Prediction of Disease Vulnerability and Treatment Response in Mood Disorders and PTSD: Personalized Medicine in Psychiatry

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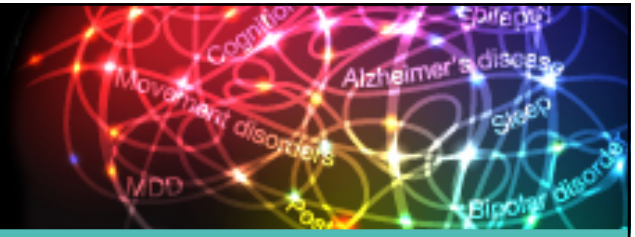
Disclosures



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- ***Stockholder***: AbbVie Inc.; Antares Pharma; Bracket Intermediate Holding Group; Celgene Corporation; Network Life Sciences Inc.; OPKO Health, Inc.; Seattle Genetics, Inc.; Xhale, Inc.
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- ***Patents***: Method and devices for transdermal delivery of lithium (US 6,375,990B1); Method of assessing antidepressant drug therapy via transport inhibition of monoamine neurotransmitters by ex vivo assay (US 7,148,027B2)
- ***Scientific Advisory Board***: American Foundation for Suicide Prevention (AFSP); Anxiety Disorders Association of America (ADAA); Bracket (Clintara); Brain & Behavior Research Foundation (BBRF) (formerly National Alliance for Research on Schizophrenia and Depression [NARSAD]); Laureate Institute for Brain Research, Inc. RiverMend Health, LLC; Skyland Trail; Xhale, Inc.
- ***Board of Directors:*** American Foundation for Suicide Prevention (AFSP); Anxiety Disorders Association of America (ADAA); Gratitude America, Inc.

Learning Objective 1

Recognize the role of genes in predicting treatment response, and prevention of disease progression in mood and anxiety disorders.

Learning Objective 2

Identify clinical and biological factors predictive of treatment outcomes in major depressive disorder (MDD).

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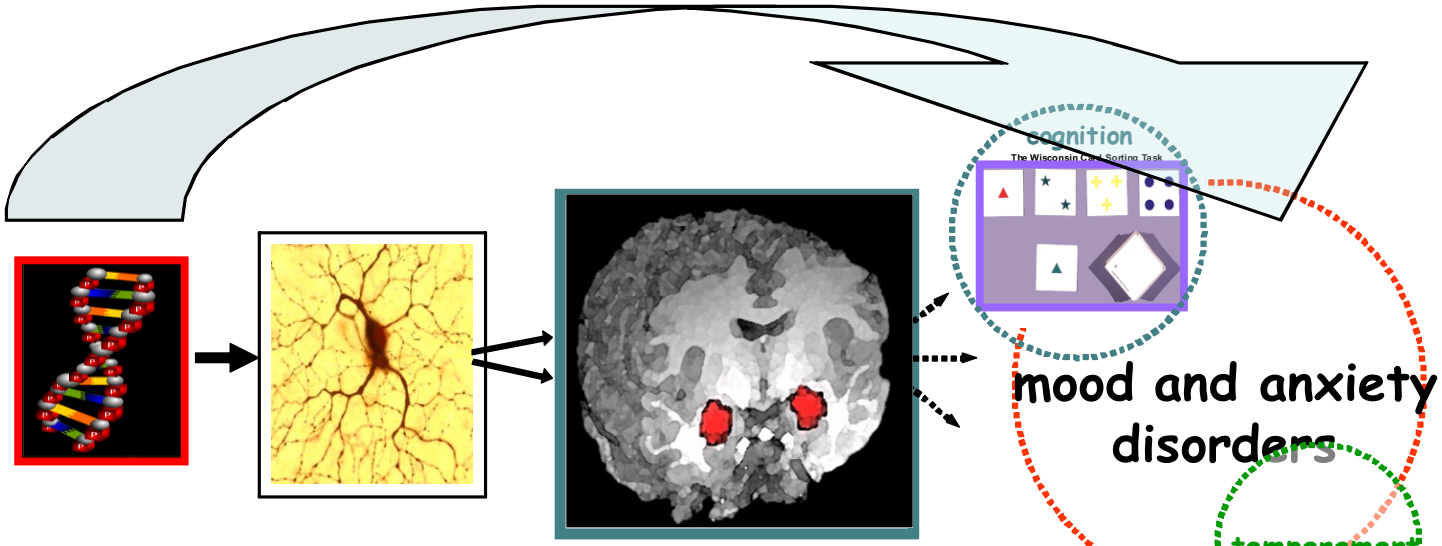
Depression and Anxiety are Ultimately About How the Brain Responds to the Environment



