilton Depression Scale (HAM-D) and Montgomery-Åsberg Depression Rating Scale (MADRS) were used.

Results: Escitalopram-treated MDD patients with higher social desirability achieved more rapid decrease in symptom severity. None of the studied traits predicted the end result of the treatment.

Conclusion: The findings suggest that specific personality traits may predict the trajectory of symptom change rather than the overall improvement rate.

ARTICLE HISTORY
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KEYWORDS
Major depressive disorder; SSRI; personality; treatment outcome; Swedish universities scales of personality

Neurobiological factors

Blood biomarkers and treatment response in major depression

Cristina Mora[a], Valentina Zonca[a,b], Marco A. Riva [b] and Annamaria Cattaneo[a,c]

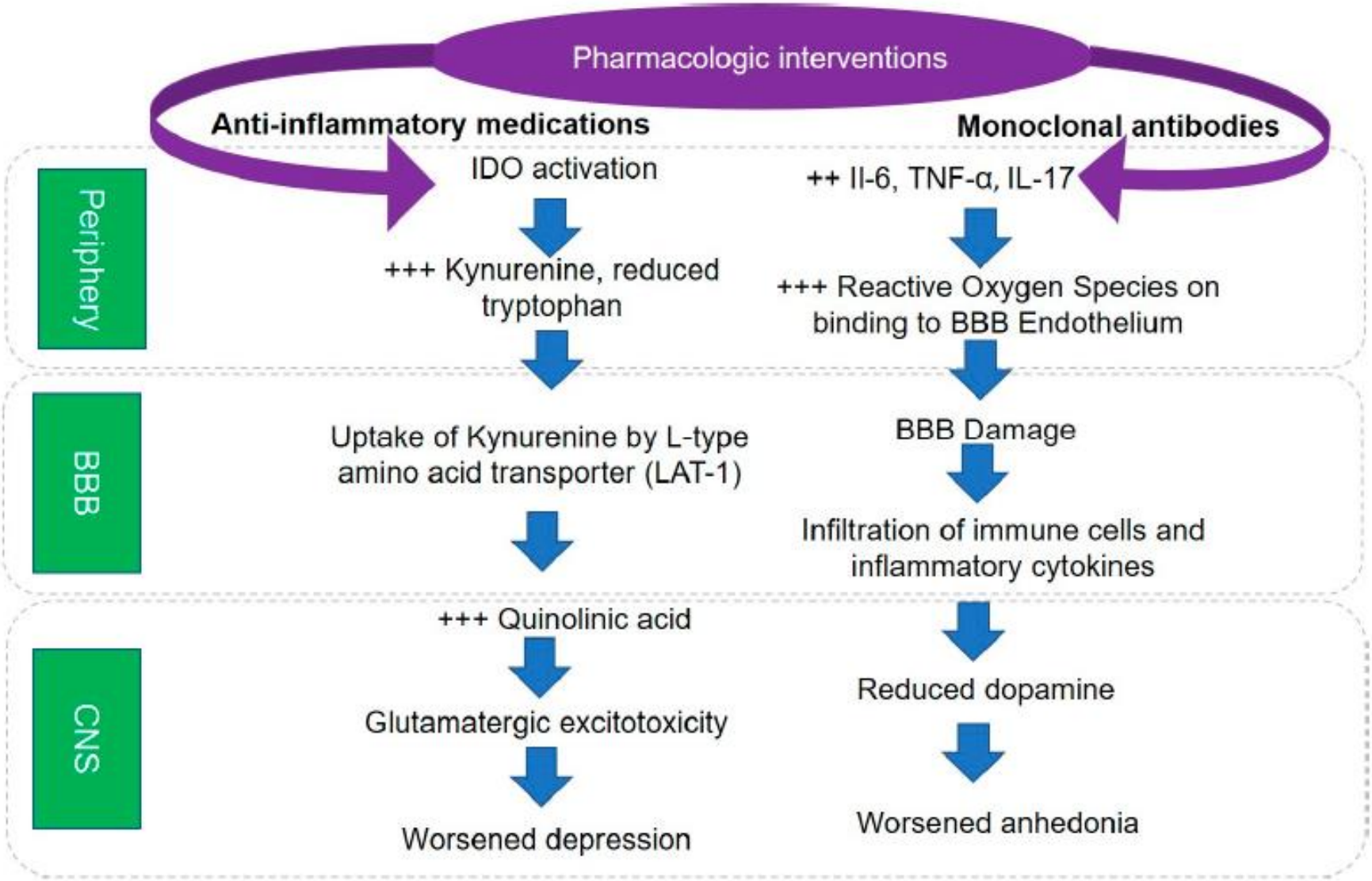
Table 3. Genetic, mRNA, and proteomic biomarker in blood for predicting antidepressant treatment outcomes.

Cytokine gene	SNP	Drug	Reference
IL1β	511C	Fluoxetine (SSRI)	Yu et al., 2003 [93]
	511 C/T	Paroxetine (SSRI)	Tadić et al., 2008 [94]
	511 T/T	Mono- or poly-therapy (SSRIs, TCAs, SNRIs, IMAOs)	Baune et al., 2010 [95]
	rs114643		Chen et al., 2015 [96]
	rs16944		
	rs1143643		
	rs16944		
IL6	rs7801617	Escitalopram (SSRI)	Uher et al., 2010 [97]
	rs2066992	Duloxetine (SNRI)	Maciukiewicz et al., 2015 [98]
	rs10242595		
IL11	rs1126757 (A/A or A/G)	Escitalopram (SSRI)	Uher et al., 2010 [97]
Cytokine mRNA	**Time**	**Drug**	**Reference**
IL1β	Baseline	Nortriptyline/Escitalopram (SSRI)	Cattaneo et al., 2013 [25]
	8 weeks of treatment	Nortriptyline/Escitalopram (SSRI)	Cattaneo et al., 2013 [25]
	3 months	Escitalopram (SSRI)	Powell et al., 2013c [100]
		Fluoxetine	Tsao et al., 2006 [101]
IL6	Baseline	Nortriptyline/Escitalopram (SSRI)	Pandey et al., 2011 [102]
	8 weeks of treatment	Escitalopram (SSRI)	Cattaneo et al., 2013 [25]
	3 months	Fluoxetine (SSRI)	Powell et al., 2013a [99]
			Tsao et al., 2006 [101]
IL11	12 weeks of treatment	Escitalopram (SSRI)	Powell et al., 2013a [99]
ABCF1	8 weeks of treatment	Escitalopram (SSRI)	Powell et al., 2013c [100]
TNF-α	Baseline	Nortriptyline/Escitalopram (SSRI)	Cattaneo et al., 2013 [25]
Cytokine Protein	**Time**	**Drug**	**Reference**
IL-6	Baseline	Fluoxetine	Lanquillon et al., 2000 [109]
	8 weeks of treatment	Ketamine	Tadić et al., 2008 [95]
	12 weeks of treatment	Paroxetine/Sertraline (SSRI)	Maes, 2001 [110]
		Desvenlafaxine (SNRI)	Manoharam et al., 2016
			Yang et al., 2015 [111]
			Yoshimura et al., 2013 [116]
			Ninan et al., 2014 [114]
TNF-α	Baseline	Amitriptyline (TCAs) and SSRIs	Lanquillon et al., 2000 [109]
	After treatment	Mirtazapine (Nassa)	Tuglu et al., 2003 [112]
	12 weeks of treatment		Eller et al., 2008 [113]
			Gupta et al., 2016 [149]
IL-10	After treatment	Vary antidepressant	Kubera et al., 2001 [150]

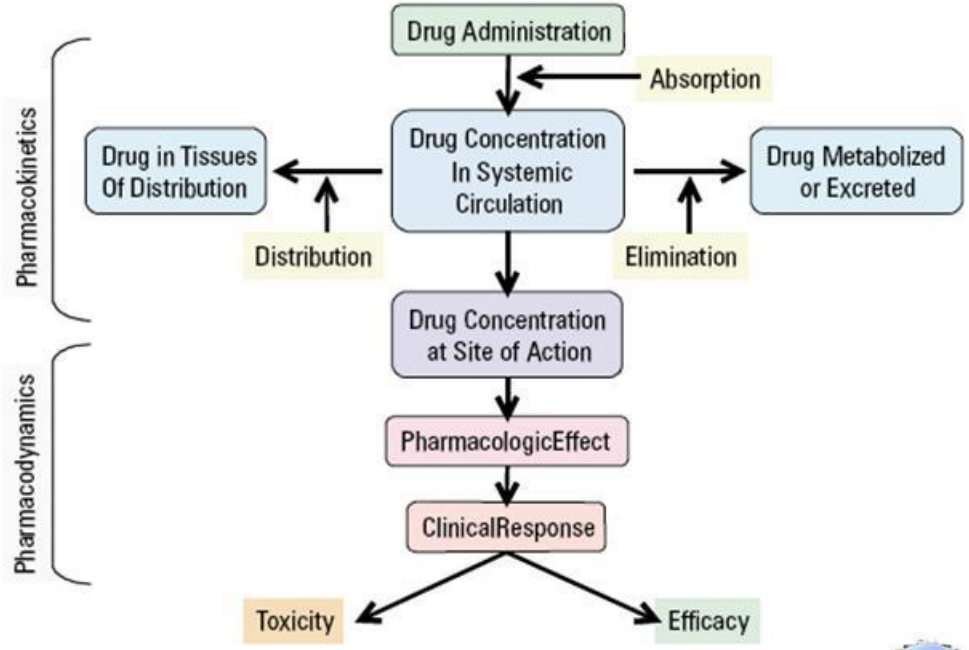
Personalized Antidepressant Selection and Pathway to Novel Treatments: Clinical Utility of Targeting Inflammation

