Making the Invisible Visible
Biomarkers in Brain Disorders

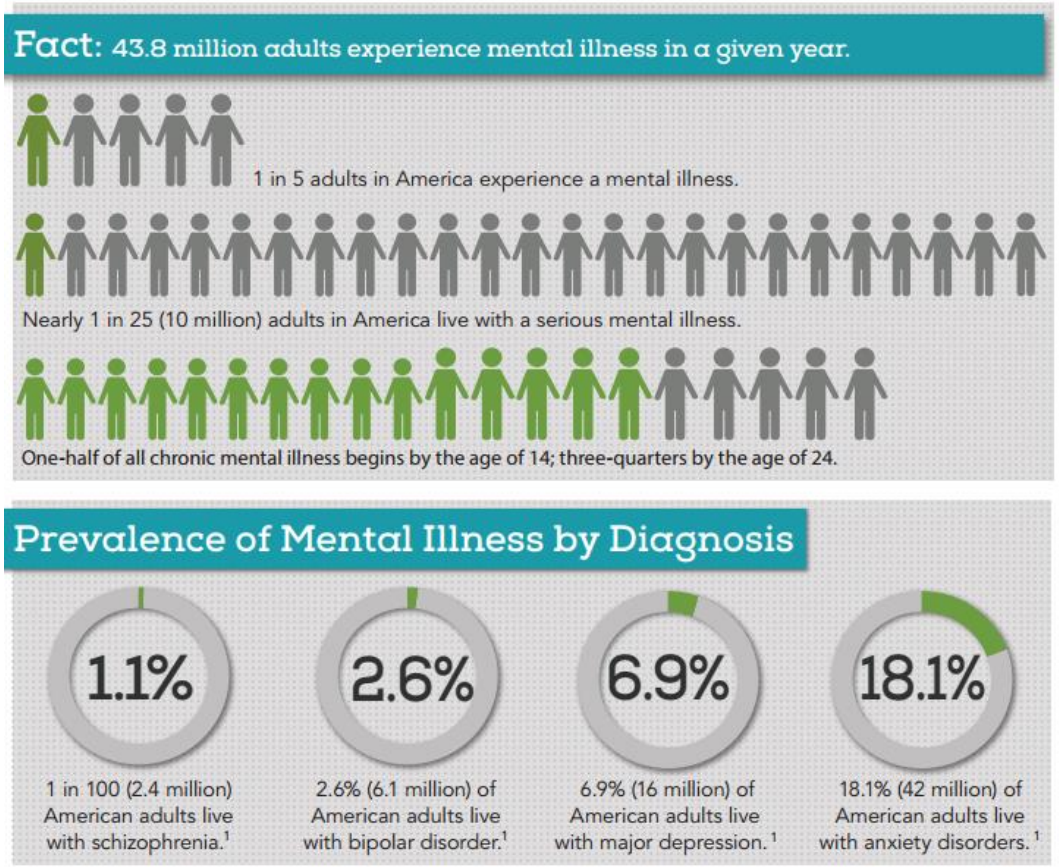
Jay Lombard DO

Continuing Medical Education Commercial Disclosure Requirement

I, Dr. Jay Lombard, have the following commercial relationships to disclose:

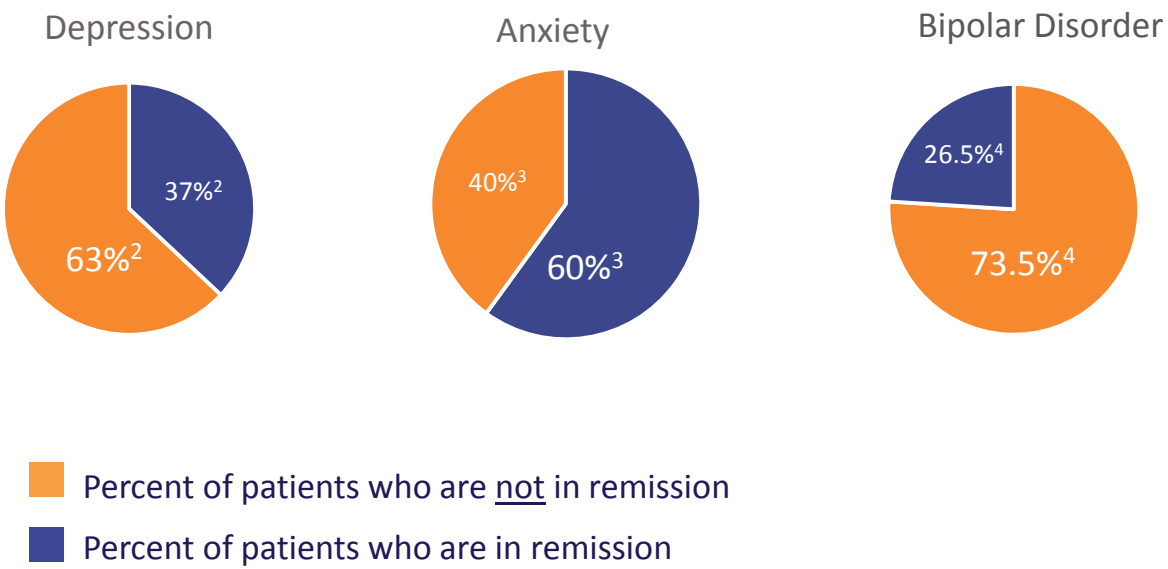
- Neurologist and Chief Scientific Officer of Genomind, Inc.

Mental Health Facts



[1] Mental Health By the Numbers. (n.d.). Retrieved May 10, 2016, from https://www.nami.org/Learn-More/Mental-Health-By-the-Numbers

Treatment Resistance in Psychiatry



[2] Warden, D et al (2007). The STAR*D project results: A comprehensive review of findings. *Current Psychiatry Reports Curr Psychiatry Rep, 9(6), 449-459. (n=2876)* – Percentages are evaluated by QIDS-SR16 after first treatment trial with citalopram

[3] Bruce, SE et al. (2005). Influence of Psychiatric Comorbidity on Recovery and Recurrence in Generalized Anxiety Disorder, Social phobia and Panic Disorder: 12 year prospective study. *Am J Psychiatry*, 162(2), 1179-87. *(n=179)* – Probability of full GAD recovery after 12 years.

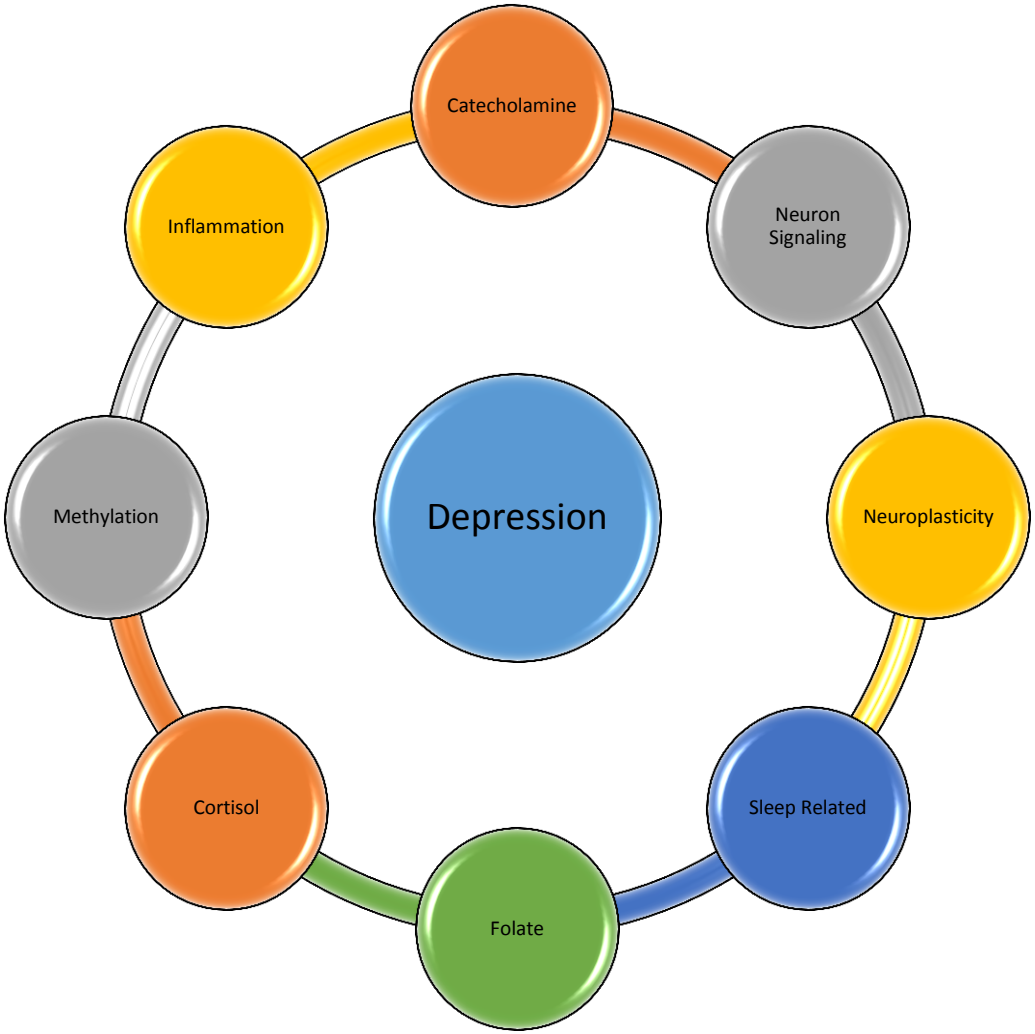
4] Perlis, RH et al. (2006). Predictors of Recurrence in Bipolar Disorder: Primary Outcomes From the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD). *Am J Psychiatry*, 163, 217-224. *(n=2000)* – Percentages are based on symptomology at study entry

Mental Health Care in the Pre-Genomic Era

Moving From DSM V to Psychiatric Neurobiological Disease Models: A Better Approach to Treatment

DSM V:

- Treat patient based on discrete categories
- Real world patients don't fall into buckets
- Real world diagnoses are fuzzy at the borders



Data on file. Genomind 2016

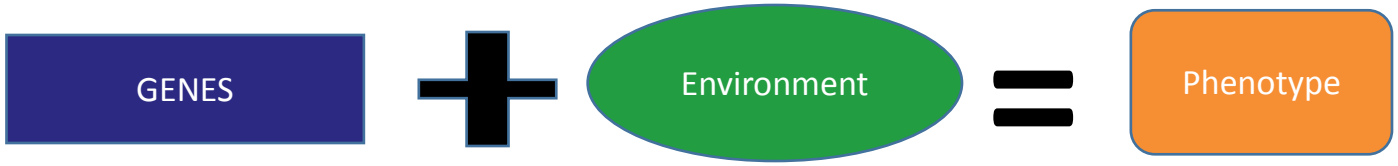
18 Gene Panel

Genes	Implications for choice of therapy
Pharmacodynamic genes	
Serotonin Transporter (SLC6A4)	Alerts for potential poor response/adverse reactions **SSRIs**; prompts consideration for **SNRIs**, and **TCAs**
Calcium Channel (CACNA1C)	Prompts consideration for **atypical antipsychotics**, **mood stabilizers**, and/or **omega-3 fatty acids**
Sodium Channel (ANK3)	Prompts consideration for **mood stabilizers** and/or **omega 3 fatty acids**
Serotonin Receptor 2C (5HT2C)	Alerts caution for weight gain with **atypical antipsychotics** and prompts consideration for **inositol** to mitigate this effect
Melanocortin 4 Receptor (MC4R)	Alerts caution for excessive weight gain with **atypical antipsychotics**
Dopamine Receptor (DRD2)	Alerts caution with **typical and atypical antipsychotics**
Catechol-O-Methyl Transferase (COMT)	Prompts consideration or alerts caution for **dopaminergic agents**
Alpha-2A Adrenergic Receptor (ADRA2A)	Prompts consideration for **stimulant agents**
Methylenetrahydrofolate Reductase (MTHFR)	Prompts consideration for **L-methylfolate** supplementation
Brain Derived Neurotrophic Factor (BDNF)	Identifies patients particularly likely to benefit from increased **physical activity/exercise**
μ–Opioid Receptor (OPRM1)	Alerts caution with **opioid** analgesics and prompts consideration non-opioid analgesics
Glutamate Receptor (GRIK1)	Prompts consideration of **topiramate** for alcohol abuse
Pharmacokinetic genes	
CYP1A2, CYP2B6, CYP2C9, CYP2C19, CYP2D6, CYP3A4/5	Alerts caution for decreased/increased drug serum levels and inefficacy; prompts consideration for **dose adjustment**

Data on file. Genomind 2016

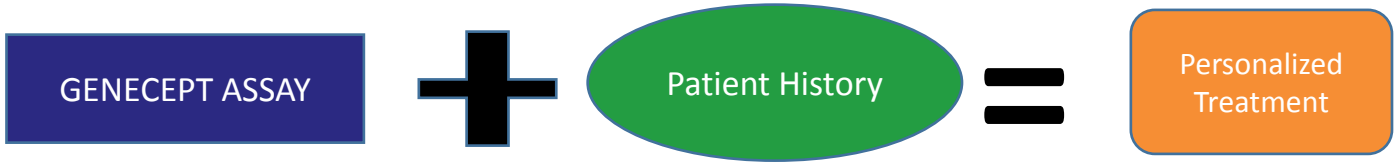
Genetics 101

Nature AND Nurture



- In psychiatry we do a good job of determining what **environmental factors** have contributed to a particular disorder

- Until now, we have not had access to a large component of our phenotype…..**genetic factors**



Bay et al 2011

Gene/Environment Interaction

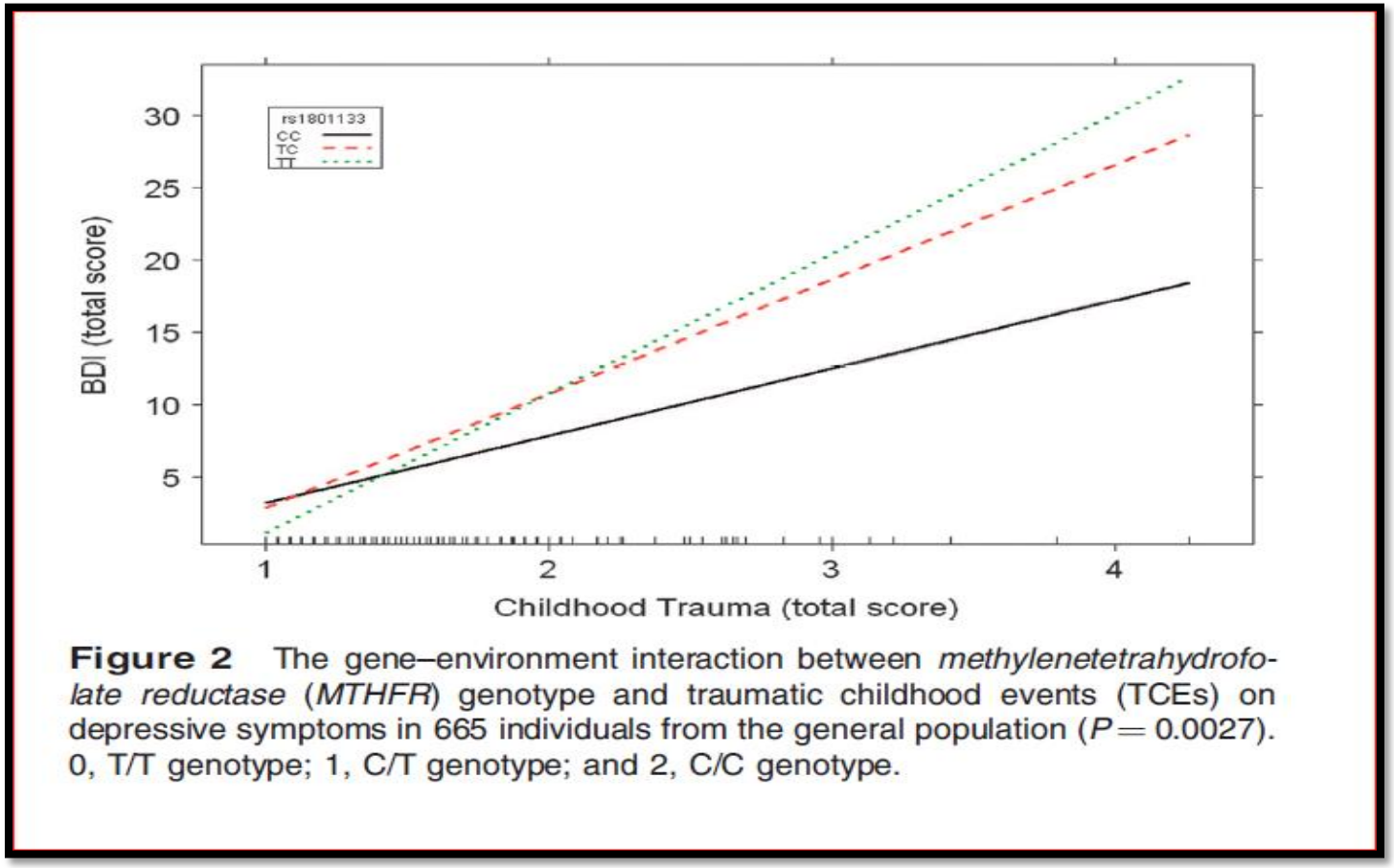


Figure 2 The gene–environment interaction between *methylenetetrahydrofolate reductase* (*MTHFR*) genotype and traumatic childhood events (TCEs) on depressive symptoms in 665 individuals from the general population ($P = 0.0027$). 0, T/T genotype; 1, C/T genotype; and 2, C/C genotype.