International Journal of *Molecular Sciences*

Manish K. Jha * and Madhukar H. Trivedi



Genetic modulation of antidepressant treatment



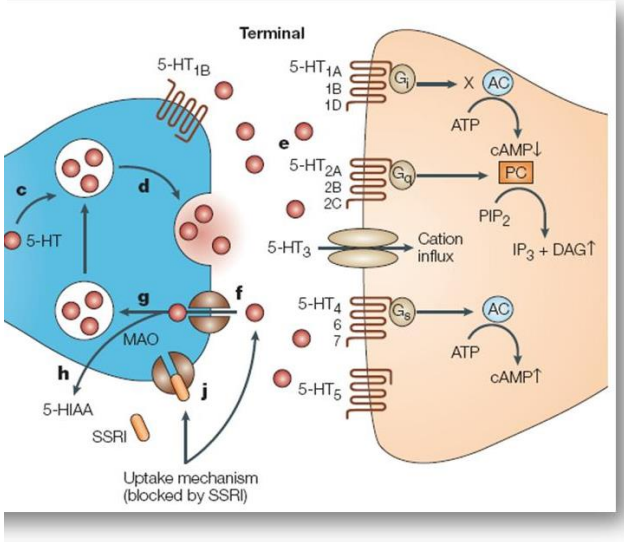
Fierz, 2004

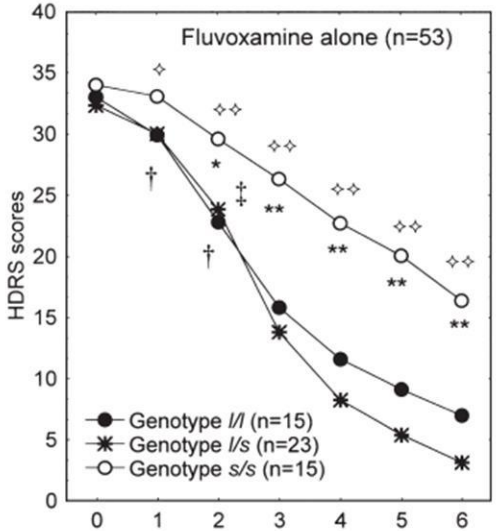
- Pharmacogenetics
  - the study of the relationship between individual gene variants and variable drug effects
- Pharmacogenomics
  - the study of the relationship between variants in a large collection of genes, up to whole genome, and variable drug effects

Roden M Dan et al., 2006, Ann Intern Med

Meta-analysis of serotonin transporter gene promoter polymorphism (5-HTTLPR) association with antidepressant efficacy

Stefano Porcelli [1], Chiara Fabbri [1], Alessandro Serretti*

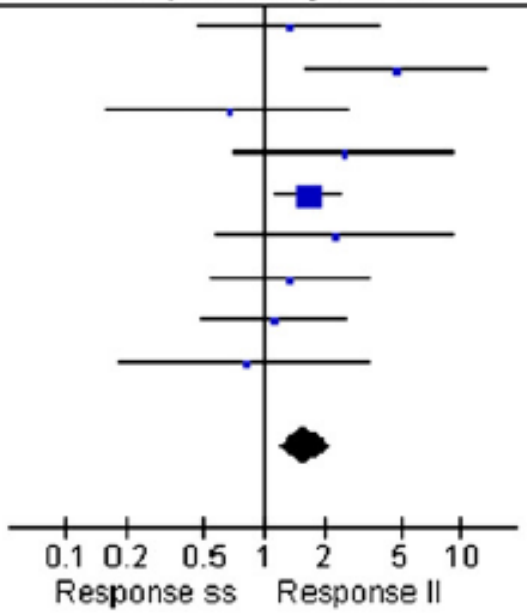


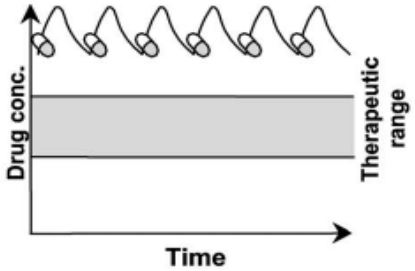
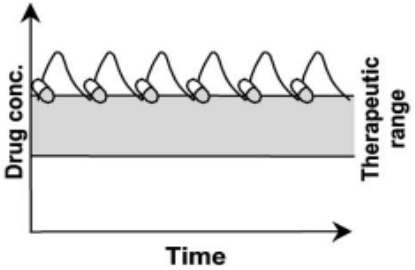
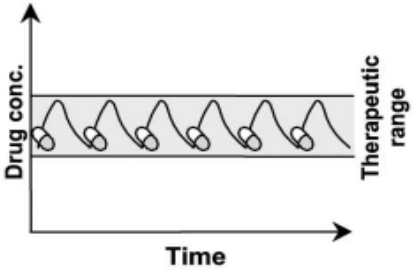
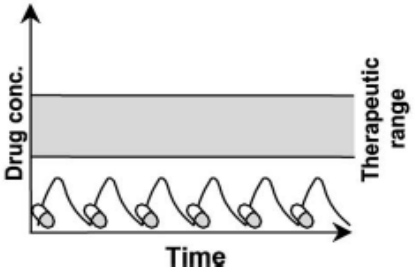


Study or Subgroup	ll Events	ll Total	ss Events	ss Total	Weight	Odds Ratio M-H, Random, 95% CI
Arias et al 2003	30	41	18	27	7.2%	1.36 [0.47, 3.92]
Bozina et al 2008	33	49	7	23	7.0%	4.71 [1.62, 13.75]
Dogan et al 2008	8	16	9	15	4.0%	0.67 [0.16, 2.77]
Gressier et al 2009	21	27	11	19	4.9%	2.55 [0.70, 9.21]
Huezo-Diaz et al 2009	170	297	62	140	49.1%	1.68 [1.12, 2.52]
Illi et al 2010	19	29	5	11	4.0%	2.28 [0.56, 9.36]
Joyce et al 2003	13	29	19	51	9.4%	1.37 [0.54, 3.46]
Kirchheiner et al 2006	32	69	13	30	10.8%	1.13 [0.48, 2.68]
Maron et al 2009	37	60	6	9	3.7%	0.80 [0.18, 3.53]
Total (95% CI)		**617**		**325**	**100.0%**	**1.62 [1.22, 2.16]**
Total events	363		150			

Heterogeneity: Tau² = 0.00; Chi² = 7.81, df = 8 (P = 0.45); I² = 0%

Test for overall effect: Z = 3.35 (P = 0.0008)



CYP2D6 function	Mutation	Effect on steady state concentration	Anticipated clinical effect	Possible consequences
Poor Metabolizer (PM) No function 6 - 8% in Caucasians Gene dose = 0	Homo- or combined heterozygous with defective enzymes or complete deletions (>15 mutations)		• Toxicity • Adverse drug effects	• Reduce dose • Change medication and avoid substrates of CYP2D6 • Ther. drug monitoring
Intermediate Metabolizer (IM) Reduced function 10 - 33% in Caucasians Gene dose = 0.5 or 1.0	Combination of dysfunctional and reduced function or normal allele		• Adverse drug effects? • Efficient therapy?	• Reduce dose? • Change medication and avoid substrates of CYP2D6? • Ther. drug monitoring?
Extensive Metabolizer (EM) Normal function Gene dose = 2.0 or 1.5	Homozygous wild type or combination of functional and reduced function allele		• Desired concentration range • Efficient therapy	
Ultra Rapid Metabolizer (UM) Enhanced function 2 - 4% in Caucasians Gene dose > 2.0	Duplication or multiplication of functional gene		• Ineffective therapy	• Avoid CYP2D6 substrates • Megadose or comedicate CYP2D6 inhibitor and monitor conc.

Pharmacogenetic biomarkers recommended by clinical guidelines:

Clinical Pharmacogenetic Implementation Consortium
Dutch Pharmacogenetics Working Group

- CYP2D6

  Isoenzyme involved in antidepressant metabolism

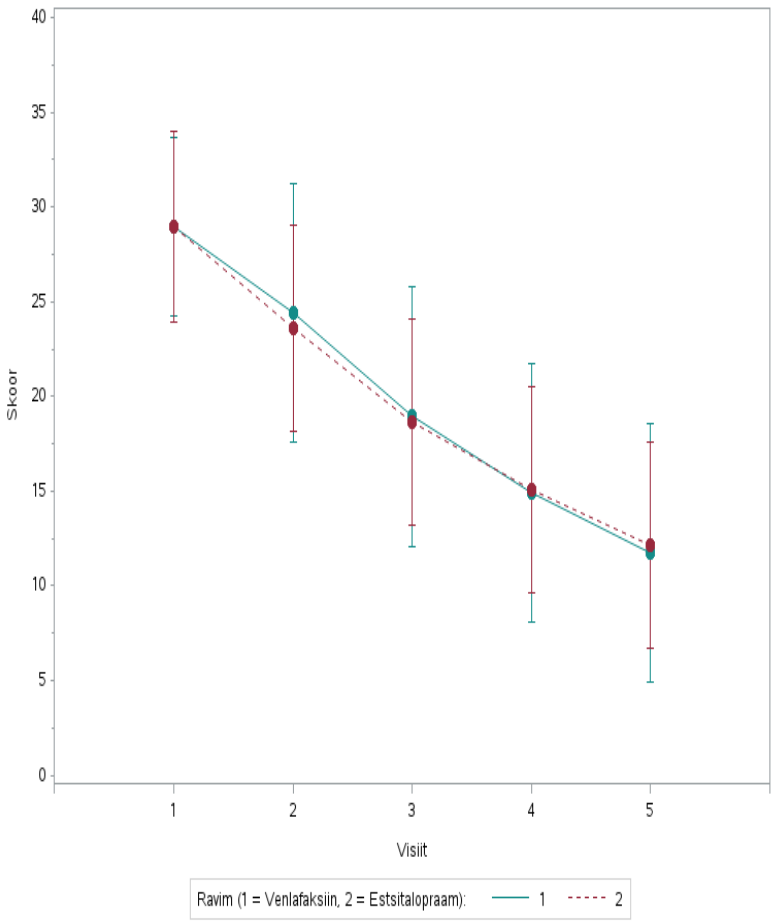
- Higher treatment efficacy in the intermediate metabolizer group; higher risk of treatment failure in ultrarapid metabolizers; higher side effects in non-extensive metabolizers

- CYP2C19

  Isoenzyme involved in antidepressant metabolism

- Higher side effects in poor metabolizers; poor metabolizers classified as citalopram tolerant may show higher remission probability

Pharmacogenetic study of escitalopram and venlafaxine treatment in depression



- 153 patients with depression
- 12 weeks, open-label
- CYP2C19, CYP3A4, CYP2D6
- Escitalopram: rs2302566, rs17885098 ($p<0.05$)
- Venlafaxine: rs35599367 ($p<0.05$)

Optimizing treatment efficacy in depression

Few optimizing options	
• Switching from SSRIs to SSRIs	24%
• Switching from SSRIs to non-SSRIs	28%
• Combination/ augmentation	30-80%
Escitalopram + Bupropion	60%

Papakostas et al 2008; Maron et al 2009

Optimizing treatment efficacy in depression

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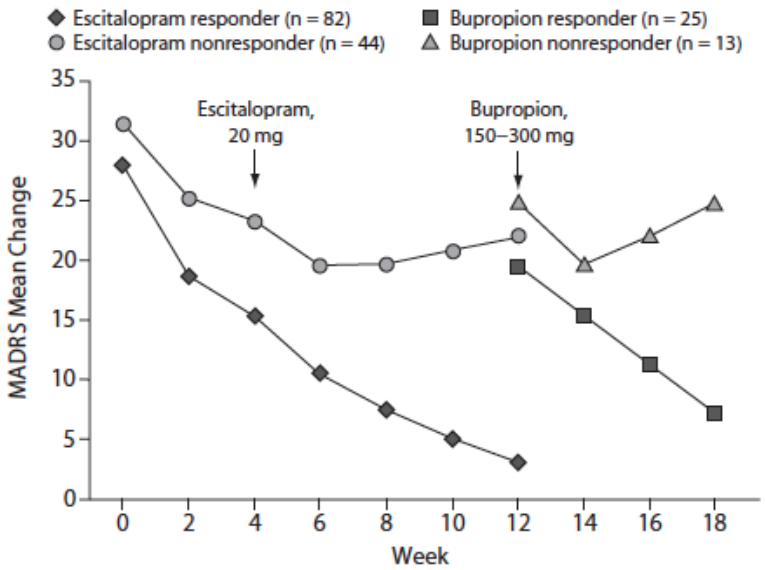
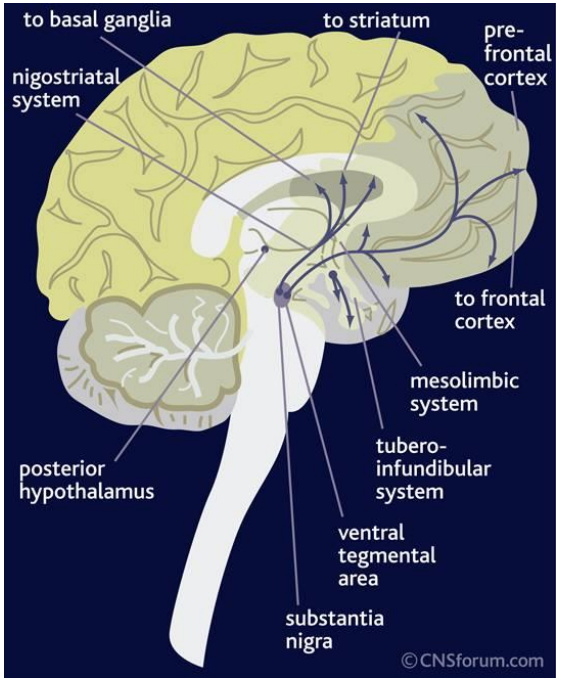
Figure 1. Mean Change in Montgomery-Asberg Depression Rating Scale (MADRS) Scores for Responders and Nonresponders to Escitalopram Monotherapy and Bupropion Augmentation[a]



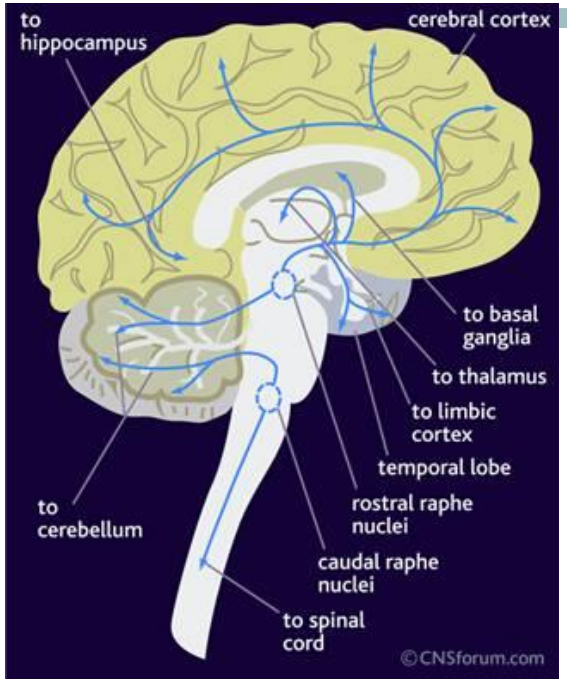
[a]At baseline, the severity of depression on the MADRS scale was significantly lower in responders to escitalopram monotherapy as compared with nonresponders ($t = 19.79$, $df = 55{,}80$; $p < .0001$). The responders to bupropion augmentation had significantly lower severity of depression on the MADRS scale before starting of augmentation (week 12) than nonresponders ($t = 2.60$; $df = 21{,}0$; $p = .01$).