- Depression scores (BDI) increase with increased childhood trauma
- MTHFR genetic risk amplifies these effects

Lok et al. (2013)

Pharmacokinetic (PK) CYP450 Variations Mediate Drug Response

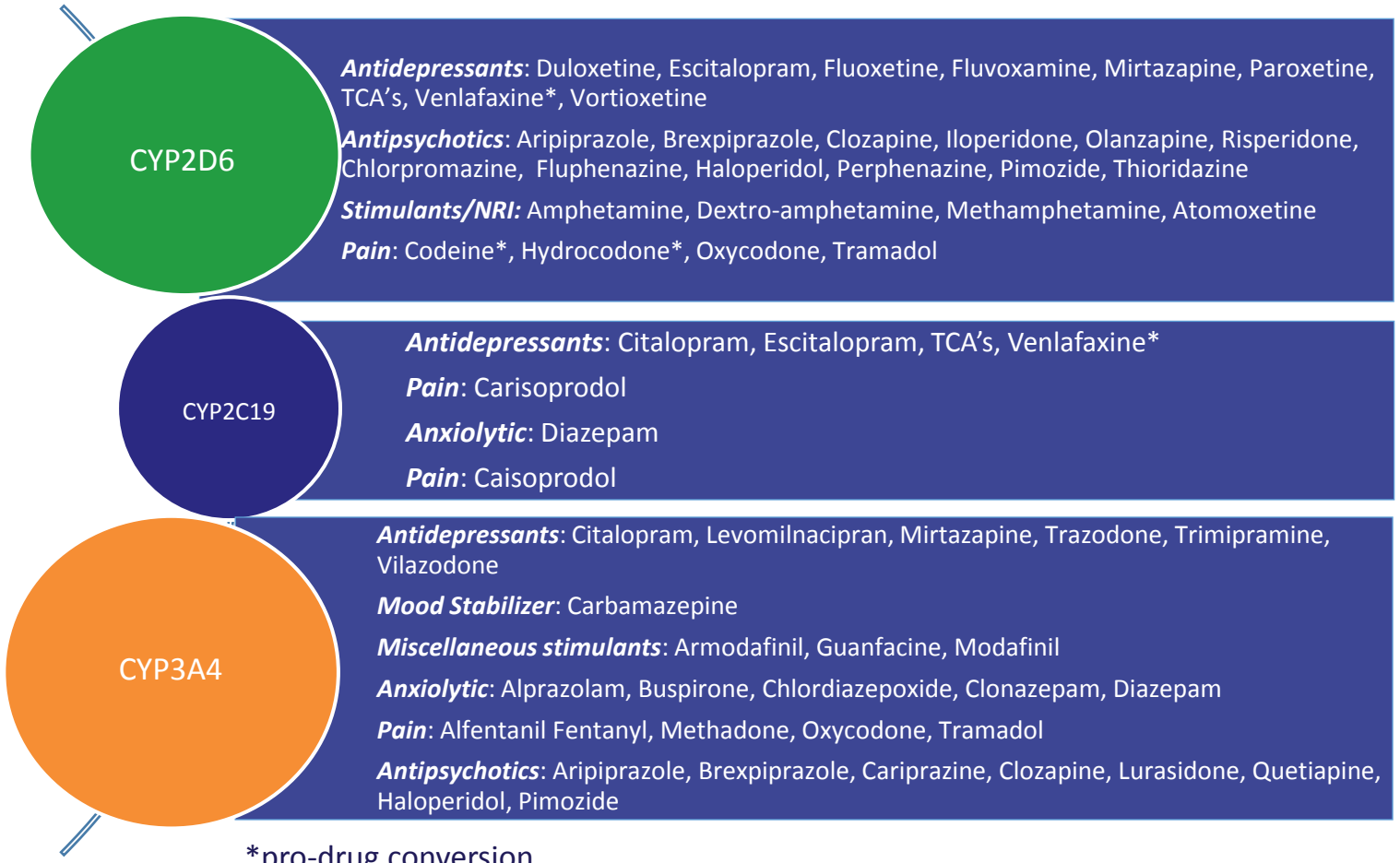
- Gene variants associated with altered liver enzyme **metabolism** activity may lead to ***side effects and toxicity***

PM	**Poor metabolizers or inhibitors** of P450 may have increased drug serum levels and adverse events.
IM	**Intermediate metabolizers or inhibitors** of P450 may have increased drug serum levels and adverse events.
EM	**Extensive metabolizers** metabolize substrates normally.
UM	**Ultra-rapid metabolizers or inducers** of P450 may have reduced drug serum levels and poor efficacy.

FDA warning (Aug 2011): Citalopram **maximum dose of 20mg in CYP2C19 poor metabolizers** and those receiving CYP2C19 inhibitors

Swen et al 2011; http://www.fda.gov/; http://www.fda.gov/Drugs/ScienceResearch/ResearchAreas/Pharmacogenetics/ucm083378.htm

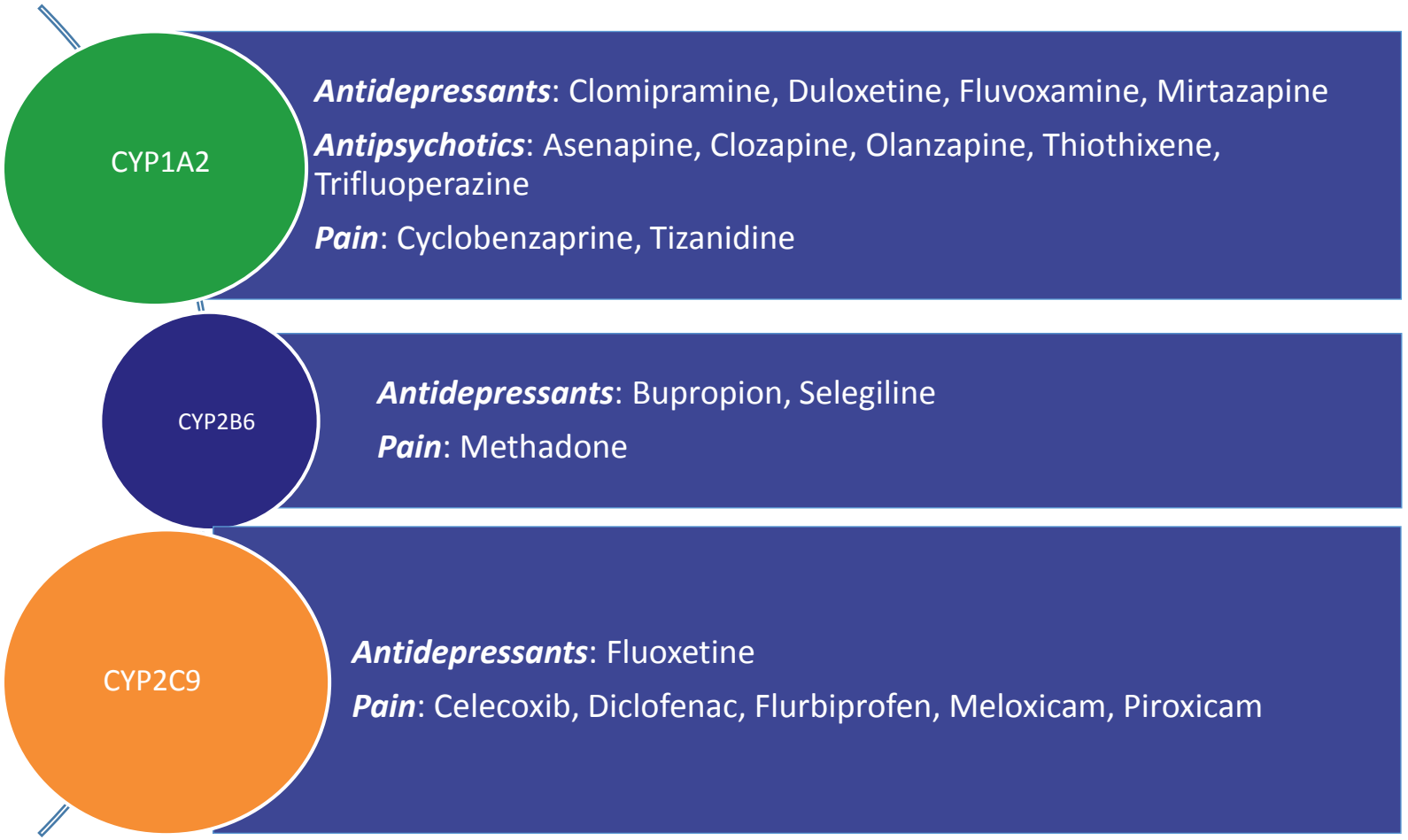
Major Psychotropic Substrates



*pro-drug conversion

Data on file. Genomind 2016

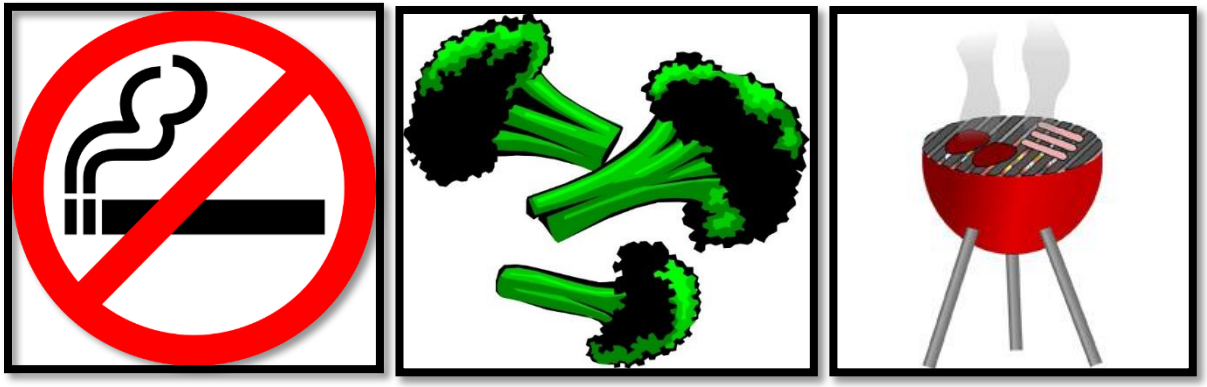
Major Psychotropic Substrates



Data on file. Genomind 2016.

Environmental Induction of CYP Genes

- CYP1A2 is highly induced by certain environmental factors
  - Tobacco smoke: CYP1A2 levels will be increased with smokers
  - Cruciferous vegetables: broccoli, cauliflower, cabbage consumption will increase CYP1A2 levels
  - Char-grilled meats: consumption of char-grilled meats will increase CYP1A2 levels



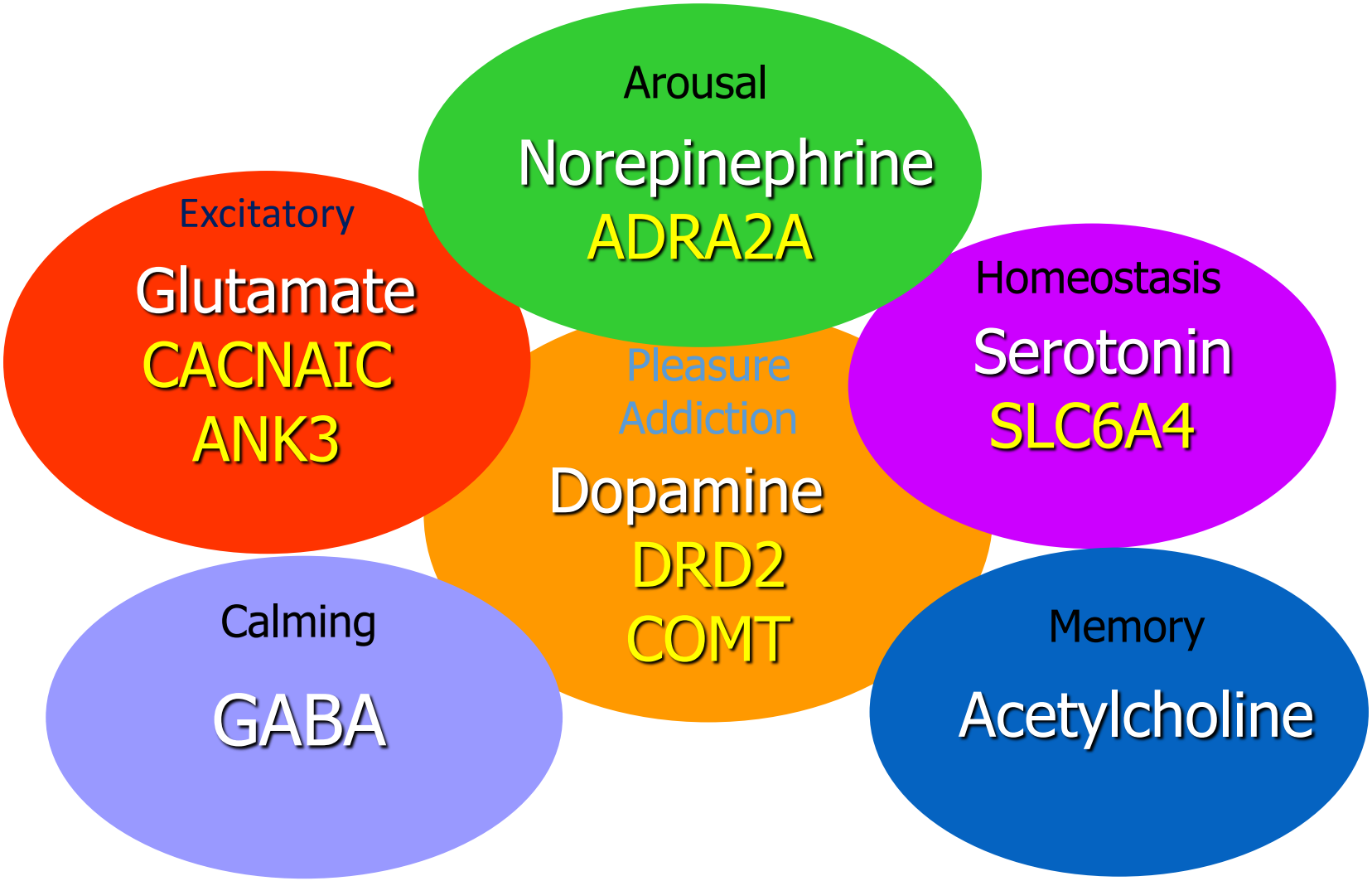
Zhou SF et al 2009; Browning SL et al 2010; 137. Gunes A and Dahl ML 2008

Herbal Interactions And CYP Genes

- Rhodiola is a CYP3A4 inhibitor (Pharmazie Dec 2013)
- Fennel is an inhibitor of CYP1A2, 2D6, and 3A4 (Phytomedicine Research April 2014)
- Kale is an inhibitor of CYP3A4, 2D6, and 2C19 and an inducer of CYP1A2 (Biomedical Research 2012)
- Goldenseal is a CYP2D6 inhibitor (Mol. Nutritional Food Research July, 2008)
- St Johns Wort is a CYP3A4 Inducer and CYP2D6 inhibitor (Effect of St John's wort on drug metabolism by induction of cytochrome P450 3A4 enzyme. JAMA. 2003 Sep 17;290(11):1500-4.)