Papakostas et al 2008; Maron et al 2009

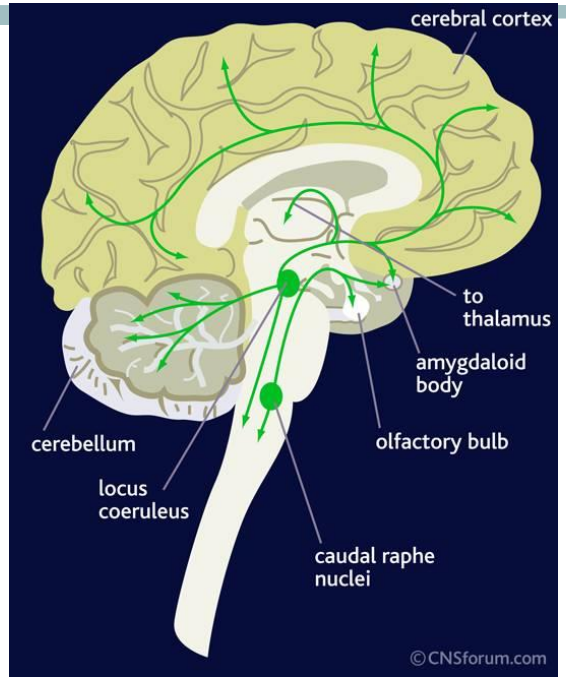
Dopamine

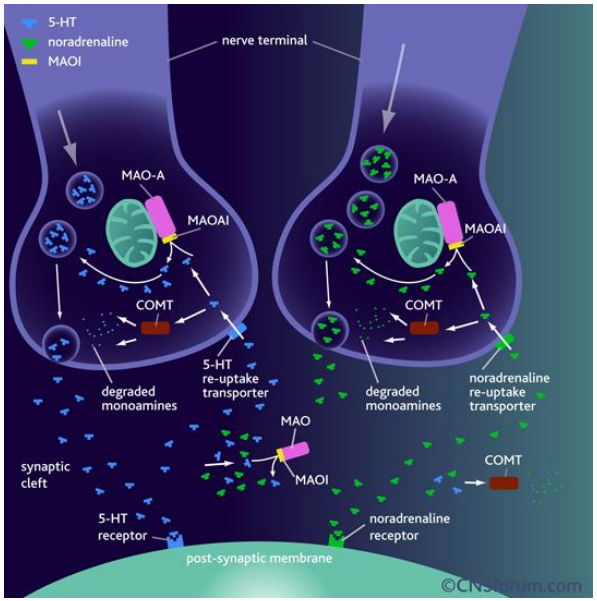


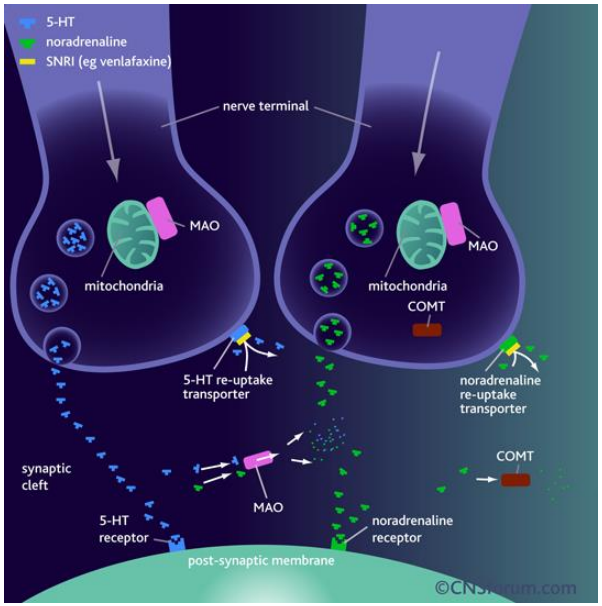
Serotonin



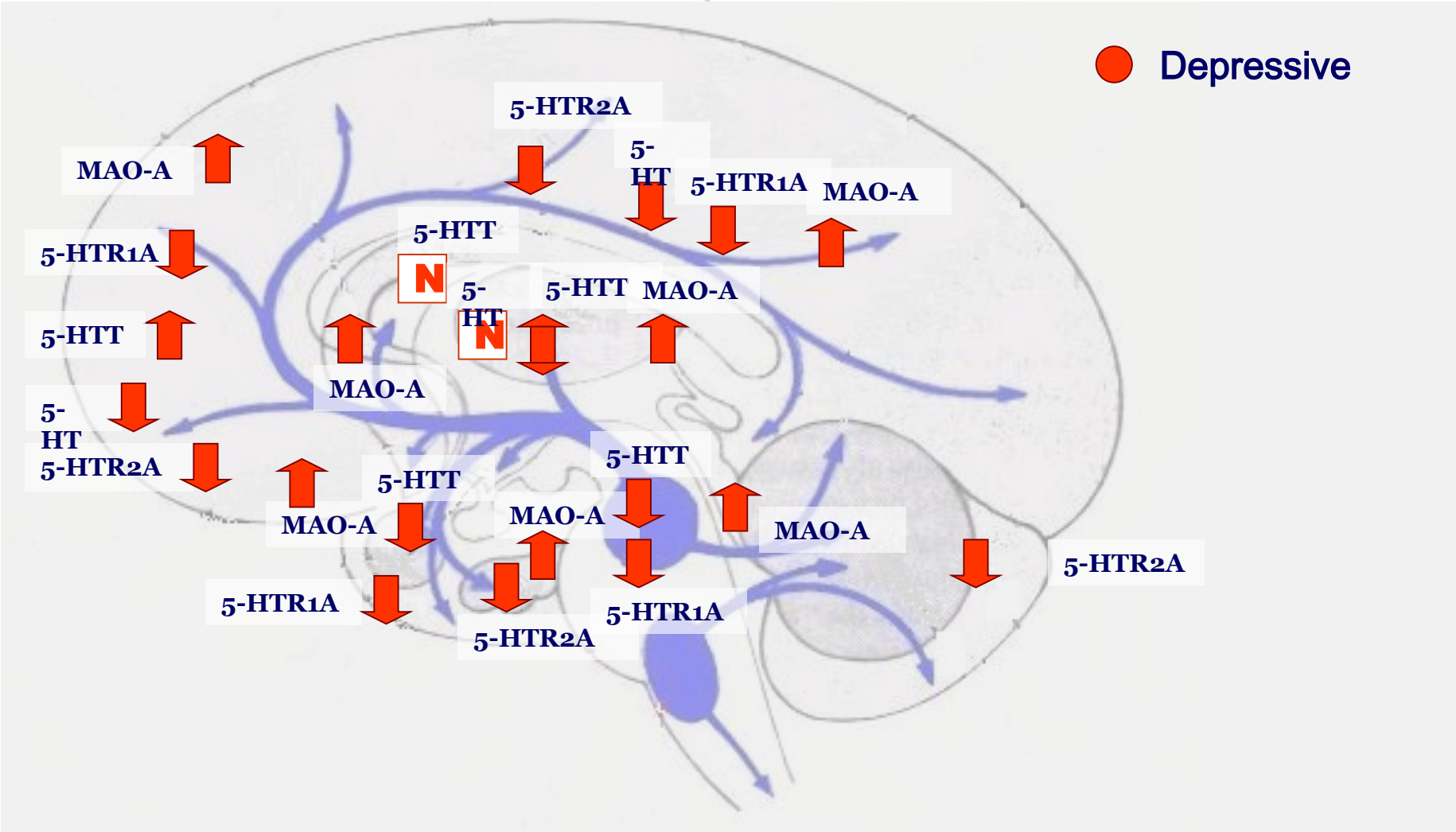
Noradrenalin





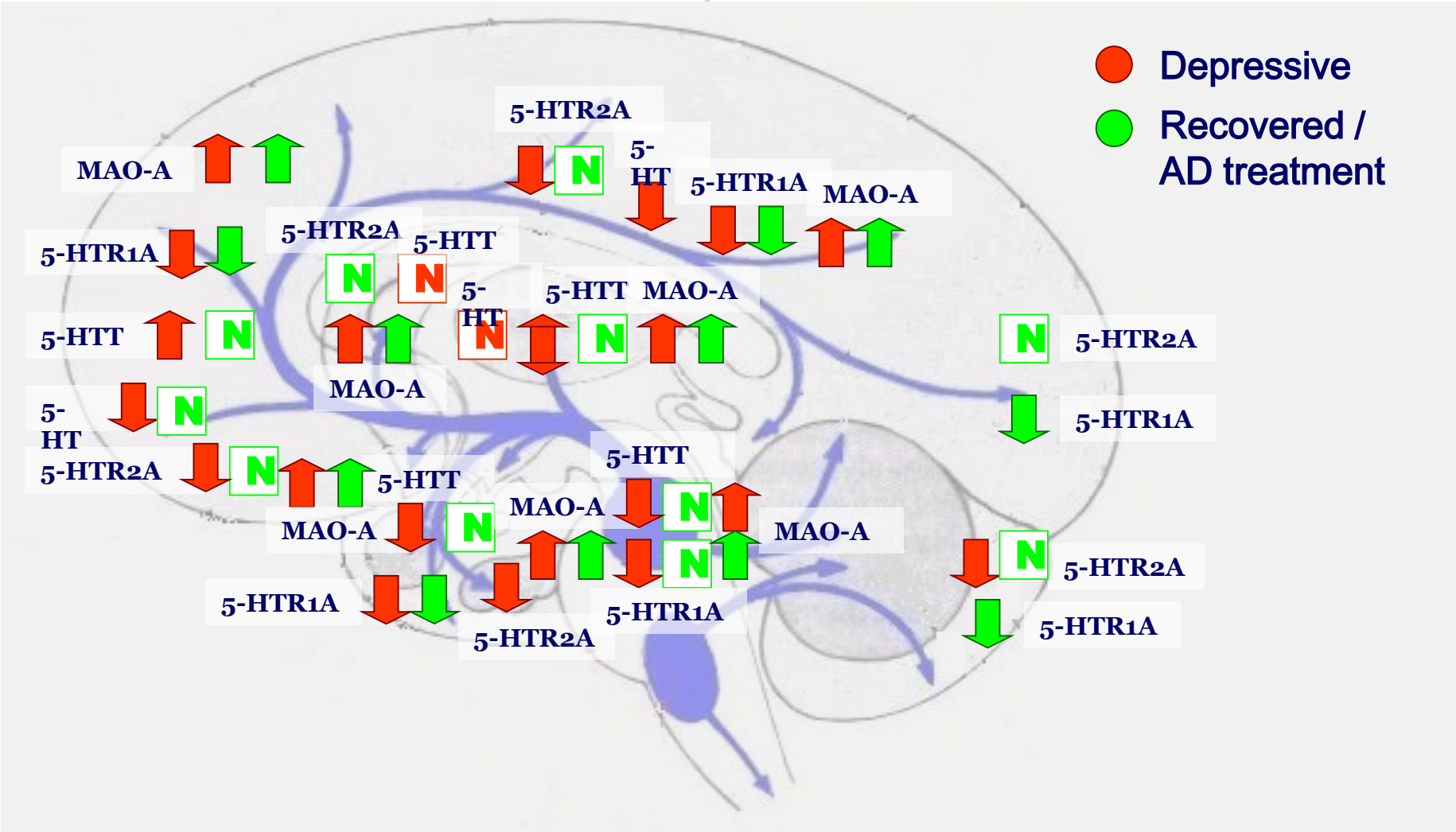


Serotonin system in depression: before and after treatment



Berney et al 2008; Bhagwagar et al 2007, 2006, 2004; Biver et al 1997; Cannon et al 2007; Drevets et al 2007; Hirvonene et al 2008; Joensuu et al 2007; Laasonen-Balk et al 2004; Lehto et al 2008; Leyton et al 2006; Malison et al 1998; Meltzer et al 2004; Meyer et al 2009; Newberg et al 2005; Parsey et al 2006; Reivich et al 2004; Rosa-Neto et al 2004; Sheline et al 2004; Staley et al 2006; Zanardi et al 2001