Mohammad-Zadeh et al 2008

Pharmacodynamic (PD) Genes affect Neurotransmitters and Behavior

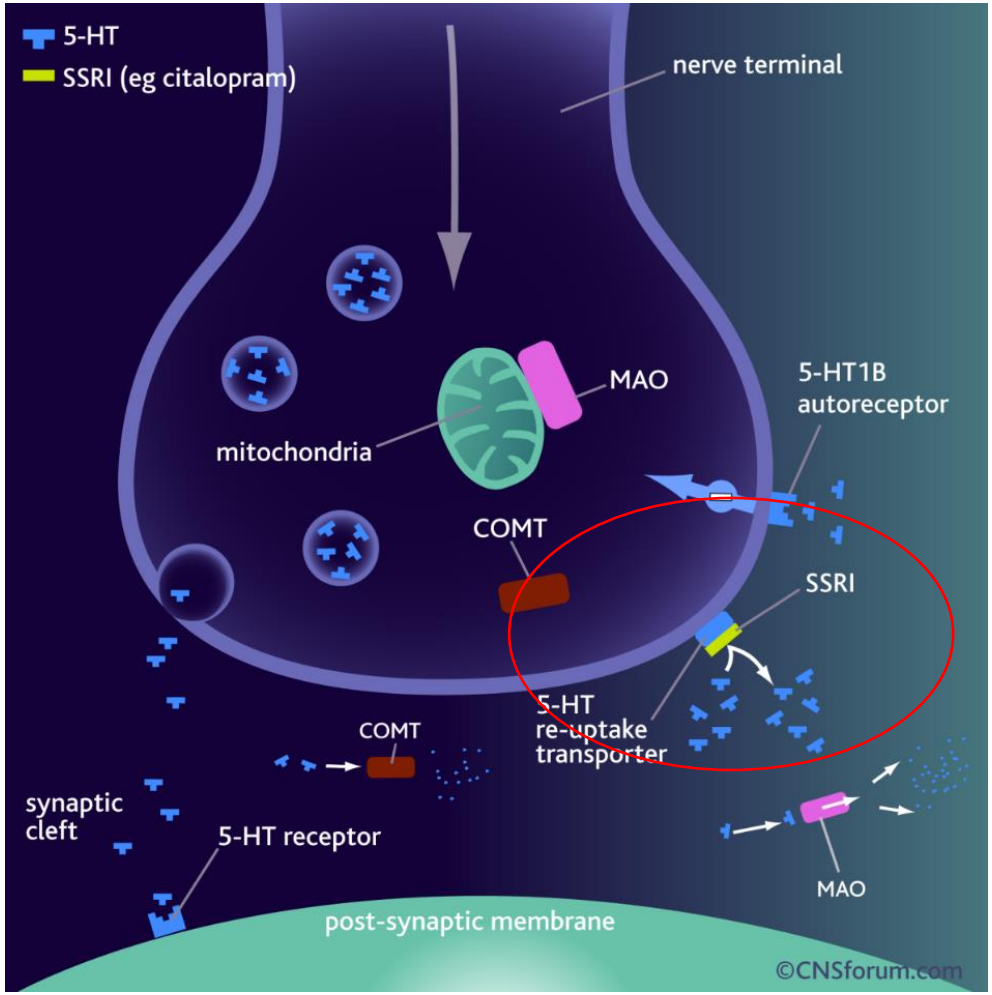


Brown and Mann 1985

Serotonin Imbalance: Core Symptoms

- Disruption in homeostasis
- Reduced appetite
- Anxiety
- Hypervigilance
- Depression
- Sleep Disorders

Serotonin Transporter (SLC6A4)



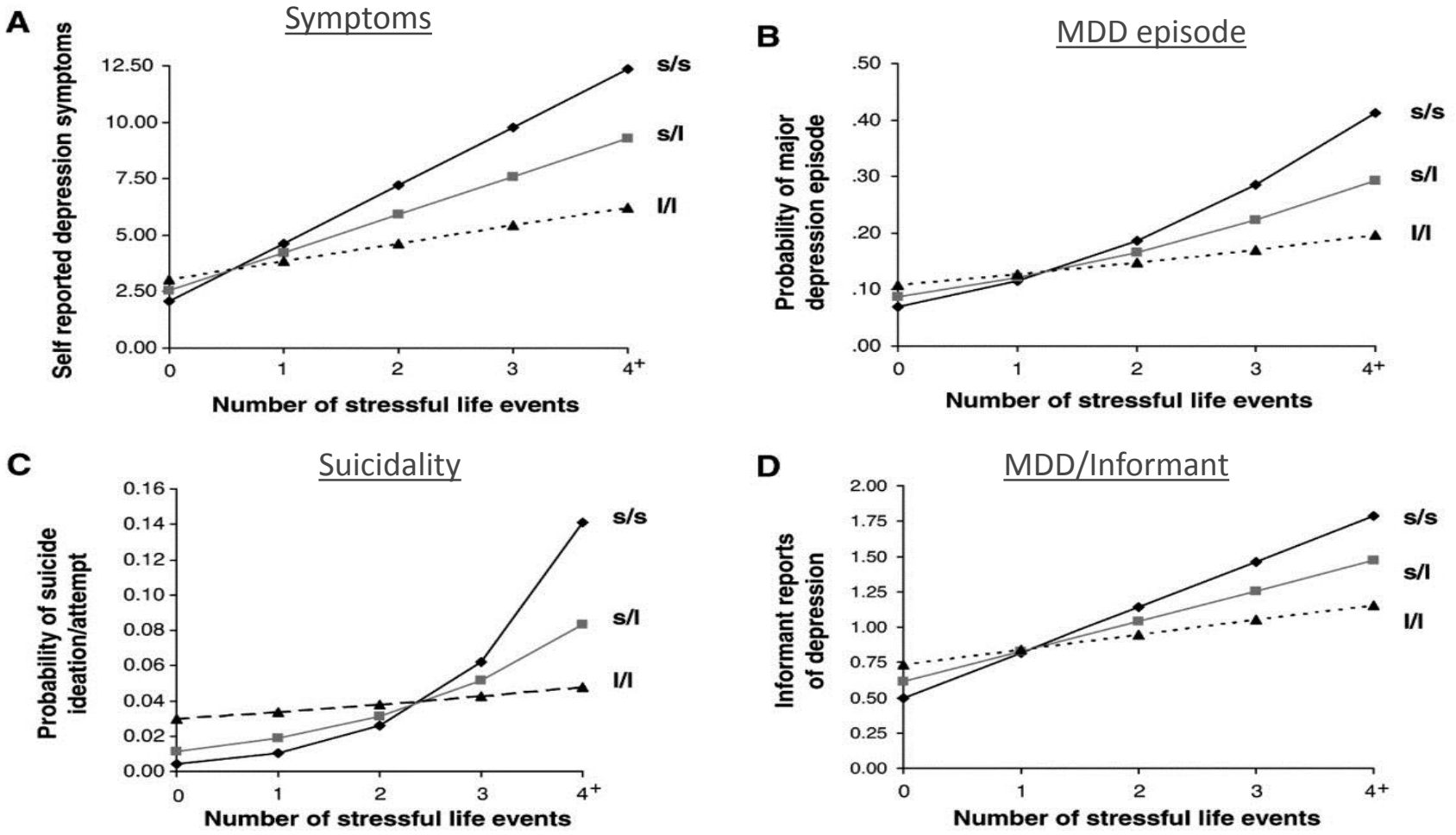
- **SLC6A4** is reported as L(A) (normal) or L(G) or S (risk)
- Patients carrying the S or L(G) allele are at *higher risk for side effects and lack of response to SSRIs*
- Altered cortisol response

Clinical Impact:

- Caution with SSRIs
- Therapeutic Options: SNRIs and Atypical Antidepressants

www.pharmgkb.org/pathway/PA161749006; Kato M and Serretti A 2010; Porcelli 2012

SLC6A4 Genotype X Stressful Life Events & Depression



Caspi et al., 2003: Science 301:386-9.

Excess Cortisol and Depression

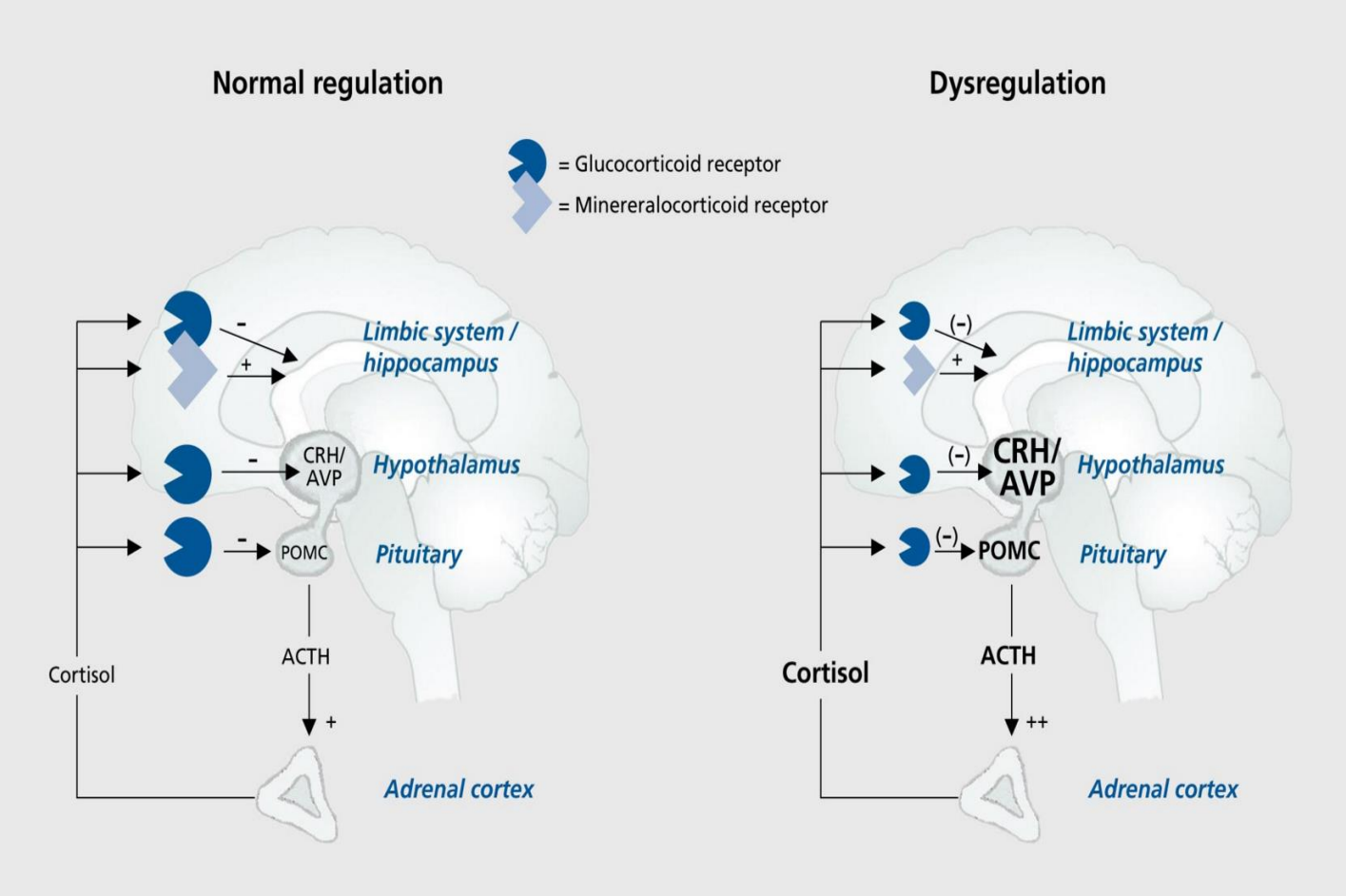
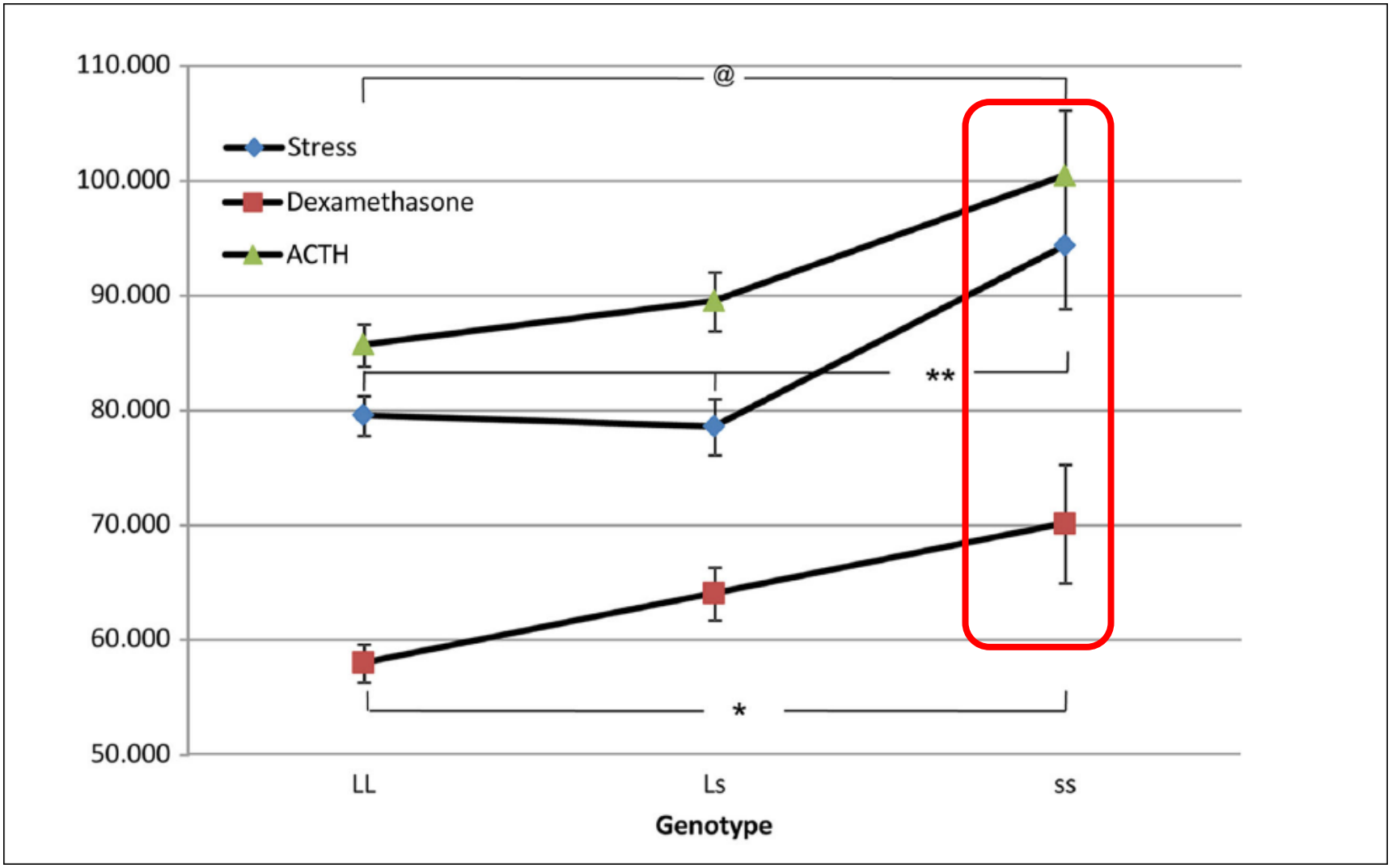


Figure. Model for normal and impaired regulation of the HPA axis. HPA, hypothalamic-pituitary-adrenocortical; CRH, corticotropin-releasing hormone; AVP, arginin-vasopressin; POMC, pro-opiomelanocortin; ACTH, adrenocorticotropic hormone

Ising M, 2006: *Dialogues in Clinical Neuroscience* 8: 433-444

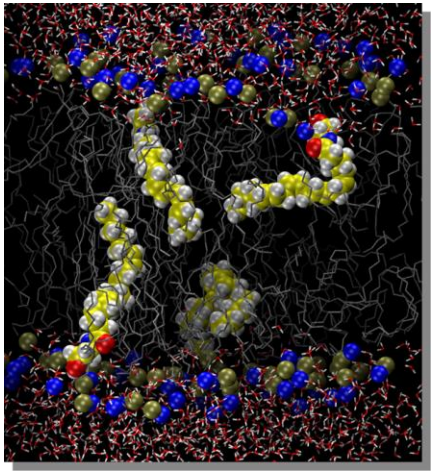
SLC6A4 “S” allele modulates cortisol



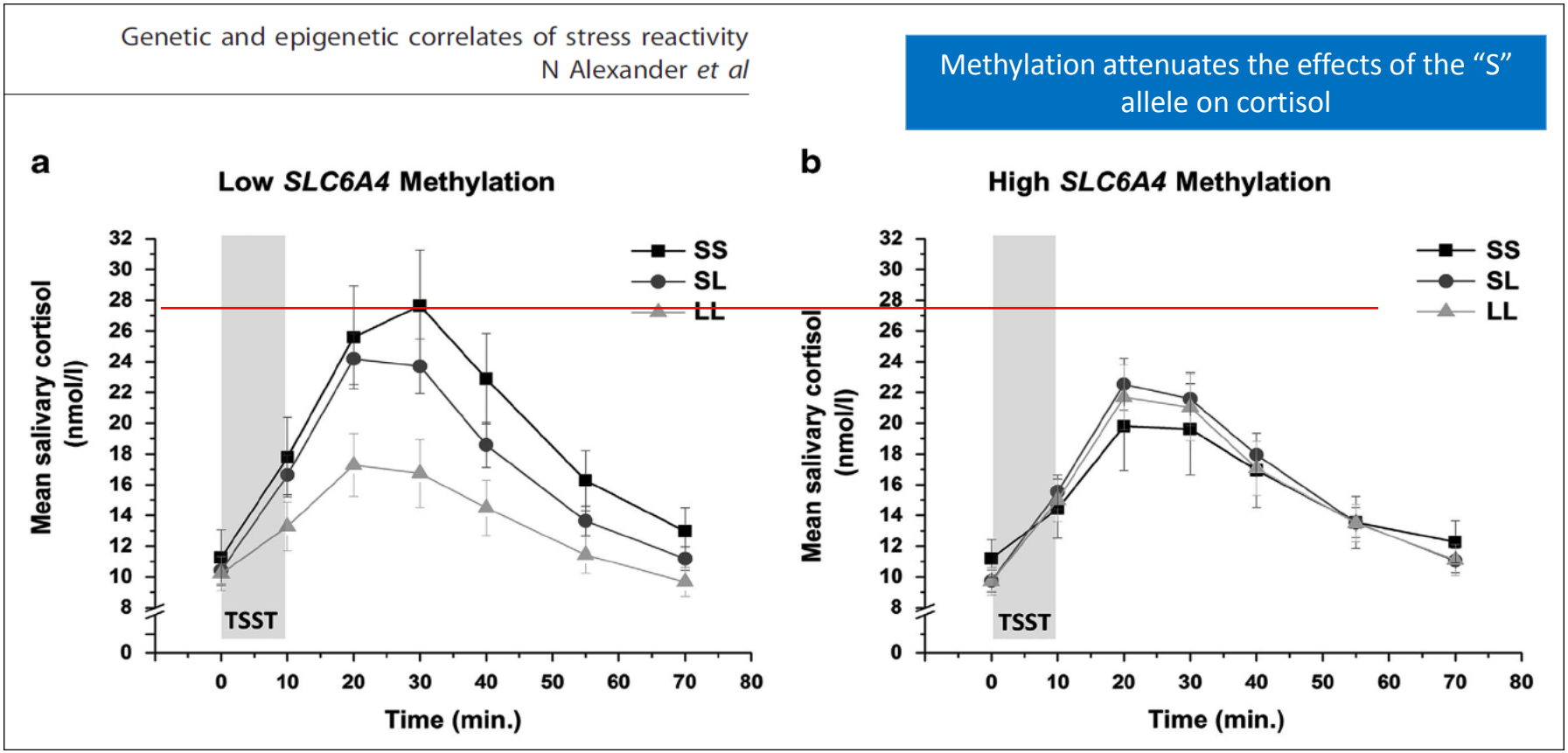
Serotonin transporter genotype modulates HPA axis output during stress: effect of stress, dexamethasone test and ACTH challenge. A Sorenson1 et al Transl Dev Psychiatry. ; 1: 21130

Cortisol regulators

- Omega 3 EPA lowers pro inflammatory cytokines and cortisol (Noreen et al., 2010)
- Phosphatidylserine increases BDNF (Nutritional Neuroscience, March 2013) and has putative antidepressant and cognitive enhancing effects (Hellhammer et al., 2014)
- Adaptogens such as ashwaghanda root (Chandrasekhar et al., 2012).
- Tryptophan, a chemical precursor to serotonin, also reduced stress-induced increases in cortisol in S/S subjects (Capello & Markus, 2014).

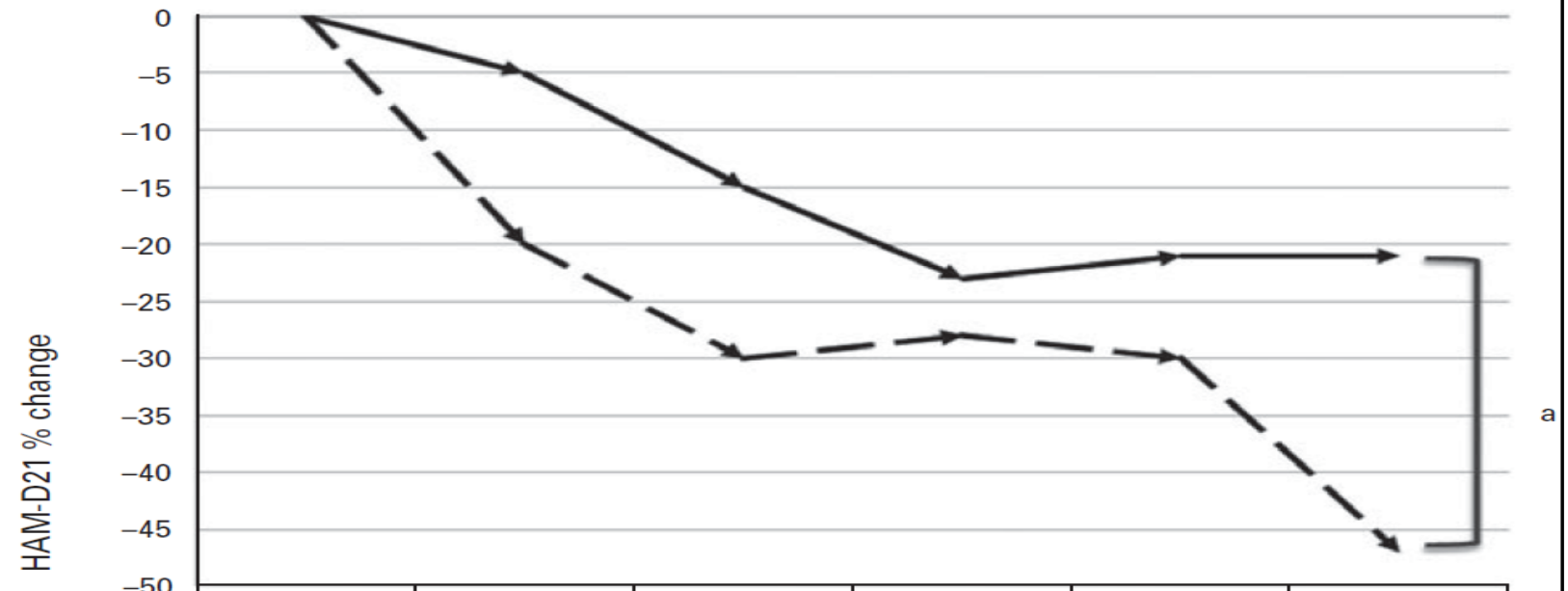


Cortisol levels and SLC6A4 gene: Methylation



Alexander et al. Citation: Transl Psychiatry (2014) 4, e443; doi:10.1038/tp.2014.88

Methylation of SLC6A4 leads to higher response rates to antidepressants



	wk1	wk2	wk3	wk4	wk5	wk6
Methylation high	0	–20	–30	–28	–30	–47
Methylation low	0	–5	–15	–23	–21	–21

[a] p=0.005 after 6 wk

Serotonin transporter gene hypomethylation predicts impaired antidepressant treatment response
Katharina Domschke1, Nicola Tidow2, Kathrin Schwarte2, Jürgen Deckert1, Klaus-Peter Lesch3, Volker Arolt2, Peter Zwanzger2 and Bernhard T. Baune4. International Journal of Neuropsychopharmacology (2014), 17, 1167–1176

Imbalance of Glutamate: CACNA1C and ANK3

- Cyclical/paroxysmal disorders
- Migraines
- Epilepsy
- Chronic pain
- Bipolar
- Treatment resistant depression

“5 Disorders Share Genetic Risk Factors, Study Finds”

The New York Times

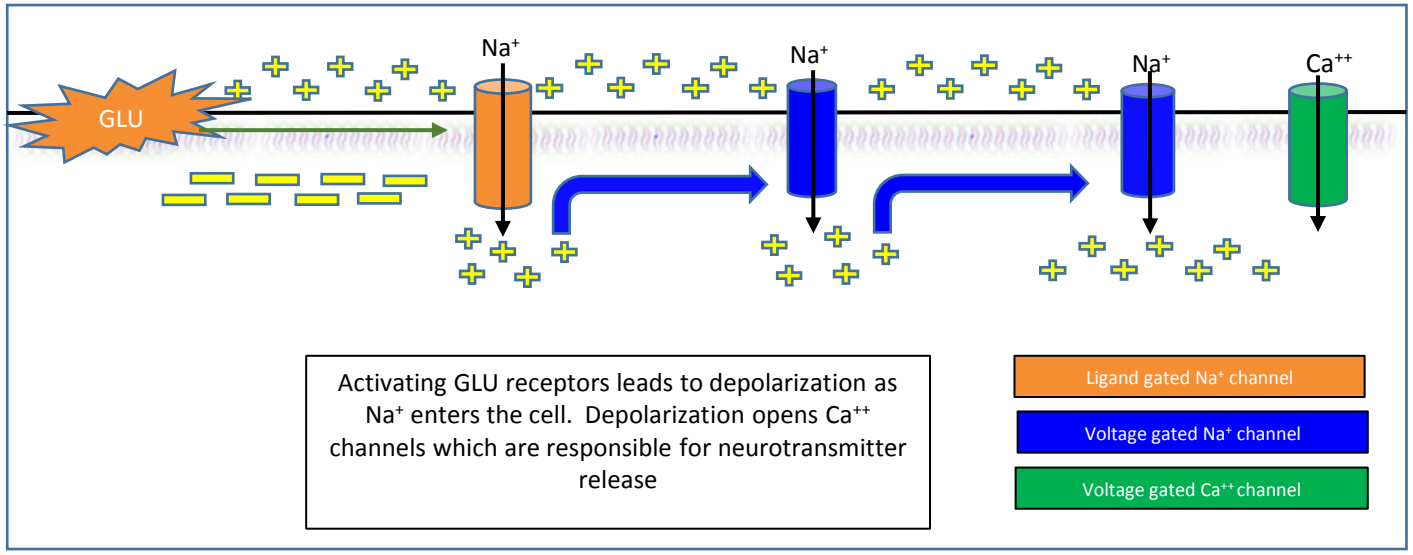
“Psychiatric illnesses seem very different — schizophrenia, bipolar disorder, autism, major depression and attention deficit hyperactivity disorder…Yet they all involve genes that are part of calcium channels, which are used when neurons send signals to the brain.”

“Findings strengthen an emerging view of mental illness that aims to make diagnoses based on genetic aberrations in CACNA1C variants”

The identification of calcium channel variations are “relevant to the goal of moving beyond descriptive symptoms and towards treatments informed by disease cause”

Kolata, G., February 28, 2013, 5 Disorders Share Genetic Risk Factors, Study Finds. New York Times, A11

Ion Channels in the Brain and Psychiatric Disorders

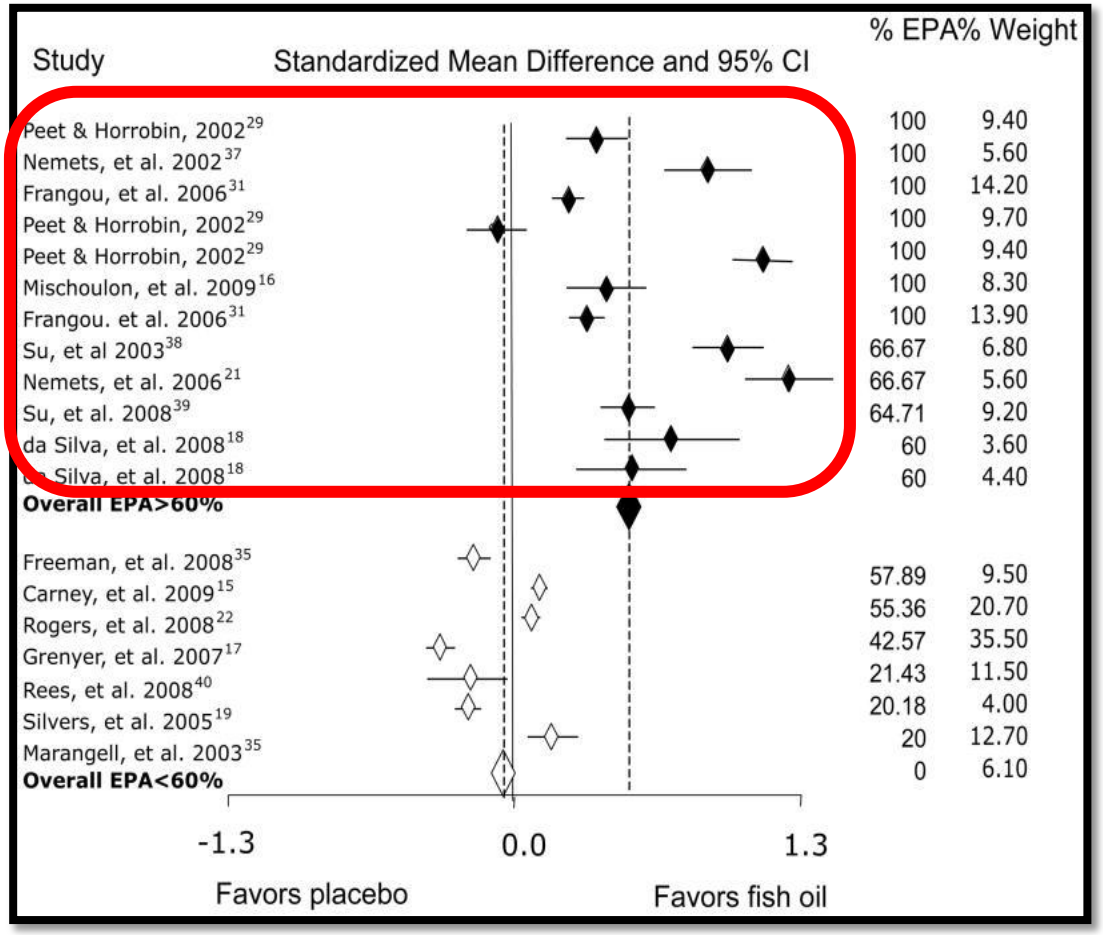


- Homozygotes of the ANK3 'T' allele or CACNA1C 'A' allele are at higher risk of altered neuronal signaling
- ***Clinical Impact***: therapeutic options include agents that reduce neuronal signaling such as mood stabilizers, atypical antipsychotics, omega 3 fatty acids

Ferreira et al., 2008

Omega 3 Meta Analysis for depression

- Omega 3 fatty acids stabilize these channels
- Anti depressant effect
  - Evidence for EPA/DHA in major depressive episodes
    - Meta analysis – 15 randomised, double blind, placebo controlled trials (916 patients) at doses up to 2200mg EPA/DHA per day concluded effective for mood disorders



Sublette, et al. Journal of Clinical Psychiatry, December: 1577-84

NAC In Psychiatry

Evidence Base for Monotherapy or Augmentative Treatment - Multiple Studies Show Success.