Serotonin system in depression: before and after treatment

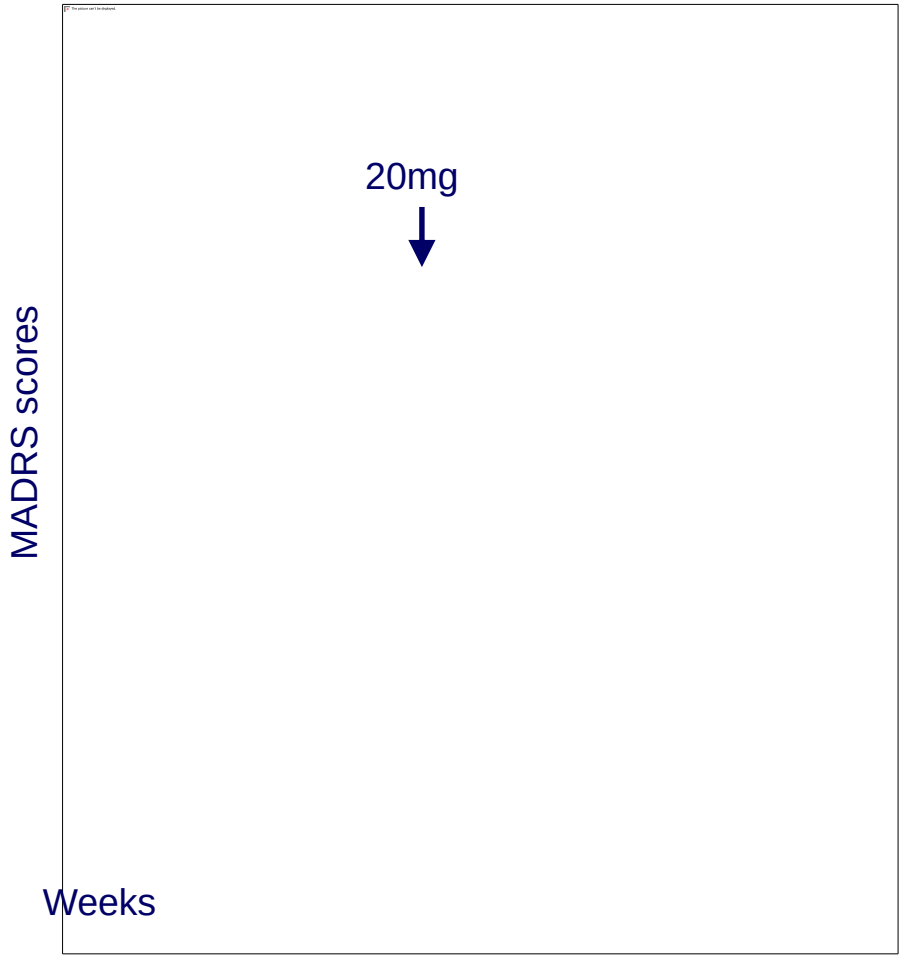


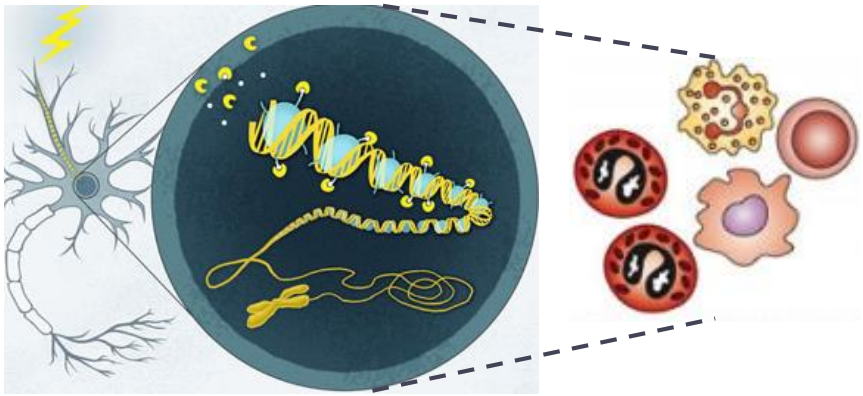
Berney et al 2008; Bhagwagar et al 2007, 2006, 2004; Biver et al 1997; Cannon et al 2007; Drevets et al 2007; Hirvonene et al 2008; Joensuu et al 2007; Laasonen-Balk et al 2004; Lehto et al 2008; Leyton et al 2006; Malison et al 1998; Meltzer et al 2004; Meyer et al 2009; Newberg et al 2005; Parsey et al 2006; Reivich et al 2004; Rosa-Neto et al 2004; Sheline et al 2004; Staley et al 2006; Zanardi et al 2001

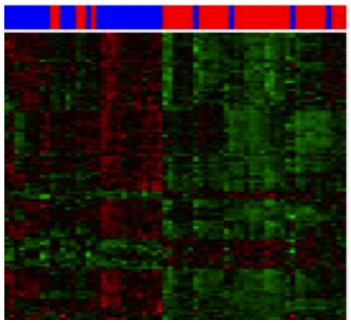
Genes underlying treatment resistance in depression

Escitalopram

- 10mg R (n=28)
- 20mg R (n=23)
- 20mg NR (n=36)







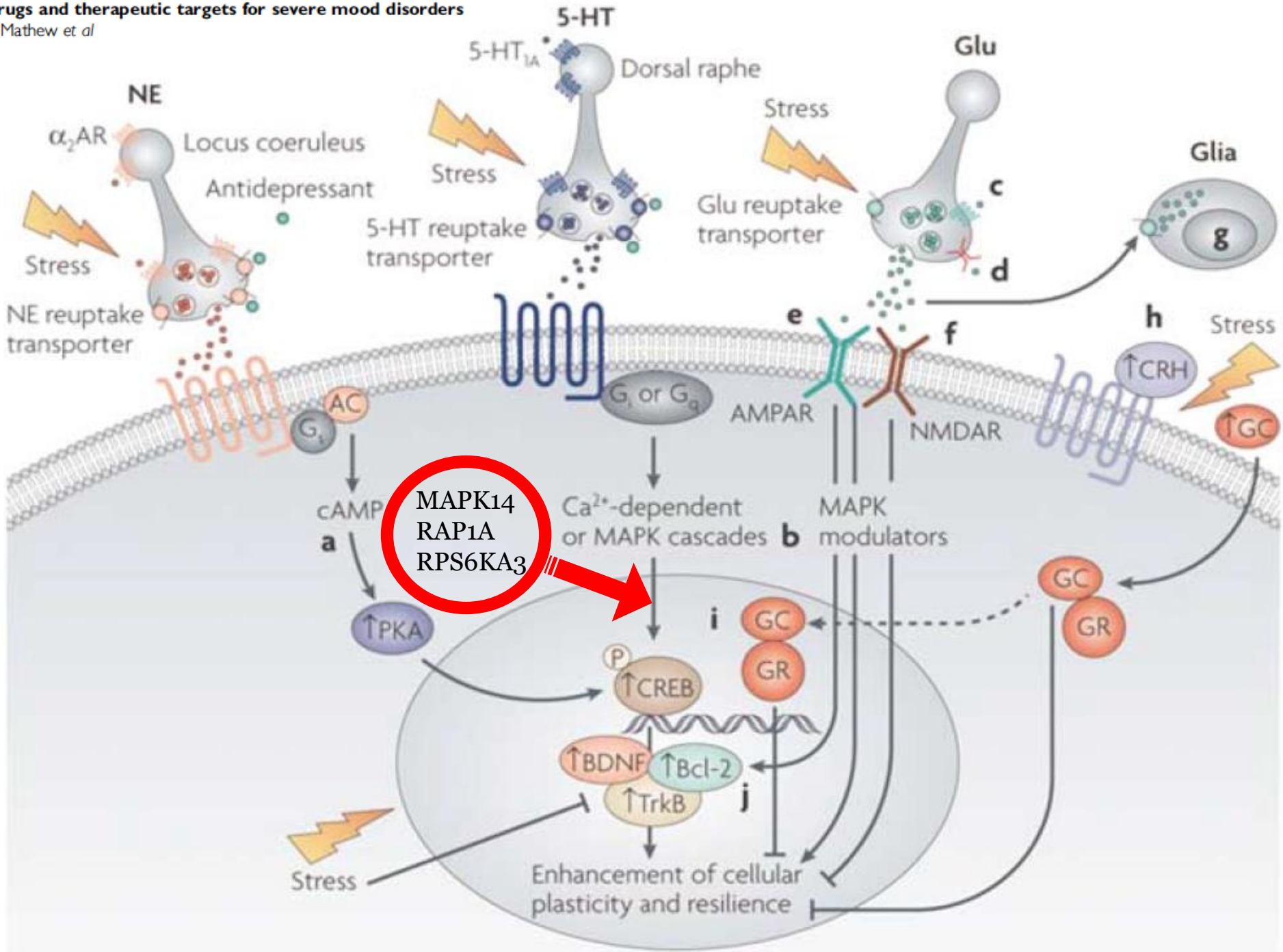
Lower expression in non-responders

YWHAZ – ADHD
MAPK14 – amyotrophic lateral sclerosis
RAP1A
RPS6KA3 – mental retardation