- Schizophrenia(SZ)
- Bipolar Disorder(BD)
- Trichotillomania
- Nail biting
- Substance Abuse

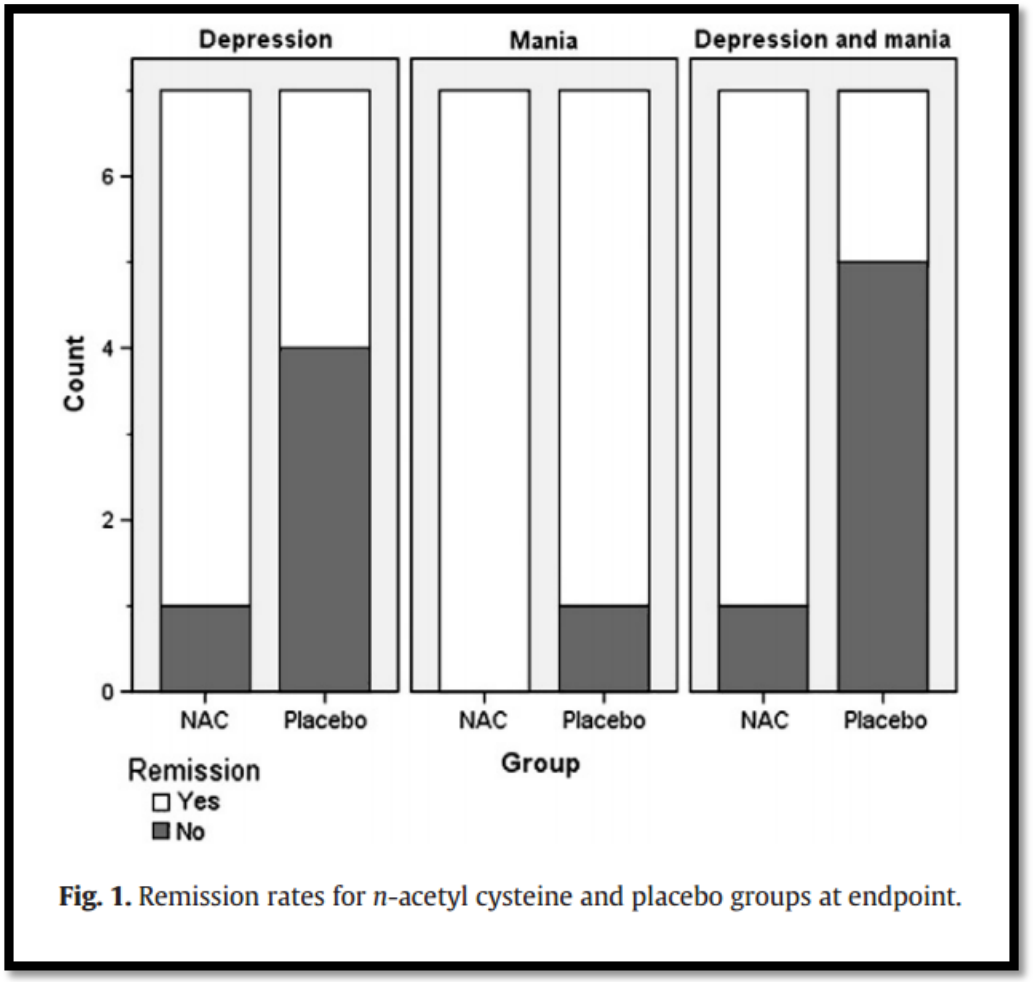
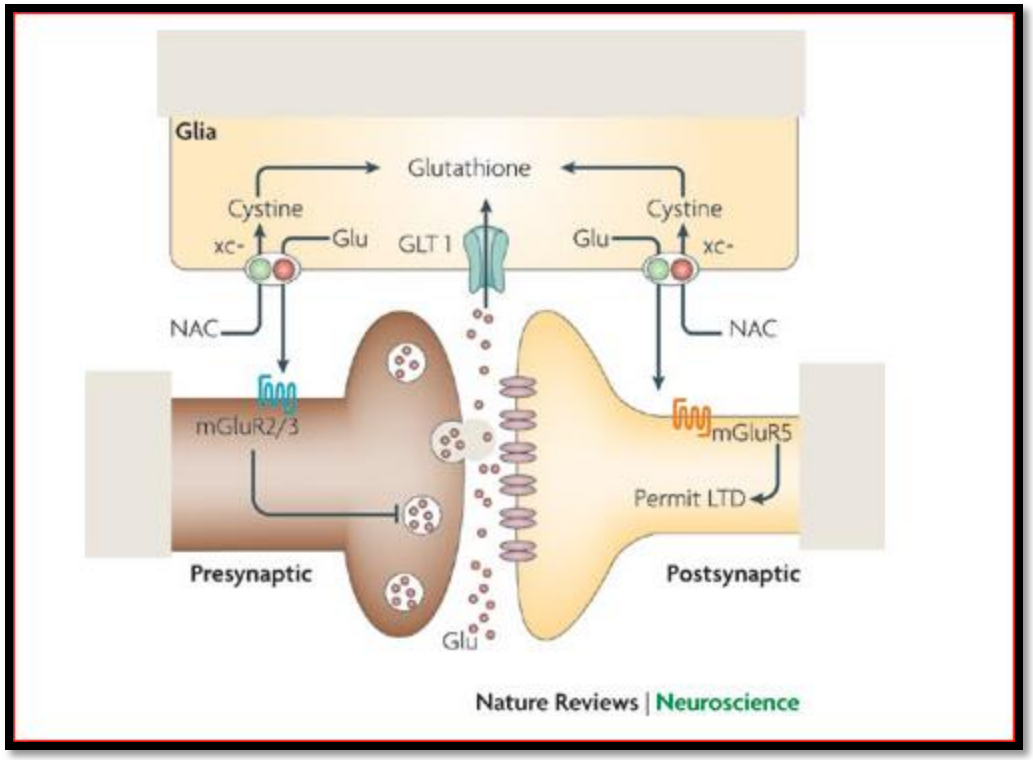


Fig. 1. Remission rates for *n*-acetyl cysteine and placebo groups at endpoint.

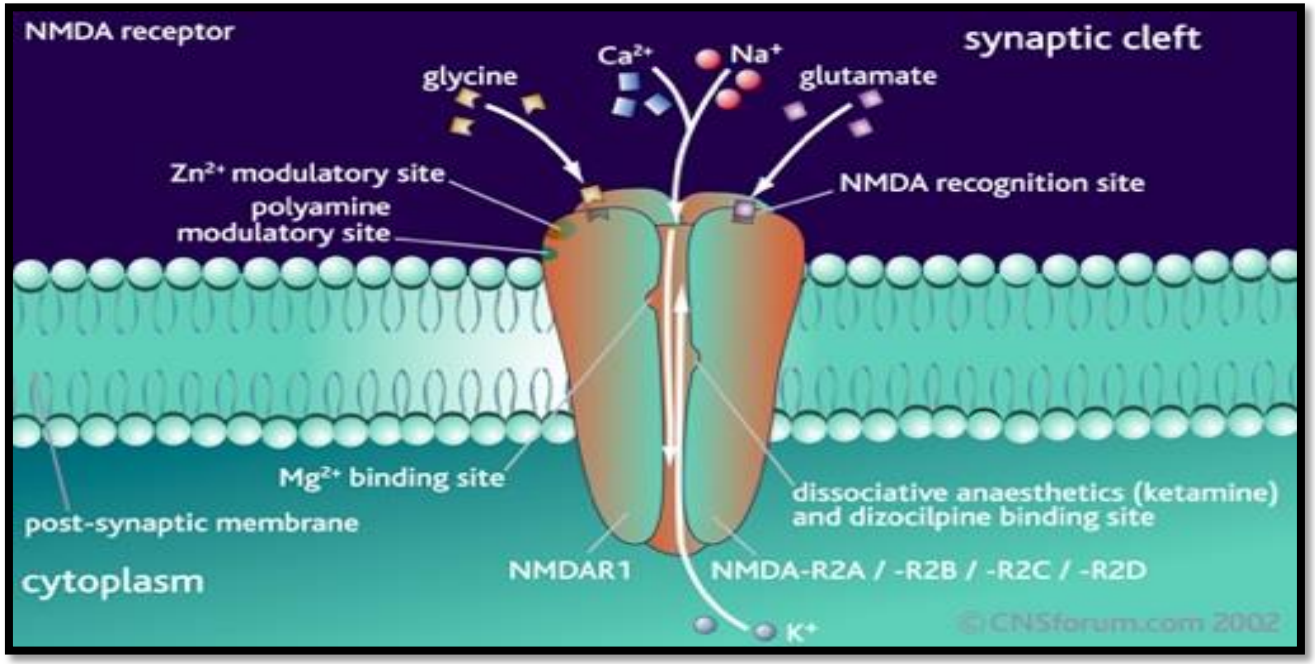
P.V. Magalhães et al. / Journal of Affective Disorders 129 (2011) 317–320 Dean, O et al, "N-Acetylcysteine in Psychiatry: Current Therapeutic Evidence and Potential Mechanisms of Action" J Psychiatry Neurosci. 2011 Mar; 36(2): 78–86

N-acetylcysteine mechanism of action

- **NAC lowers Glutamate** through Cysteine-Glutamate antiporter (trades out)
- **NAC increases glutathione**
- Cysteine + glutamate + glycine =
  - Glutathione
- Glutathione is potent CNS antioxidant
- **NAC Increases dopamine (DA)** release
- DA Mediates Reward, Reinforcement, and Relapse



Magnesium and Calcium Channels

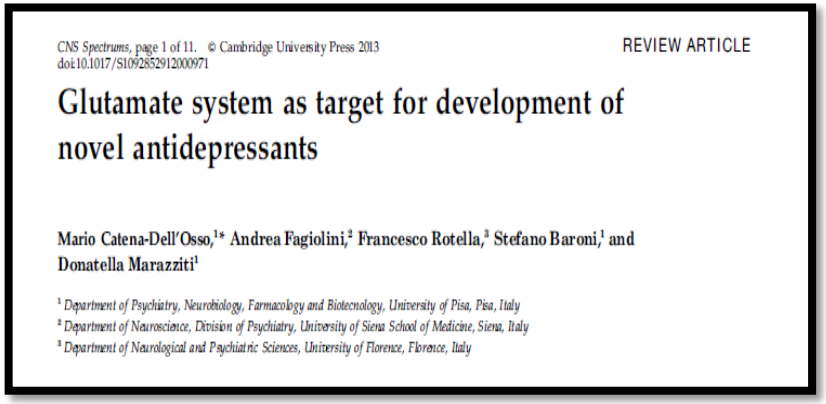


Magnesium is a natural Ca^{++} channel antagonist and data indicates that magnesium can block excitatory signaling (Shimosawa et al., 2004)

- There is an inverse relationship between $Mg2^{+}$ and anxiety
- A dysregulated HPA axis may contribute to hyper-emotionality in $Mg2^{+}$ deficient patients

Sartori et. al."Magnesium Deficiency Induces Anxiety and HPA Axis Dysregulation: Modulation by Therapeutic Drug Treatment," Neuropharmacology. 2012 Jan; 62(1): 304–312. http://www.purelabvitamins.com/Magnesium-Research.php

Targeting Glutamate



CNS Spectrums, page 1 of 11. © Cambridge University Press 2013
doi:10.1017/S1092852912000971

REVIEW ARTICLE

Glutamate system as target for development of novel antidepressants

Mario Catena-Dell'Osso,[1]* Andrea Fagiolini,[2] Francesco Rotella,[3] Stefano Baroni,[1] and Donatella Marazziti[1]

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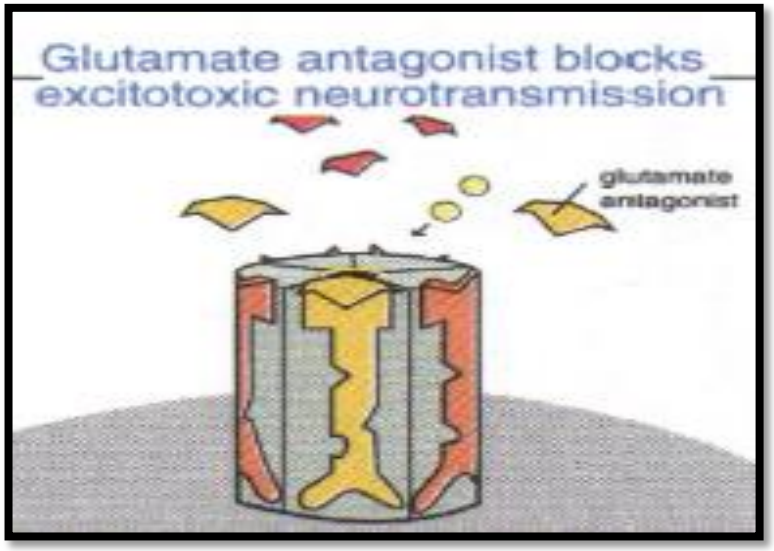
[2] Department of Neuroscience, Division of Psychiatry, University of Siena School of Medicine, Siena, Italy
[3] Department of Neurological and Psychiatric Sciences, University of Florence, Florence, Italy

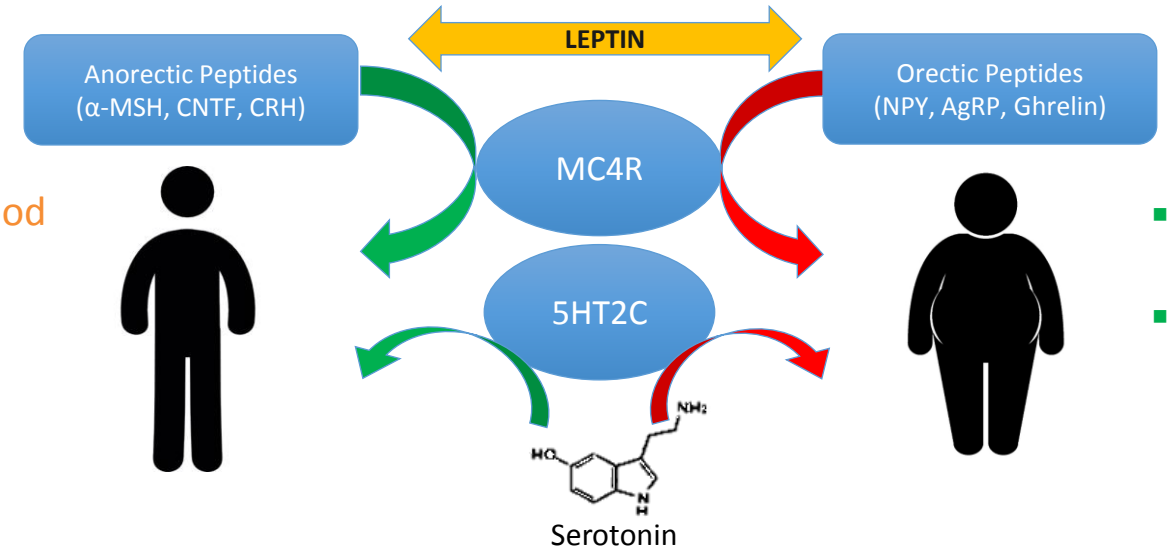


- Lamotrigine/Valproic Acid
- Nuedexta, Riluzole
- Ketamine-9 trials supporting its use
- >5 pipeline drugs NMDA antagonist class in 2011
- Omega-3s 65/35 EPA/DHA
- Mg2+
- NAC, or N-Acetylcysteine
- Progesterone
- Memantine

Stahl's Essentials of Psychopharmacology; CNS Spectrums 2013

Genetics of Atypical Antipsychotic Metabolic Effects

- The regulation of feeding behavior and energy balance is highly complex and controlled mainly in the hypothalamus
  - Serotonin signaling regulates satiety through activation of 5HT2C receptors
  - MC4R is activated by anorectic peptides to induce satiety and inhibited by orectic peptides to inhibit satiety



- Decreased food intake
- Increased energy expenditure

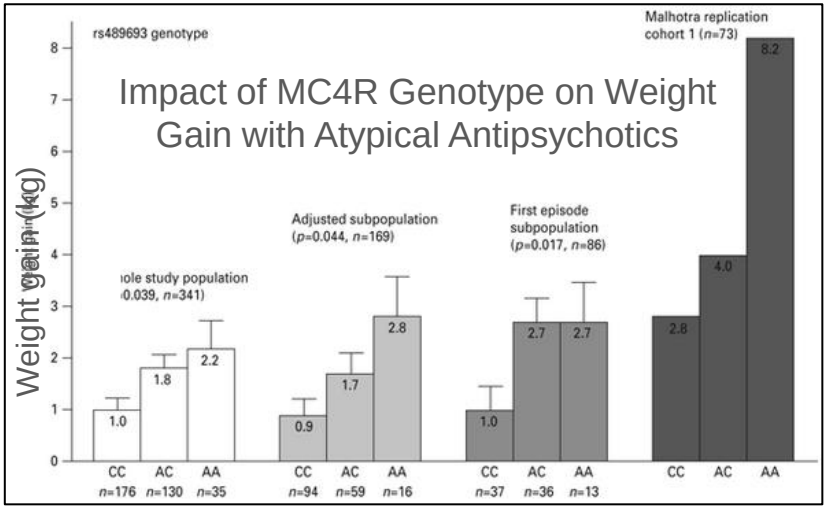
- Increased food intake
- Decreased energy expenditure

Halford JC and Harrold JA 2012; Tschritter et al 2011; Cole et al 2010; Qi, 2008

Serotonin Receptor 2C (5HT2C) & Melanocortin Receptor (MC4R)

Mutation:

- 5HT2C C allele is wildtype, however T mutation confers protective affect against weight gain
- MC4R A allele may increase risk for weight gain and higher BMI



Clinical Impact:

- Atypical antipsychotics exacerbate the risk for weight gain for A allele carriers
- Use caution with atypical antipsychotics
  - High risk medications: clozapine and olanzapine
  - Medium risk medications: aripiprazole; iloperidone; paliperidone; quetiapine; risperidone
  - Low risk medications: asenapine; brexpiprazole; cariprazine; lurasidone; ziprasidone