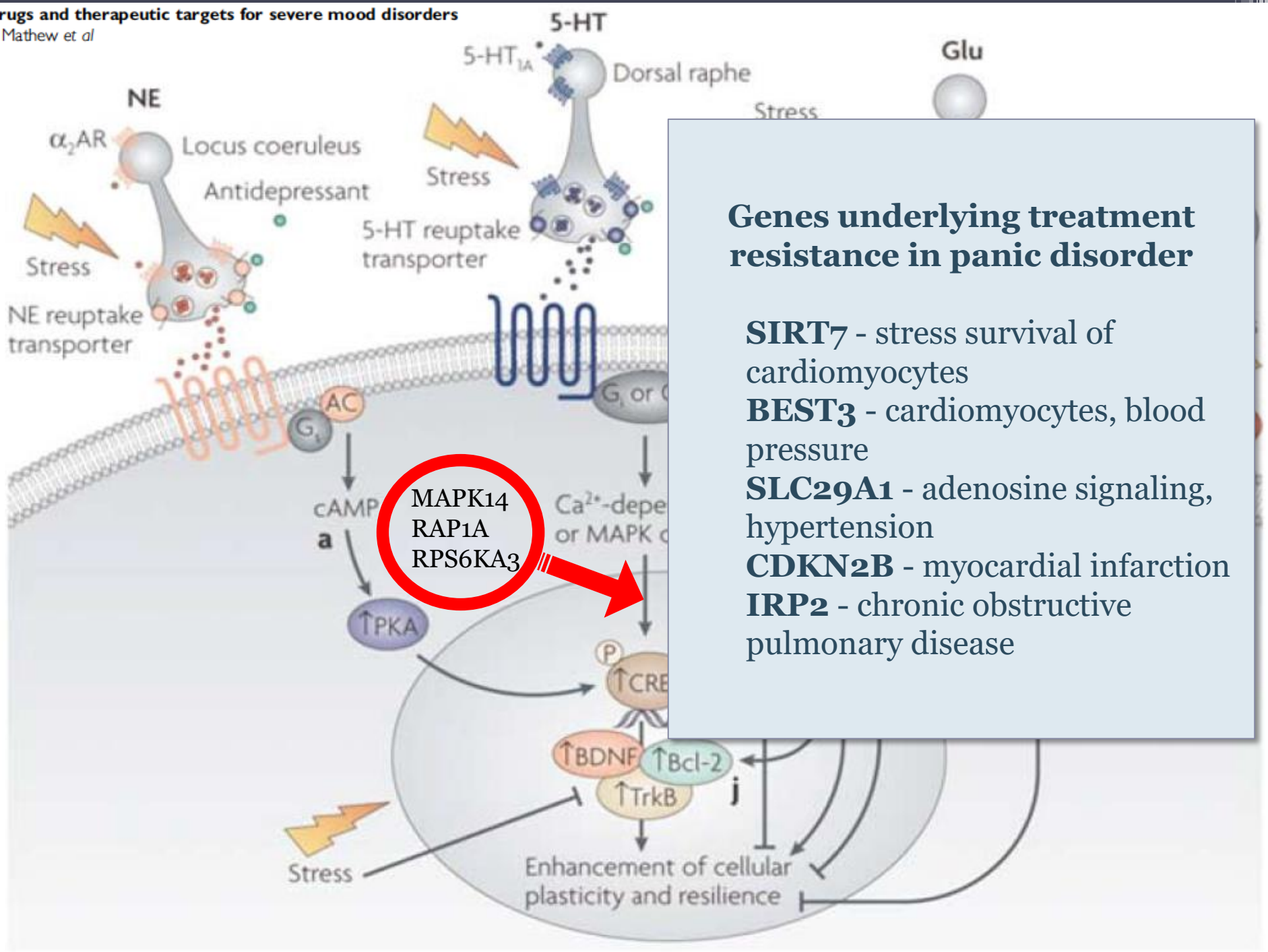
Pettai et al 2016

Drugs and therapeutic targets for severe mood disorders

SJ Mathew *et al*



Drugs and therapeutic targets for severe mood disorders
SJ Mathew *et al*



Genes underlying treatment resistance in panic disorder

SIRT7 - stress survival of cardiomyocytes
BEST3 - cardiomyocytes, blood pressure
SLC29A1 - adenosine signaling, hypertension
CDKN2B - myocardial infarction
IRP2 - chronic obstructive pulmonary disease

Peripheral Gene Expression Profiling of CCK-4-Induced Panic in Healthy Subjects

Eduard Maron,[1,2,3]* Kristi Kallassalu,[4,5] Anu Tammiste,[4] Raivo Kolde,[6] Jaak Vilo,[6] Innar Tõru,[2] Veiko Vasar,[2] Jakov Shlik,[7] and Andres Metspalu[3,4,5]

AMERICAN JOURNAL OF medical genetics PART B
Neuropsychiatric Genetics

Symbol	Map location	Fold change	*P*-value	FDR	Phenotype or function
A. Gene expression differences between panic and non-panic groups					
PHF11	13q14.3	−1.234	8.01E−07	0.017	Asthma, IgE levels QTL
CLEC1B	12p13.2	1.405	6.03E−06	0.026	Cytotoxicity and cytokine secretion
CTSL	9q21–q22	−1.246	4.59E−06	0.026	Myofibril necrosis in myopathies, myocardial ischemia, renal tubular response to proteinuria
IFI44	1p31.1	−1.881	4.75E−06	0.026	Immune response
IRF7	11p15.5	−1.504	4.73E−06	0.026	Transcription factor activity, inflammatory response
SHC4	15q21.1–q21.2	1.065	5.54E−06	0.026	Focal adhesion, natural killer cell mediated cytotoxicity, insulin signaling pathway, glioma, chronic myeloid leukemia
OAS2	12q24.2	−1.442	1.70E−05	0.048	Transferase activity, immune response
B. CCK-4-induced changes in gene expression profiles in total group					
IDUA	4p16.3	−1.228	3.89E−07	0.013	Mucopolysaccharidosis
SURF1	9q34.2	−1.113	6.10E−07	0.013	Leigh syndrome, due to cytochrome *c* oxidase deficiency
CRTC1	19p13.11	−1.113	4.18E−06	0.015	Mucoepidermoid salivary gland carcinoma
LBR	1q42.1	1.237	4.23E−06	0.015	Greenberg dysplasia, Pelger–Huet anomaly
SREBF2	22q13	−1.198	2,76E−06	0.015	Cholesterol homeostasis
STIP1	11q13	−1.209	1.79E−06	0.015	Response to stress
EHMT1	9q34.3	−1.104	5.98E−06	0.018	Chromosome 9q subtelomeric deletion syndrome
PER1	17p13.1–17p12	−1.108	1.07E−05	0.018	Circadian rhythm
SUMO4	6q25	1.150	9.58E−06	0.018	Diabetes mellitus, insulin-dependent
UCK1	9q34.13	−1.096	6.88E−06	0.018	Pyrimidine metabolism
POMT2	14q24	−1.104	3.42E−05	0.031	Walker–Warburg syndrome
ADRB2	5q31–q32	1.264	7.02E−05	0.044	Nocturnal asthma, reduced response to beta-2-adrenoreceptor agonist, obesity
CEL	9q34.3	−1.081	7.12E−05	0.044	Diabetes and pancreatic exocrine dysfunction
VIPR1	3p22	−1.162	7.61E−05	0.046	Smooth muscle relaxation, exocrine and endocrine secretion, and water and ion flux in lung and intestinal epithelia

Peripheral Gene Expression Profiling of CCK-4-Induced Panic in Healthy Subjects

Eduard Maron,[1,2,3]* Kristi Kallassalu,[4,5] Anu Tammiste,[4] Raivo Kolde,[6] Jaak Vilo,[6] Innar Tõru,[2] Veiko Vasar,[2] Jakov Shlik,[7] and Andres Metspalu[3,4,5]

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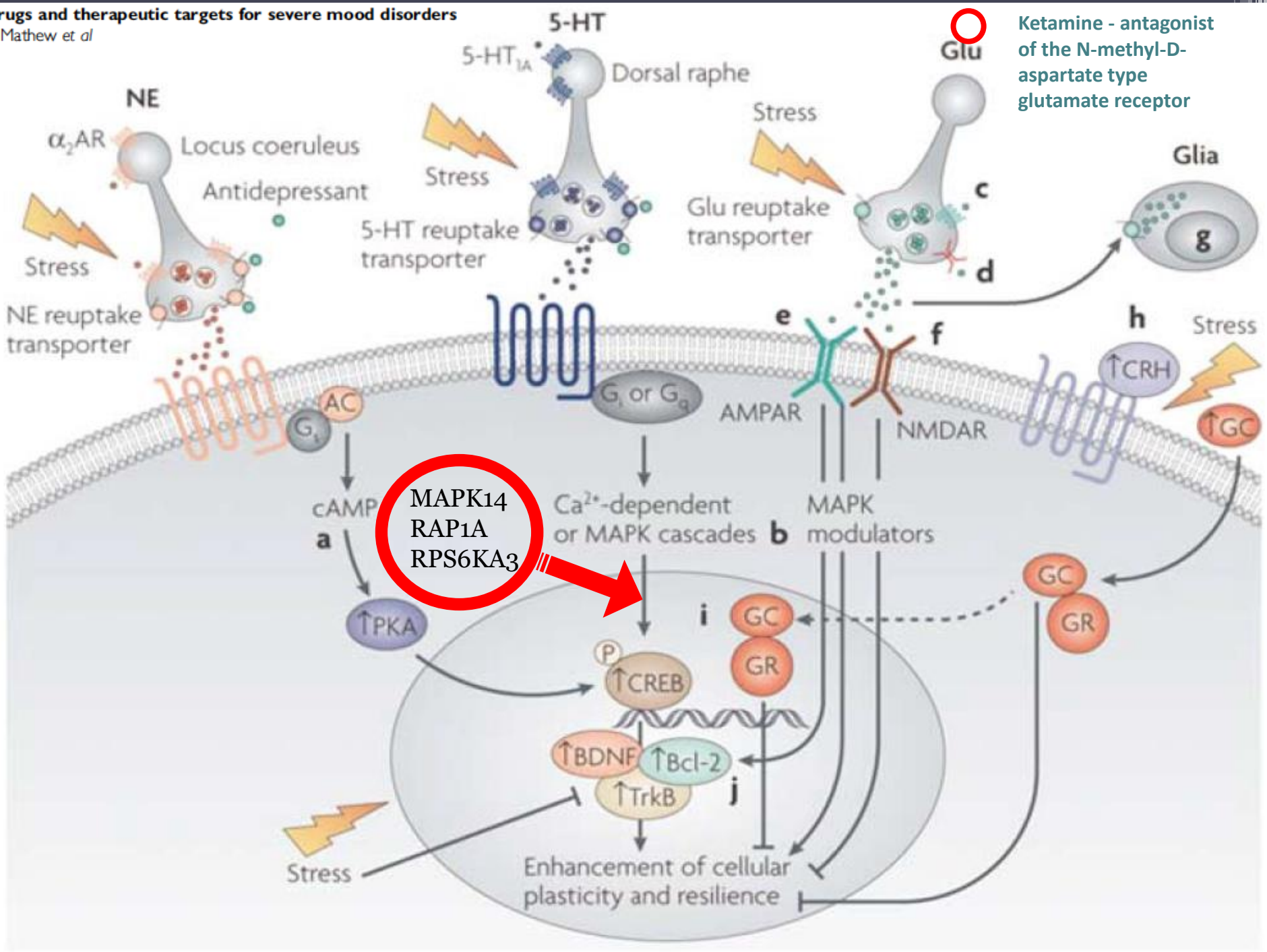
Neuropsychiatric Genetics

Symbol	Map location	Fold change	*P*-value	FDR	Phenotype or function
A. Gene expression differences between panic and non-panic groups					
PHF11	13q14.3	−1.234	8.01E−07	0.017	Asthma, IgE levels QTL
CLEC1B	12p13.2	1.405	6.03E−06	0.026	Cytotoxicity and cytokine secretion
CTSL	9q21–q22	−1.246	4.59E−06	0.026	Myofibril necrosis in myopathies, myocardial ischemia, renal tubular response to proteinuria
					esponse
					cytotoxicity,
					se deficiency
					lrome
PER1	17p13.1–17p12	−1.108	1.07E−05	0.018	Circadian rhythm
SUMO4	6q25	1.150	9.58E−06	0.018	Diabetes mellitus, insulin-dependent
UCK1	9q34.13	−1.096	6.88E−06	0.018	Pyrimidine metabolism
POMT2	14q24	−1.104	3.42E−05	0.031	Walker–Warburg syndrome
ADRB2	5q31–q32	1.264	7.02E−05	0.044	Nocturnal asthma, reduced response to beta-2-adrenoreceptor agonist, obesity
CEL	9q34.3	−1.081	7.12E−05	0.044	Diabetes and pancreatic exocrine dysfunction
VIPR1	3p22	−1.162	7.61E−05	0.046	Smooth muscle relaxation, exocrine and endocrine secretion, and water and ion flux in lung and intestinal epithelia

systems. Other distinctive mRNA transcripts were from the genes known to be related to phenotypes associated with increased occurrence of panic attacks, such as asthma, diabetes, or myocardial ischemia. Our findings provide preliminary evidence for genetic substrates of panic attacks on the transcriptional level and indicate potential biological proximity between acute panicogenesis and several somatic conditions.

Drugs and therapeutic targets for severe mood disorders
SJ Mathew *et al*

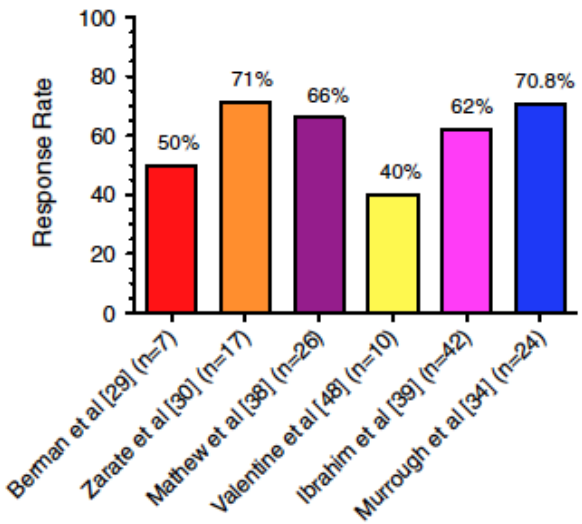
Ketamine - antagonist of the N-methyl-D-aspartate type glutamate receptor



Safety and Efficacy of Repeated-Dose Intravenous Ketamine for Treatment-Resistant Depression

Marije aan het Rot, Katherine A. Collins, James W. Murrough, Andrew M. Perez, David L. Reich, Dennis S. Charney, and Sanjay J. Mathew