Sicard et al 2012; Giordano et al 2011; Gerli et al 2007; Capasso et al 2013; Malhotra et al 2012; Corell et al 2011

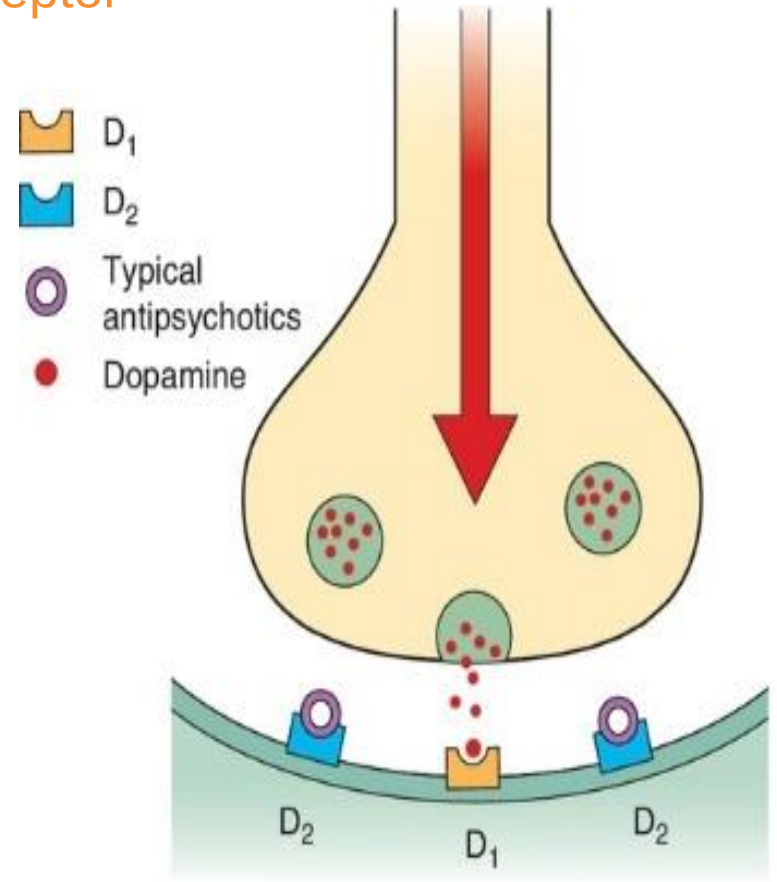
5HT2C and Inositol

- Research has indicated that insulin acts on the Serotonin Receptor 2C (5HT2C) to inhibit its activity.
  - Variations in 5HT2C and atypical antipsychotics can impede insulin signaling and lead to insulin resistance leading to increased risk for weight gain and metabolic syndrome
  - Inositol is an insulin sensitizing agent which may attenuate these effects
    - Shown to be affective at attenuating weight gain rather than dieting alone

Dopamine Receptor (DRD2)

- Antipsychotic clinical efficacy is highly correlated with the binding affinity to the Dopamine 2 Receptor
- Deletions (**DEL**) in the dopamine receptor gene can alter receptor density leading to poorer outcomes with atypical and typical antipsychotics.
- Indicates that antipsychotics are less likely to be effective and more likely to cause weight gain
- Meta analysis showed an increased risk of opiate abuse with (**DEL**) carriers

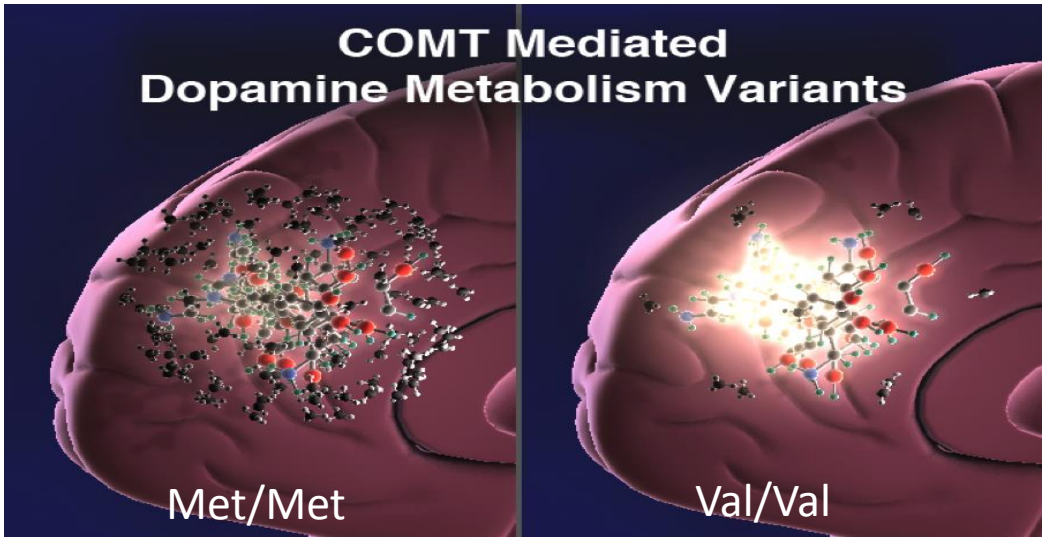
Clinical Impact: Use with caution or alternative agent



Zang et al 2010; Chen et al. (2011)

Catechol-o-methyltransferase (COMT)

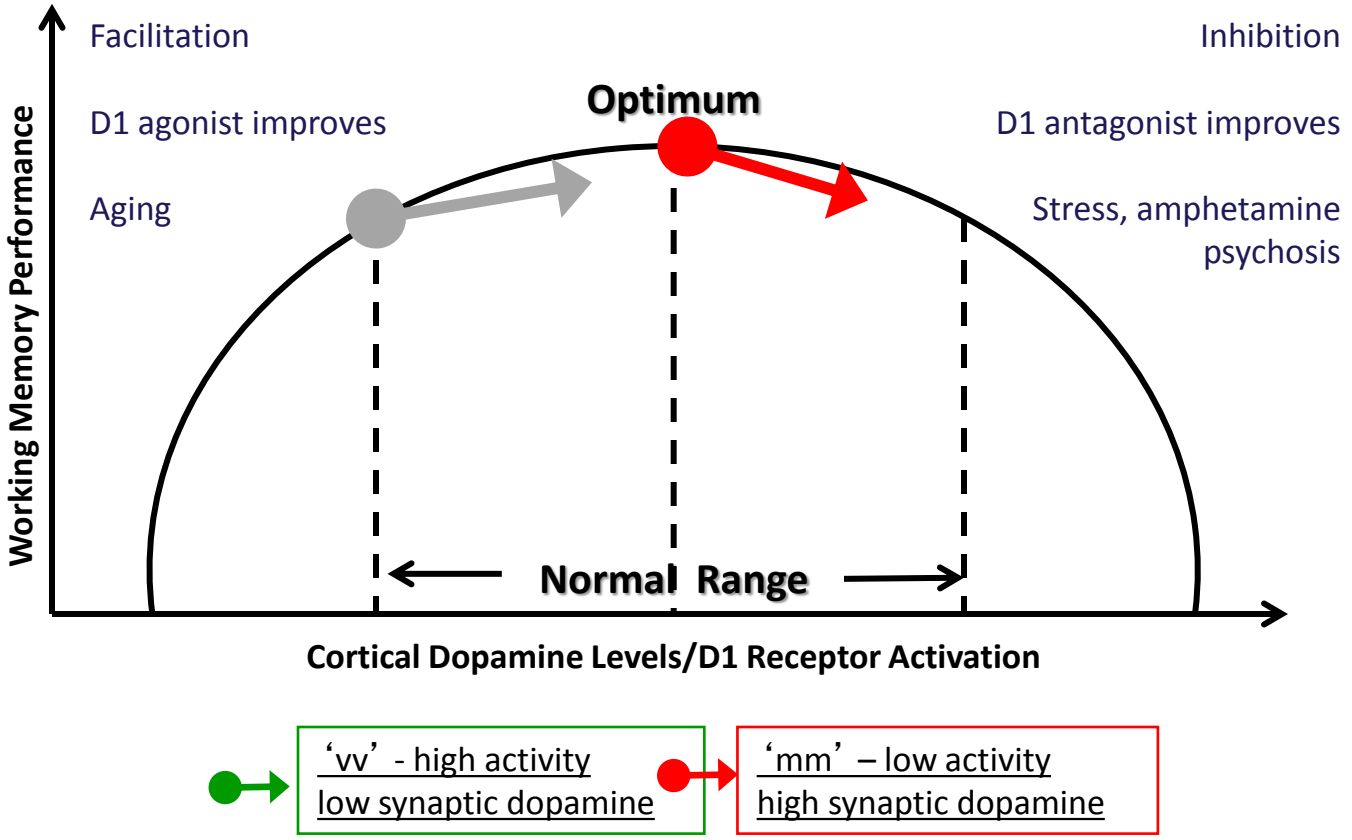
- COMT is the primary enzyme responsible for dopamine degradation in the prefrontal cortex
- COMT VAL158MET gene can identify the two extremes of dopamine metabolism



COMT Activity	DA Levels	Clinical Impact
High (Val/Val)	Low ↓	• Impaired working memory • Higher response with dopaminergic stimulants • Cognitive improvement with COMT inhibitors
Low (Met/Met)	High ↑	• Improved working memory • Lower response to dopaminergic stimulants • Improved response to SGAs

COMT graphic; Barnett et al. (2007); Hamidovic et al, (2010) Schacht (2016)

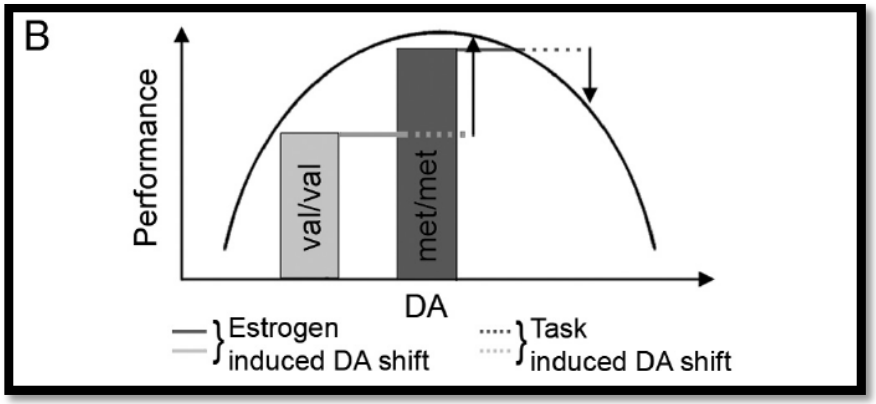
Predicted Effect of COMT Genotype and Response to Amphetamine

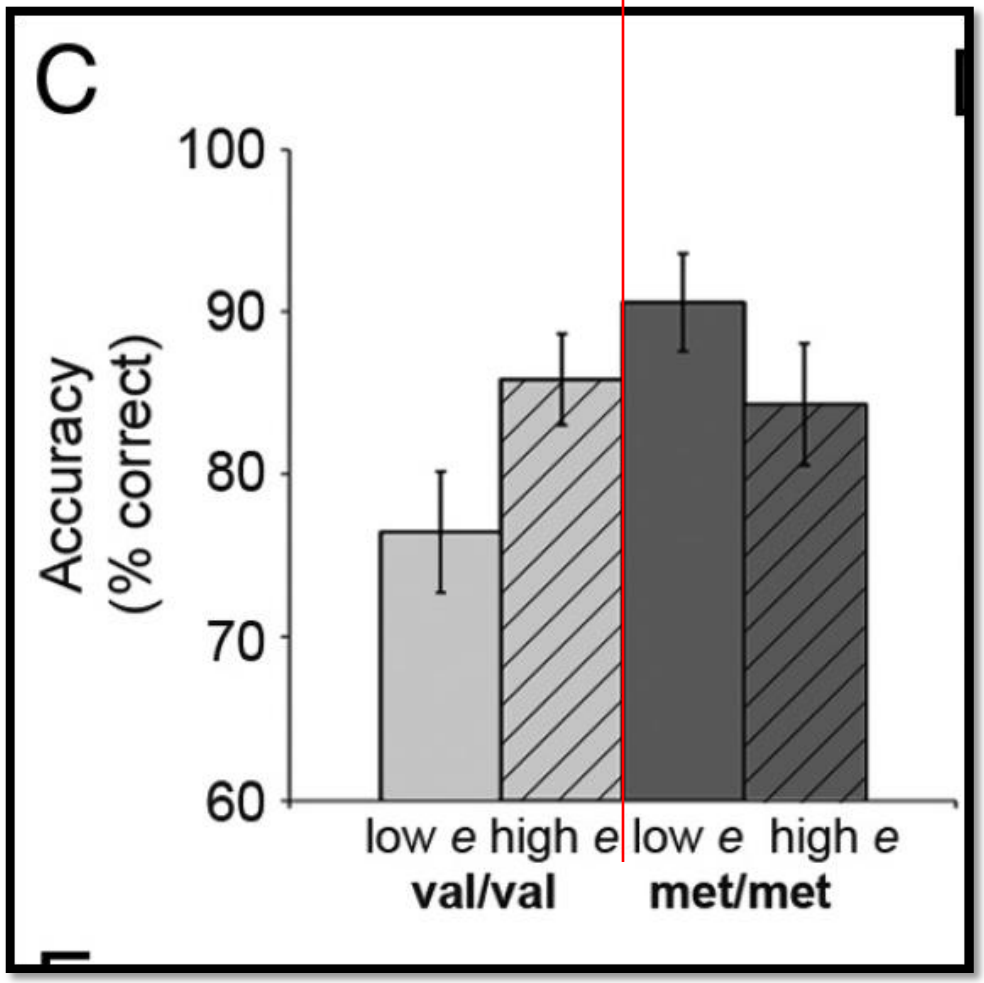


Tunbridge et al. (2006)

Estrogen and COMT

- Estradiol can compensate for the negative working memory associated with VAL/VAL patients
- Estradiol impact on cognition is dependent on VAL/VAL vs. MET/MET genotype

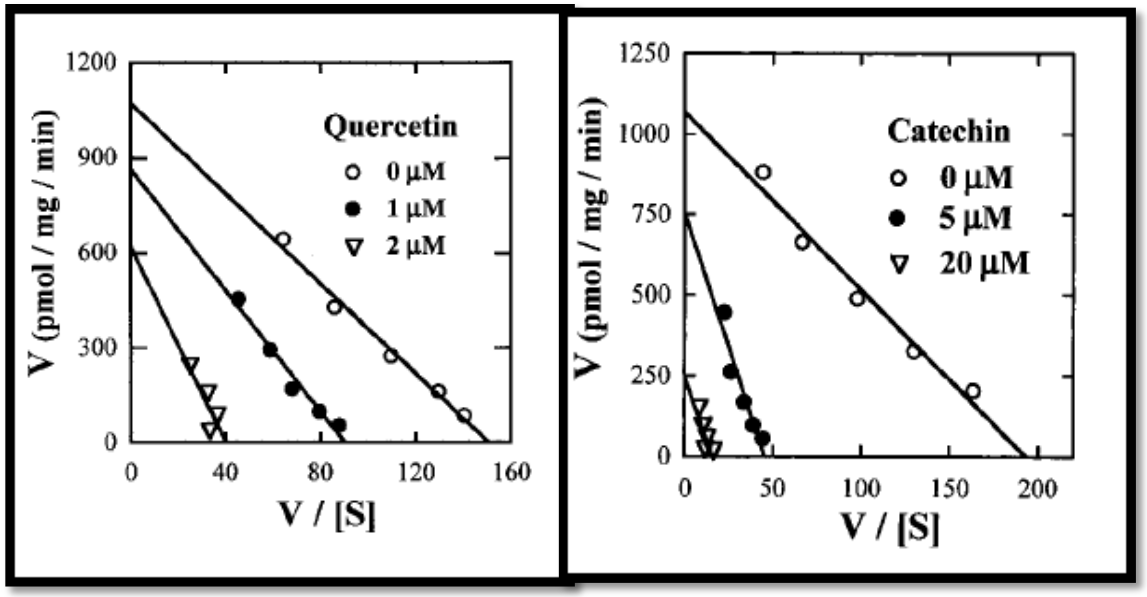




Jacobs & D'Esposito. J. Neurosci., April 6, 2011 • 31(14):5286 –5293

Green tea extracts and Quercetin as COMT inhibitors

- Tea catechins and Quercetin have been shown to be potent COMT inhibitors
- COMT VAL/VAL genotypes have genetically HIGH activity COMT