BIOL PSYCHIATRY 2010;67:139–145



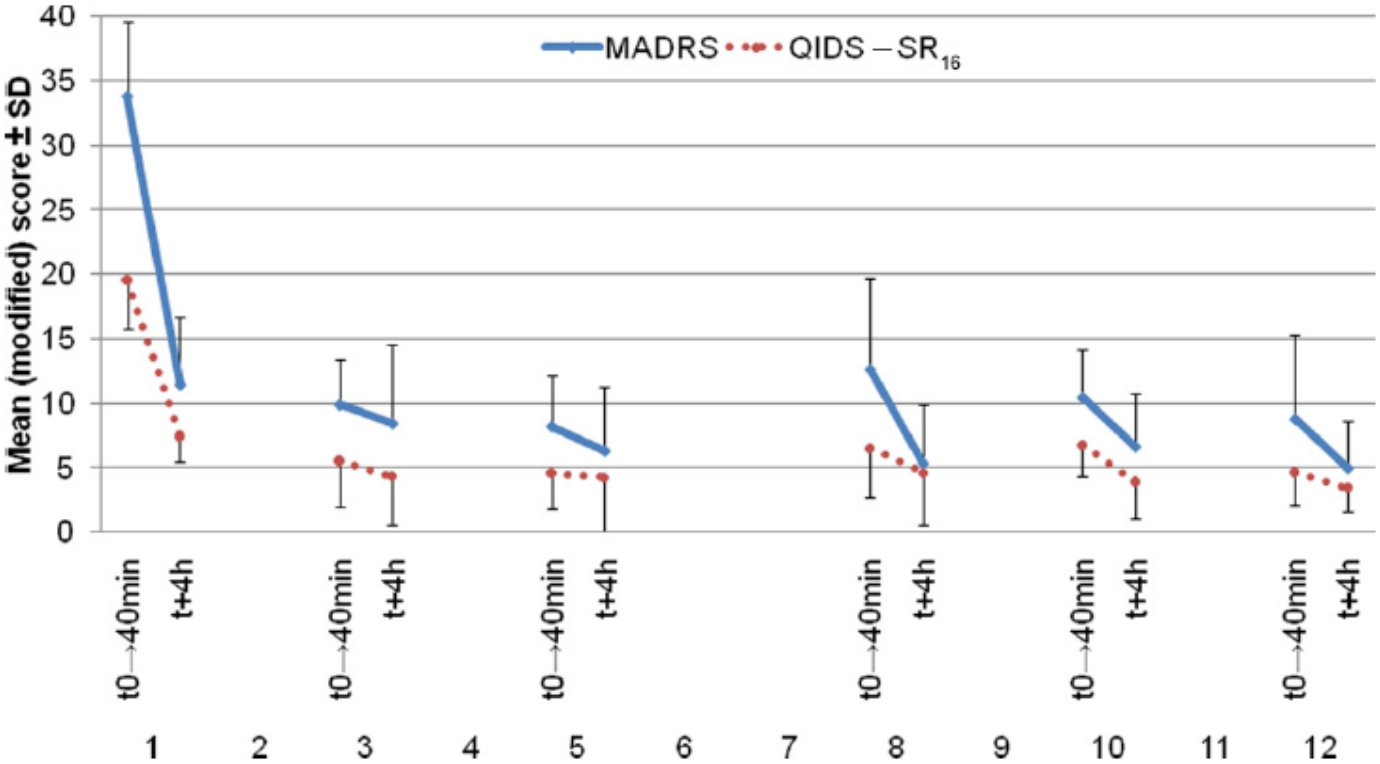


Figure 2. Mean (modified) Montgomery-Åsberg Depression Rating Scale (MADRS) and Quick Inventory of Depressive Symptoms, Self-Report Version ($QIDS\text{-}SR_{16}$) scores before (t_0) and 4 hours after (t_{+4h}) six intravenous ketamine infusions in nine patients who responded to a single infusion and subsequently received five additional infusions.

mTOR-Dependent Synapse Formation Underlies the Rapid Antidepressant Effects of NMDA Antagonists

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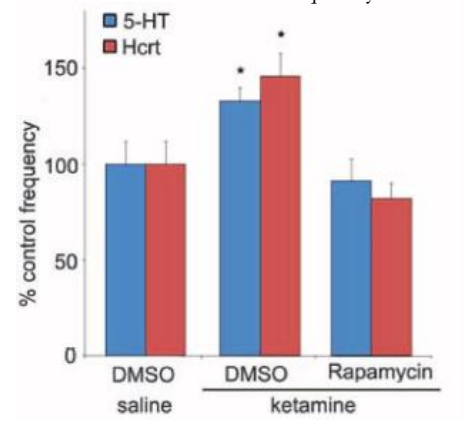
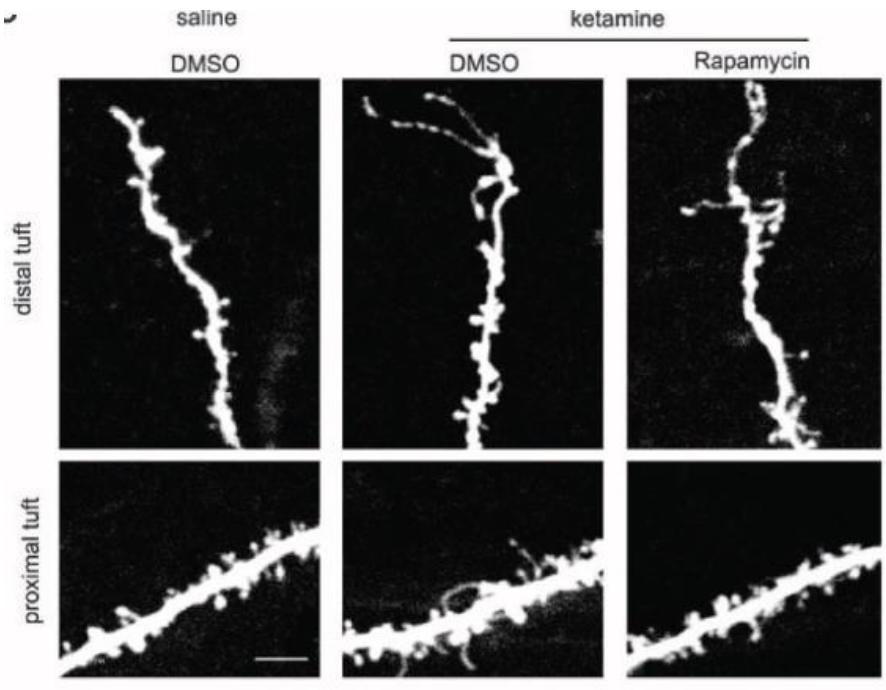
Science
AAAS

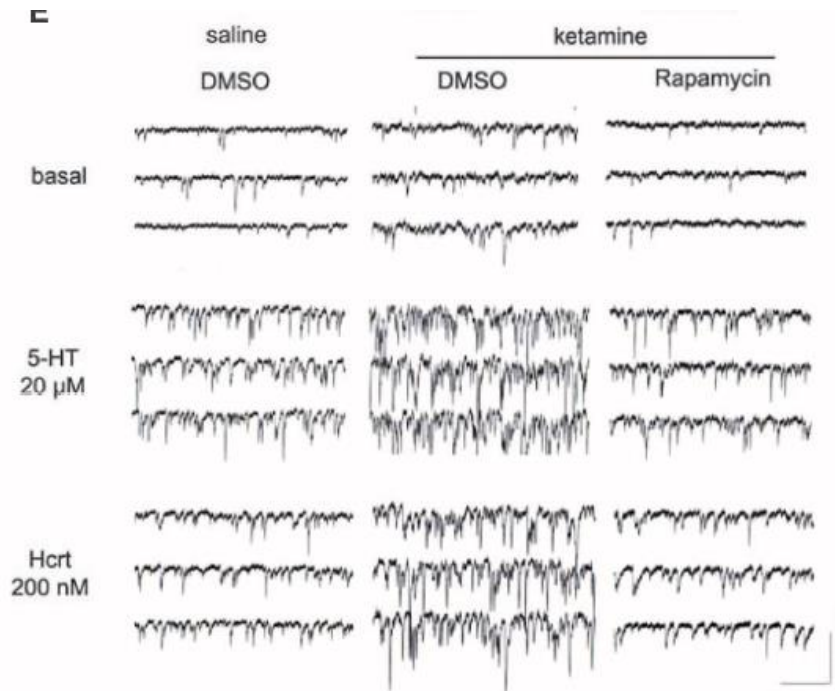
Nanxin Li, Boyoung Lee, Rong-Jian Liu, Mounira Banasr, Jason M. Dwyer, Masaaki Iwata, Xiao-Yuan Li, George Aghajanian, Ronald S. Duman*

The rapid antidepressant response after ketamine administration in treatment-resistant depressed patients suggests a possible new approach for treating mood disorders compared to the weeks or months required for standard medications. However, the mechanisms underlying this action of ketamine [a glutamate N-methyl-D-aspartic acid (NMDA) receptor antagonist] have not been identified. We observed that ketamine rapidly activated the mammalian target of rapamycin (mTOR) pathway, leading to increased synaptic signaling proteins and increased number and function of new spine synapses in the prefrontal cortex of rats. Moreover, blockade of mTOR signaling completely blocked ketamine induction of synaptogenesis and behavioral responses in models of depression. Our results demonstrate that these effects of ketamine are opposite to the synaptic deficits that result from exposure to stress and could contribute to the fast antidepressant actions of ketamine.

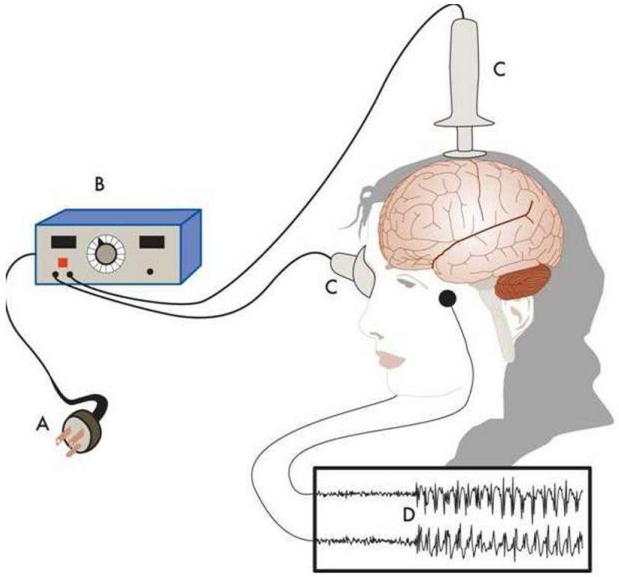
frequency of 5-HT– and hypocretin-induced EPSCs







Genetic and neurobiological factors associated with treatment response to ECT in affective disorders



- Neuroanatomical (MRI, fMRI)
- Genetic (gene expression)
- Neuropsychological (cognition)
- Biomarker (neuroendocrine)

- The rate of ECT response is 60% among patients with medication failure
- The mechanism of action remains poorly understood: targeting neurotransmitter, neuroendocrine dysregulation, molecular level.