Nagai et al. Drug Metabolism and Disposition. 2004. DMD 32:497–504, 2004

Adrenergic α2A-receptor (ADRA2A)

- The G allele is associated with better response to methylphenidate for ADHD
- Improved inattentive scores for “G” carriers

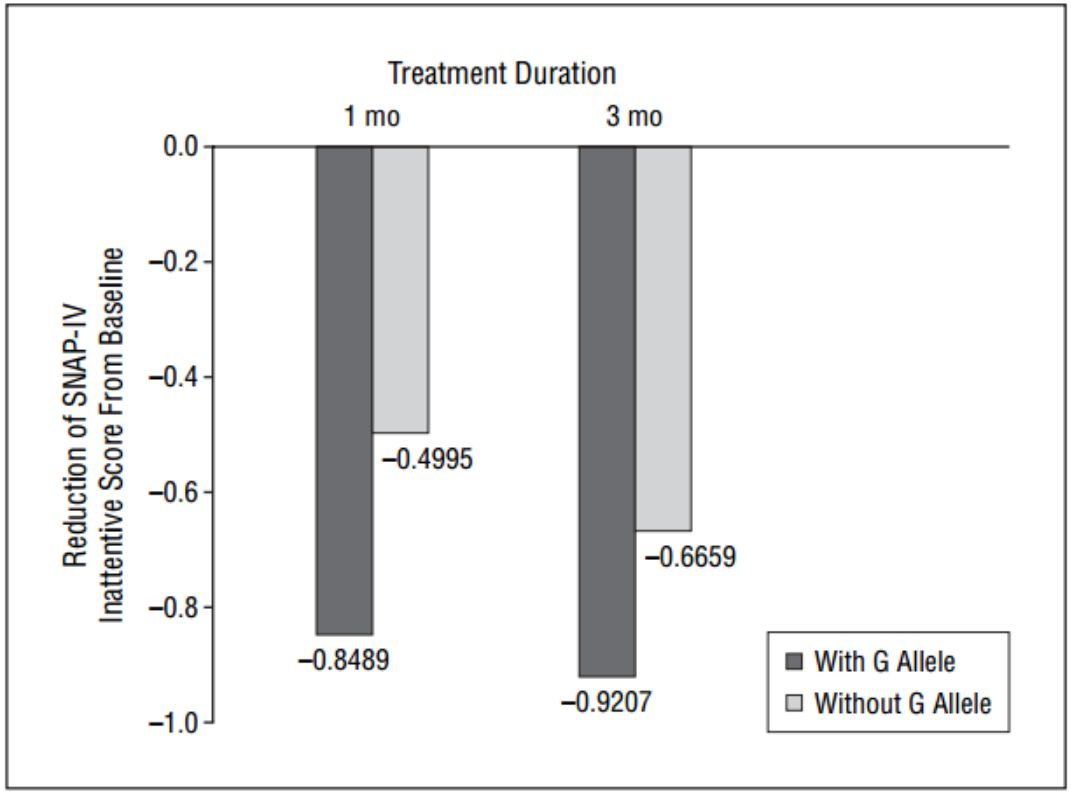
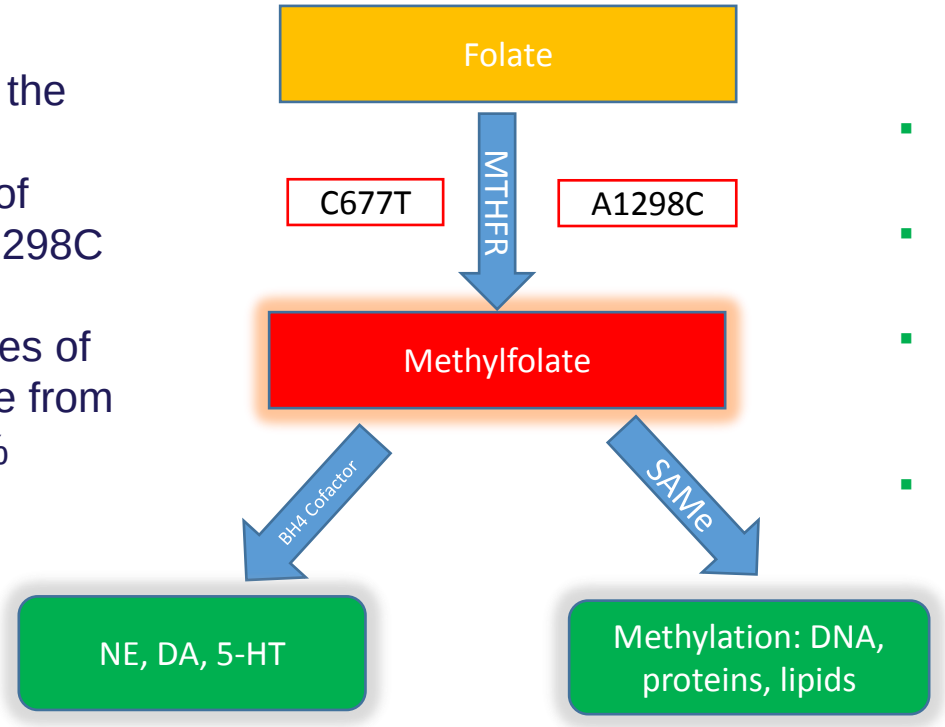


Figure 2. Effect of the presence of the G allele on mean reductions in Swanson, Nolan, and Pelham Scale version IV (SNAP-IV) inattentive scores from baseline in a mixed-effects model (n=106). Presence of the G allele: $F_{1,101.9}=6.6$; $P=.01$.

da Silva et al 2008; Polanczyk et al 2007

Folate Metabolism

Depending on the different combinations of C677T and A1298C alleles, total conversion rates of folic acid range from 100% to <30%



Low folate and methylfolate is associated with:

- Impairment in the synthesis and release of monoamine neurotransmitters: 5-HT, NE, and DA
- 6X lower rates of response to antidepressant therapy
- Incidence of depression; reported in 15%-56% of depressed patients
- Increased severity of depressive episode, length of episode, and delayed onset of clinical improvement
- Increased incidence of Bipolar disorder and Schizophrenia

C677T
T = 35% reduction

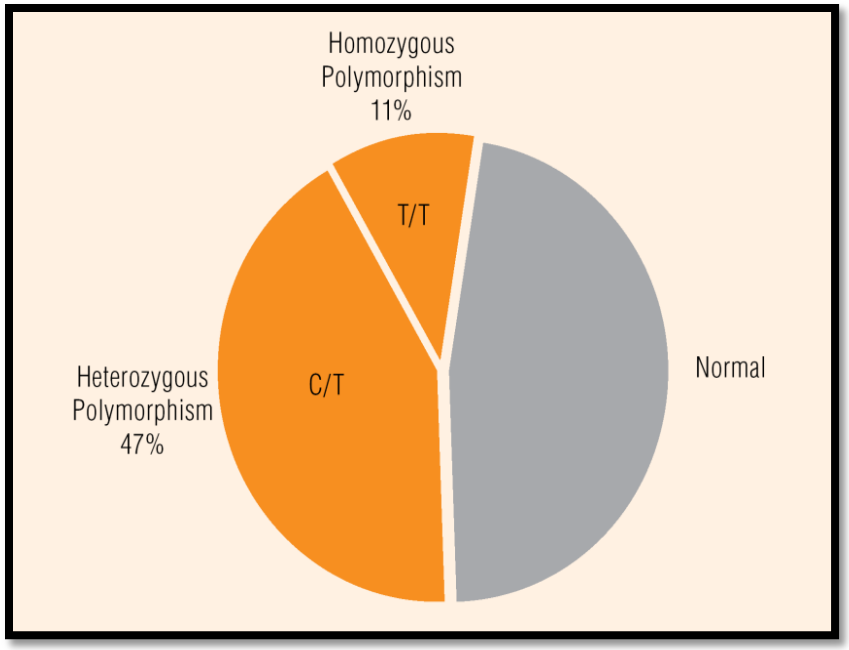
A1298C
C=20% reduction

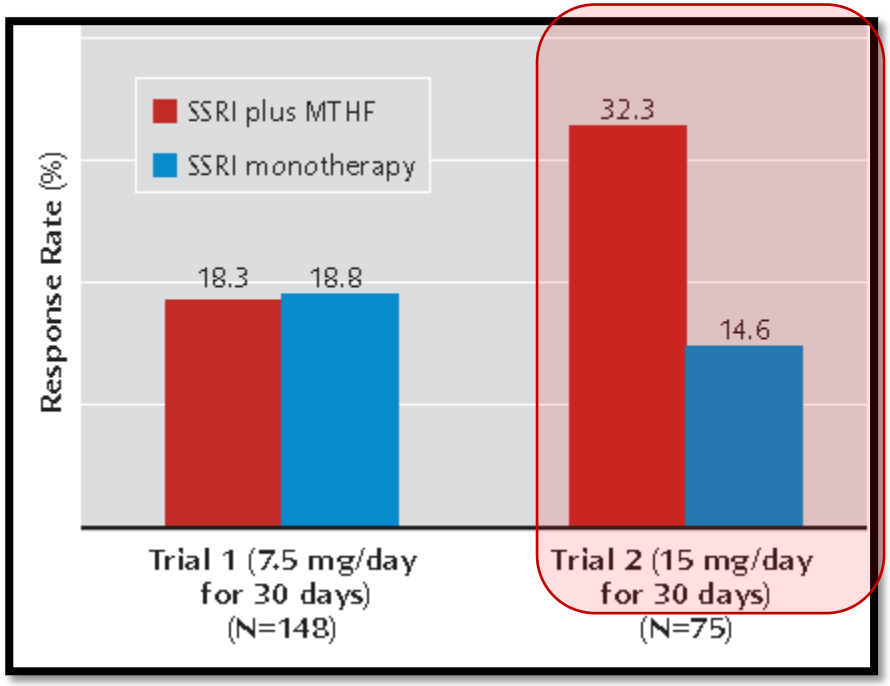
Procopciuc, 2005; Arinami 1997; Bjelland et al 2003; Kelly B 2004; Stahl 2008; Robinson 2009; Wu YL et al 2013; Gilbody S et al 2007; Peerbooms OL et al 2001;

MTHFR Polymorphism

Clinical Impact:

- L-methylfolate supplementation may be relevant in patients with the T allele



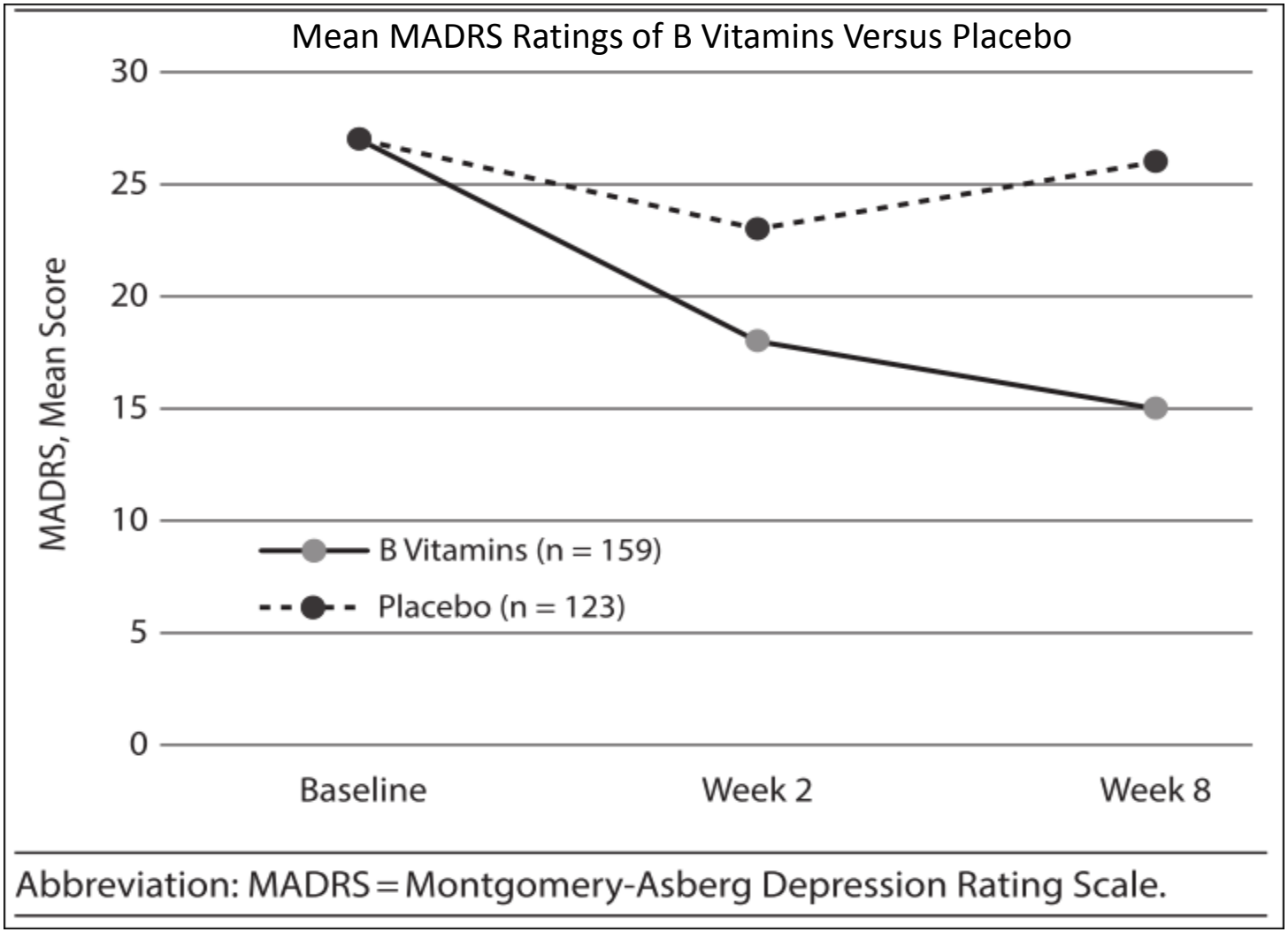


- Papakostas et al., 2012
- Methylfolate is a beneficial augmentation to SSRIs

Papakostas et al 2012; Ginsberg et al 2011; Wade et al 2014; Papakostas et al 2014;

Enlyte® methylfolate compound for MDD

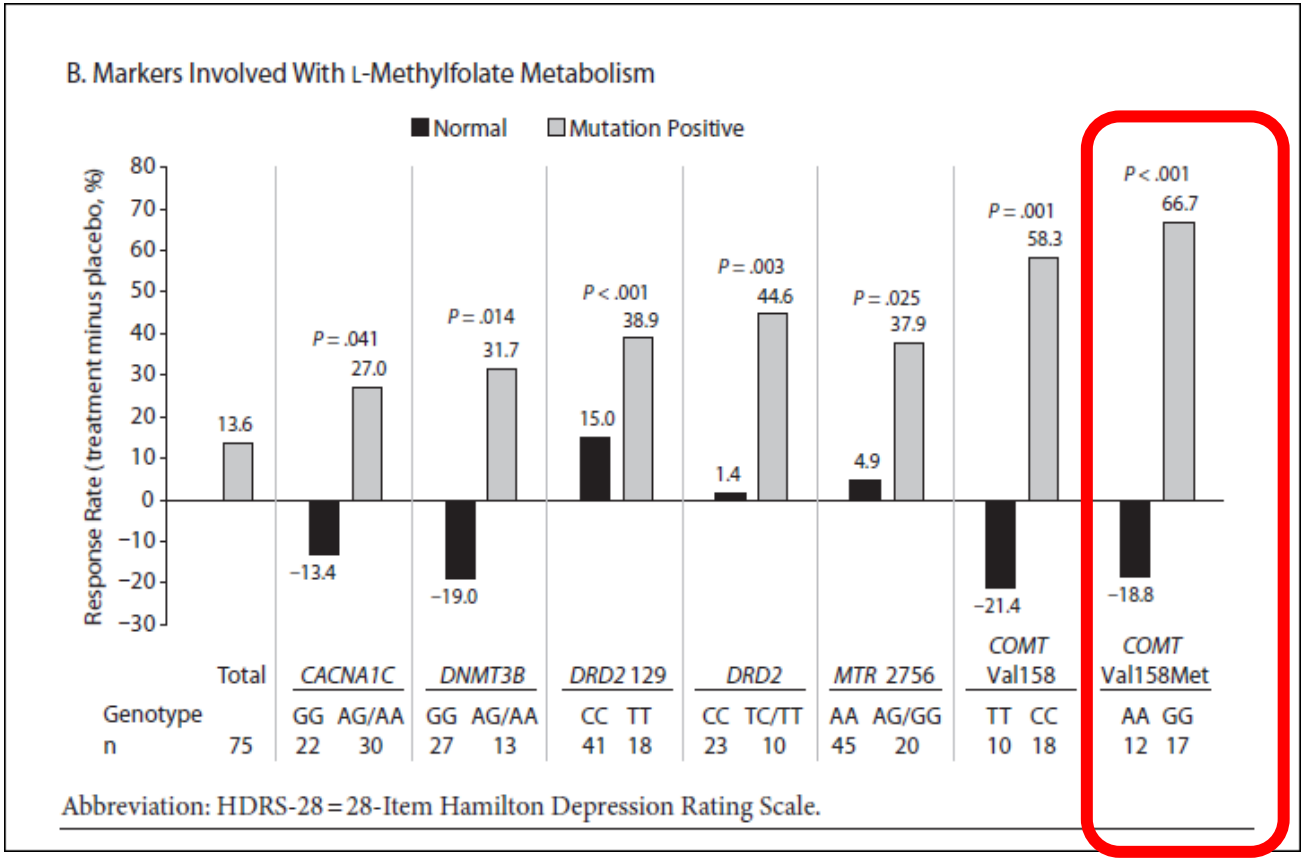
42% remission rates in treatment group



Mech and Farah 2016

BioMarkers: L-methylfolate response rates

- COMT
- DRD2
- CACNA1C
- BMI
- CRP
- HCY



Effect of Adjunctive L-Methylfolate 15 mg Among Inadequate Responders to SSRIs in Depressed Patients Who Were Stratified by Biomarker Levels and Genotype: Results From a Randomized Clinical Trial

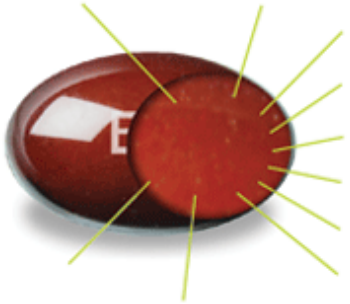
George I. Papakostas, MD; Richard C. Shelton, MD; John M. Zajecka, MD; Teodoro Bottiglieri, PhD; Joshua Rothman, MD; Clair Cassiello, BA; Stephen M. Stahl, MD, PhD; and Maurizio Fava, MD

Papakostas et al 2012; Ginsberg et al 2011; Wade et al 2014; Papakostas et al 2014;

Methylfolate Formulas

Prescription Medical Foods

- **Deplin** methylfolate 7.5 or 15 mg
- **Enlyte** L-methylfolate, folinic acid, B1, B2, B3, B6, B12, Zinc
- **Cerefolin NAC** L methylfolate 5mg , methylcobalamin 2mg, NAC 600 mg
- **Metanx** L-methylfolate 3 mg, B6 P5P 35 mg, Methylcobalamin 2 mg

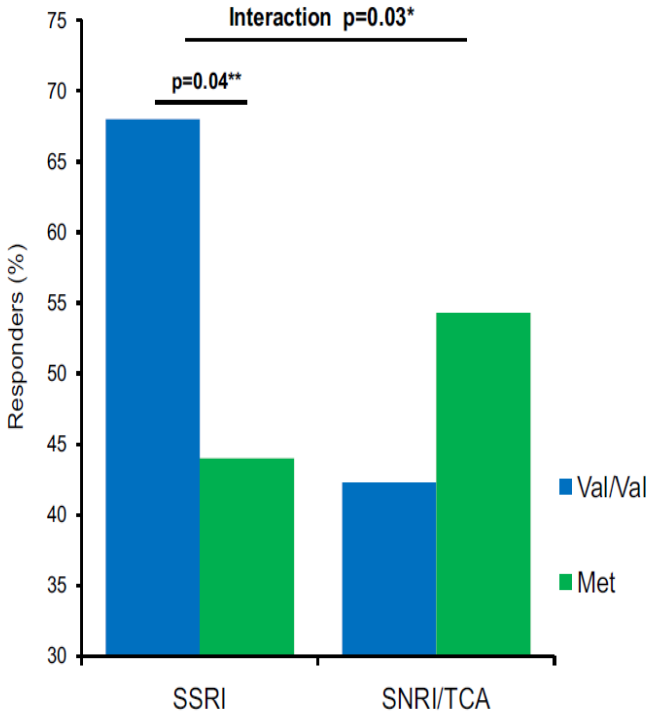


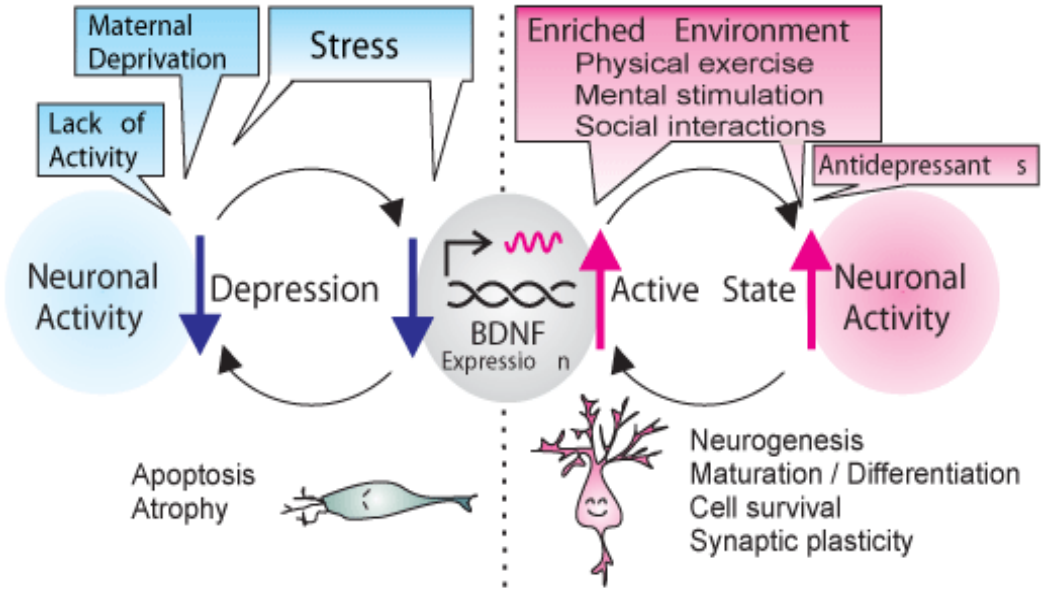
OTC Options (often labeled as 5 MTHF)

- Methylpro.com
- Nutraceutical products: Designs for Health, Thorne, Metagenics

http://umm.edu/health/medical/altmed/supplement/vitamin-b12-cobalamin

Brain-derived Neurotrophic Factor (BDNF)





Mutation

- rs6265 (Val66Met) – Met linked to impaired cellular secretion and transport, which may indirectly affect expression levels

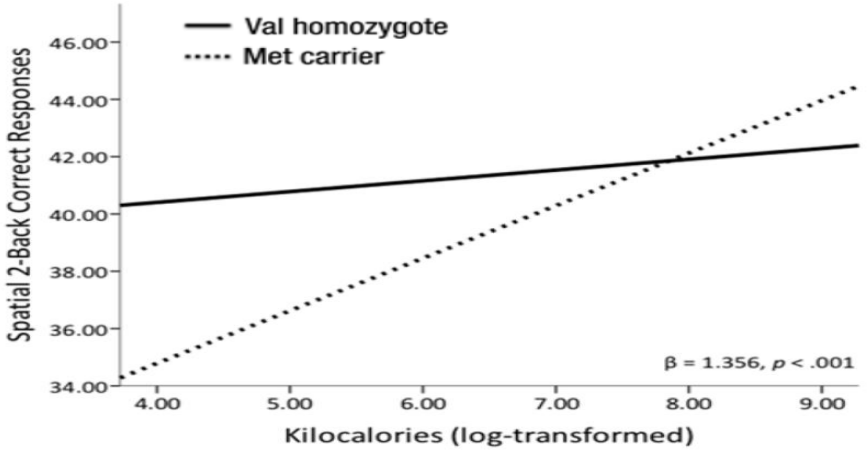
Martinez-Levy GA, Cruz-Fuentes CS 2014; Hosand et al 2014; Colle et al 2015;

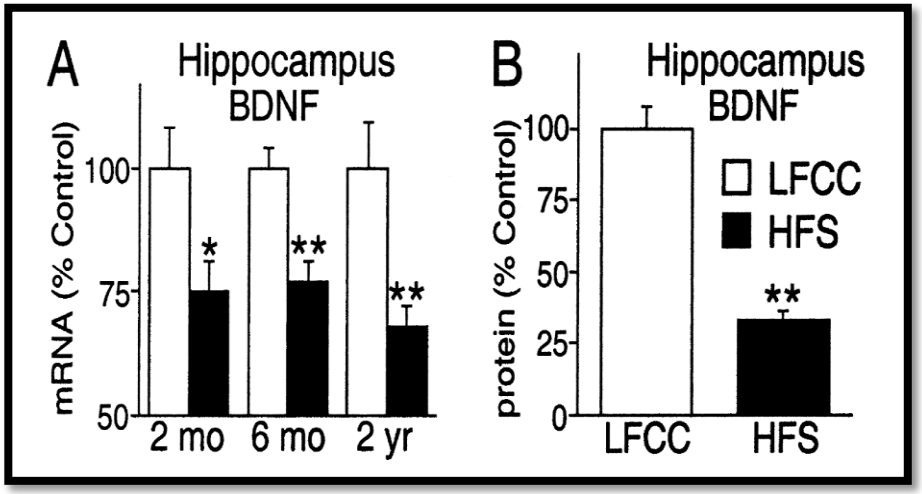
BDNF and Lifestyle

Clinical Impact:

Greater levels of physical activity can offset the deleterious effect of Met allele on working memory (Erickson, 2013)

- Exercise has been linked to improved cognition, working memory, and higher BDNF levels
- In rodents, a diet that is high in saturated fat and refined sugar results in reduced hippocampal BDNF expression





Erickson et al 2013; Colle et al 2015

Lithium increases BDNF gene expression

- Lithium enhances BDNF and BCL-2, which are Neuroprotective factors
- Lithium was shown to increase expression of the BDNF gene in rat hippocampus
- This resulted in increases in dendritic length and number
- Also protected against glutamate toxicity

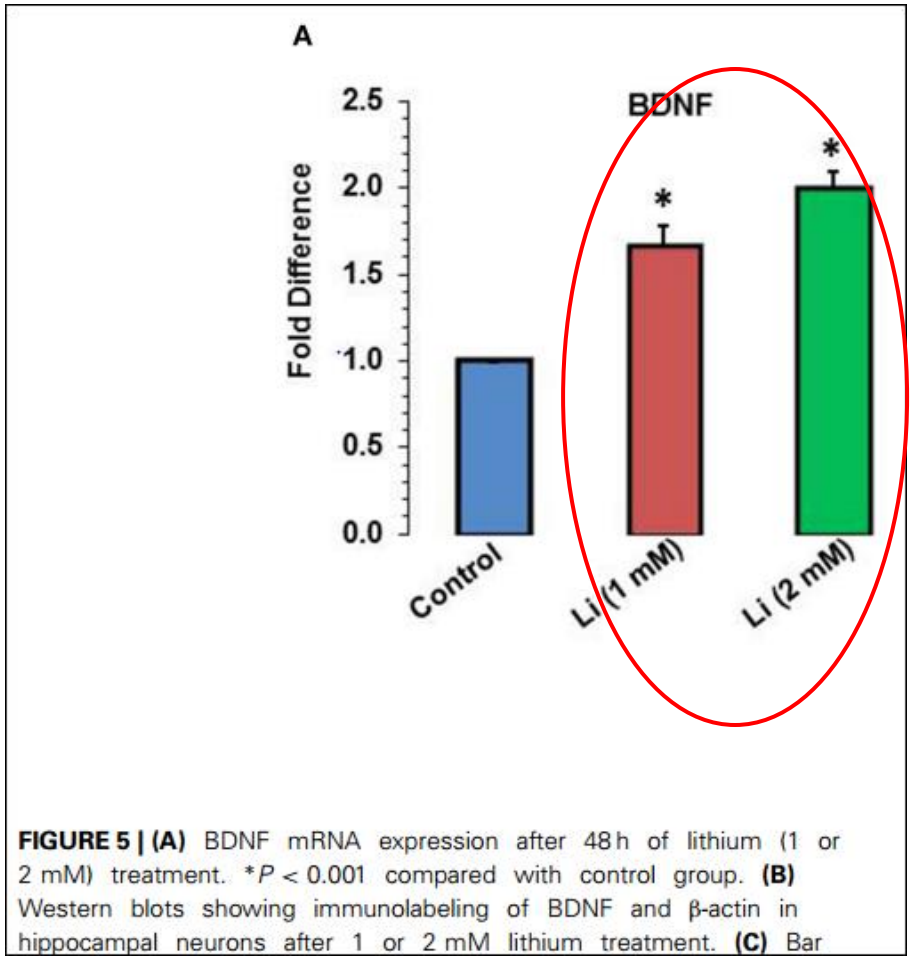


FIGURE 5 | (A) BDNF mRNA expression after 48 h of lithium (1 or 2 mM) treatment. $*P < 0.001$ compared with control group. **(B)** Western blots showing immunolabeling of BDNF and β-actin in hippocampal neurons after 1 or 2 mM lithium treatment. **(C)** Bar

1) Lithium induces brain-derived neurotrophic factor and activates TrkB in rodent cortical neurons: An essential step for neuroprotection against glutamate excitotoxicity. R Hashimoto et al *Neuropharmacology* Volume 43, Issue 7, December 2002, Pages 1173–1179

μ-Opioid Receptor (OPRM1)

Mutation

- The G allele is associated with decreased response to opioids and increased risk for addiction

Clinical Impact

- Clinicians may increase dose for G allele carriers, however these patients are at risk for substance abuse
- Non-opioid analgesics may be recommended for G allele carriers

Table 2

Genotype frequency, demand and consumed morphine dose in milligrams for the patients who received patient-controlled analgesia alone.

	Genotype frequency (%)	Demand in first 24 h	Demand in second 24 h	Demand in first 48 h	Dose in first 24 h	Dose in first 48 h
AA	62	24.3 (15.4)	9.5 (9.4)	39.0 (24.7)	16.0 (8.0)	25.3 (15.5)
GG	11	36.1 (15.2)	18.3 (14.9)	57.8 (24.7)	22.3 (10.0)	40.4 (22.1)
AG	27	22.2 (14.6)	10.5 (8.5)	35.3 (23.3)	14.8 (7.1)	25.6 (11.7)
AA vs. GG		*$P = 0.033$	*$P = 0.028$	*$P = 0.026$	*$P = 0.018$	*$P = 0.003$
GG vs. AG		*$P = 0.021$	$P = 0.059$	*$P = 0.012$	*$P = 0.010$	*$P = 0.008$

AA, wild-type homozygous; AG, mutant heterozygous; GG, mutant homozygous.
The morphine consumed doses are expressed as mean (standard deviation).
Demand is the dose that represents the number of times the patient pushed the release button of the patient-controlled analgesia device.
P-value for one-way analysis of variance (ANOVA) with *post hoc* tests (*$P < 0.05$).

Crist RC et al 2014; Ren ZY et al 2015; Hajj et al 2015; Haerian BS et al 2013; Chou et al. 2006

Integrative Pain Management Strategies

- **Excessive inflammation increases free-radical damage of tissues and impedes healing mechanisms**
  - Anti-inflammatory diet
  - Antioxidants
    - A Mayo Clinic study discovered that pain patients with insufficient levels of vitamin D were taking twice the amount of opioids for twice as long as patients without a deficiency
    - Vitamin B12 and folate deficiencies are well known to be associated with pain and neuropathic changes
  - Turmeric
  - Bromelain
  - Resveratrol

- **Mind Body Medicine**
  - Acupuncture
  - Hypnosis
  - Meditation

PAIN: CLINICAL UPDATES • MAY 2014; http://umm.edu/health/medical/altmed/; https://health.clevelandclinic.org/2015/07/9-diet-tips-to-help-you-fight-inflammation

Glutamate Receptor Kainate 1 (GRIK1)

- The GRIK1 encodes a subunit of the kainite receptor which is part of the kainate family of glutamate receptors
- Predominant excitatory neurotransmitter receptors in the brain
- Target gene for alcohol dependence
  - Polymorphism associated with increased response to topiramate for alcohol abuse

Clinical Impact

- Topiramate blocks glutamate receptors, notably ones with GRIK1, as well as sodium and calcium channels
- Topiramate is more likely to cause side effects in A allele carriers
- The C/C genotype is associated with better response to topiramate in the treatment of alcohol abuse/alcoholism

Kranzler et al Apr 2014

Thank you