Genes:

sequence variants and variable gene processing

Cells:

molecular pathways

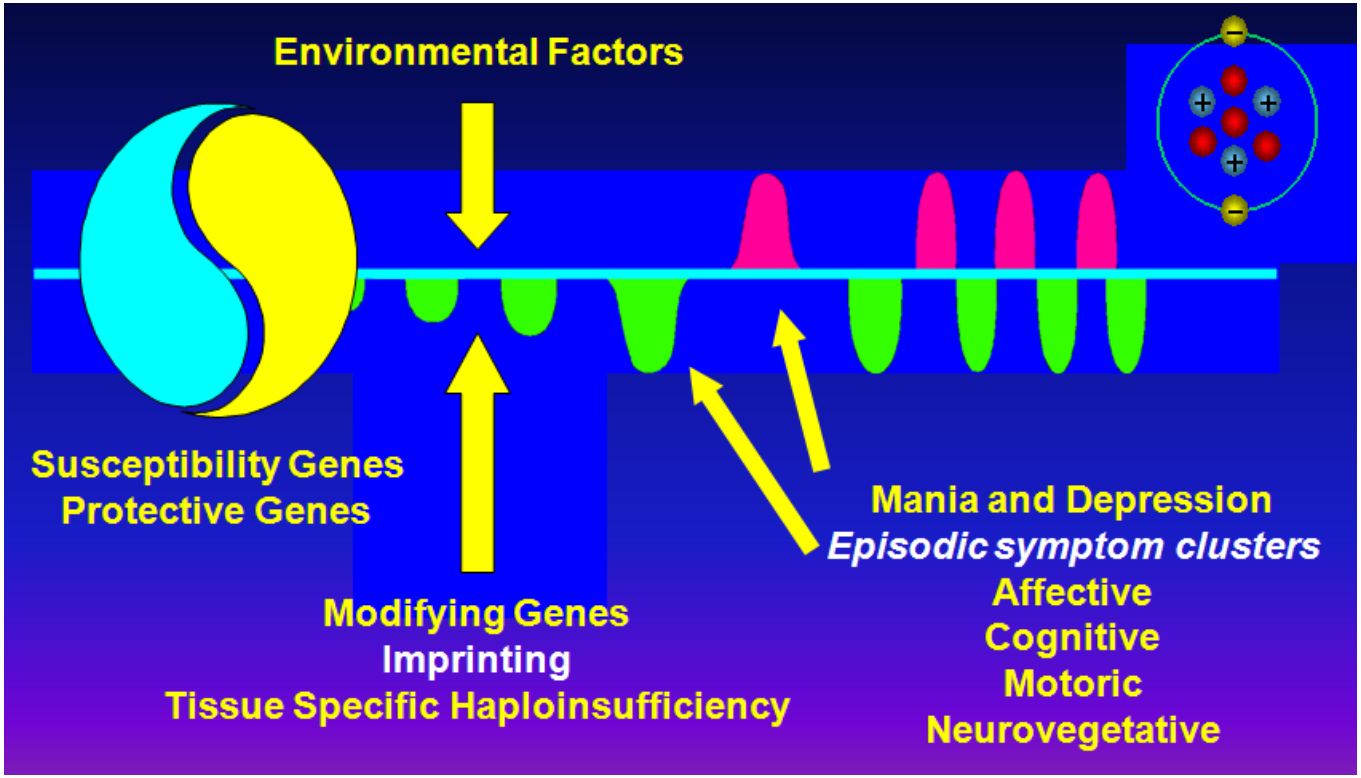
Systems:

activity in emotion processing circuitry

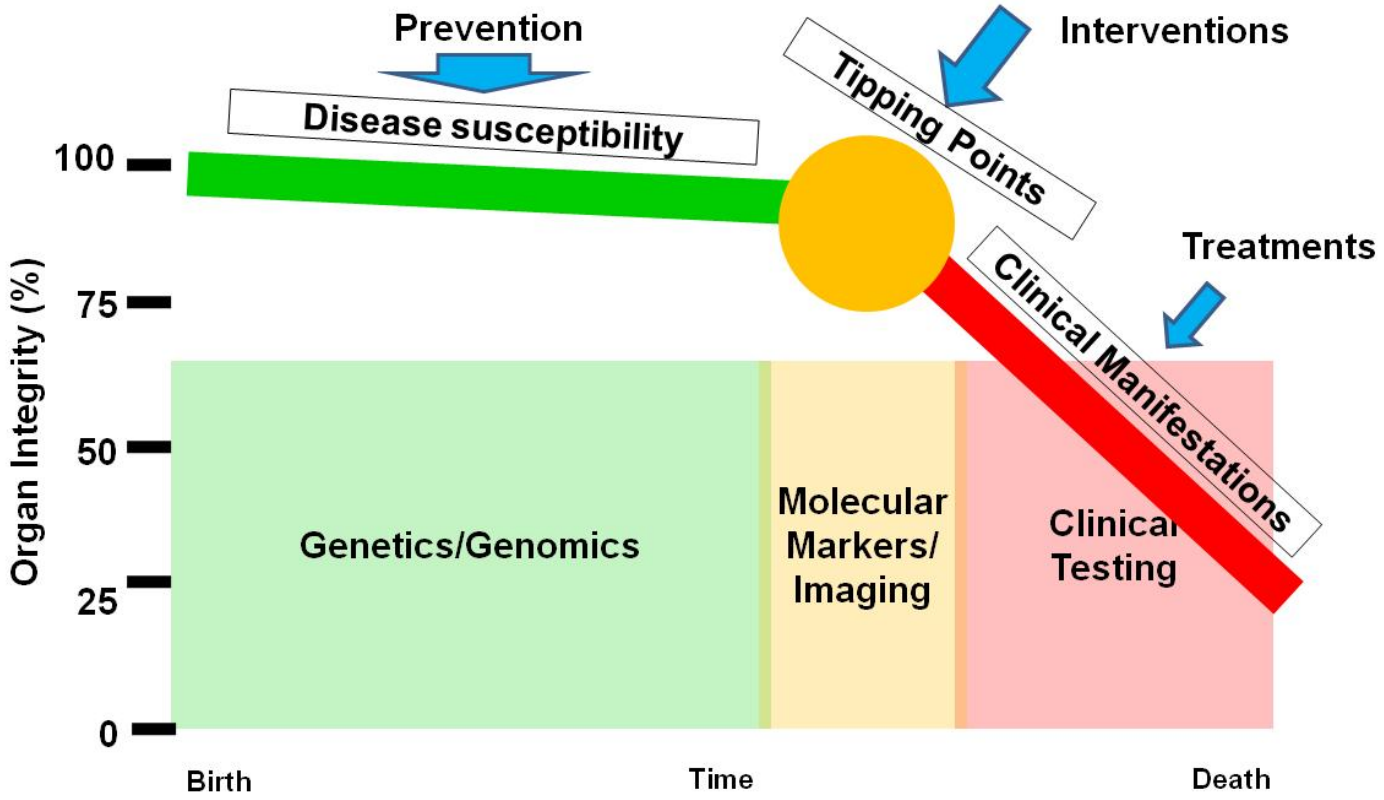
Behavior:

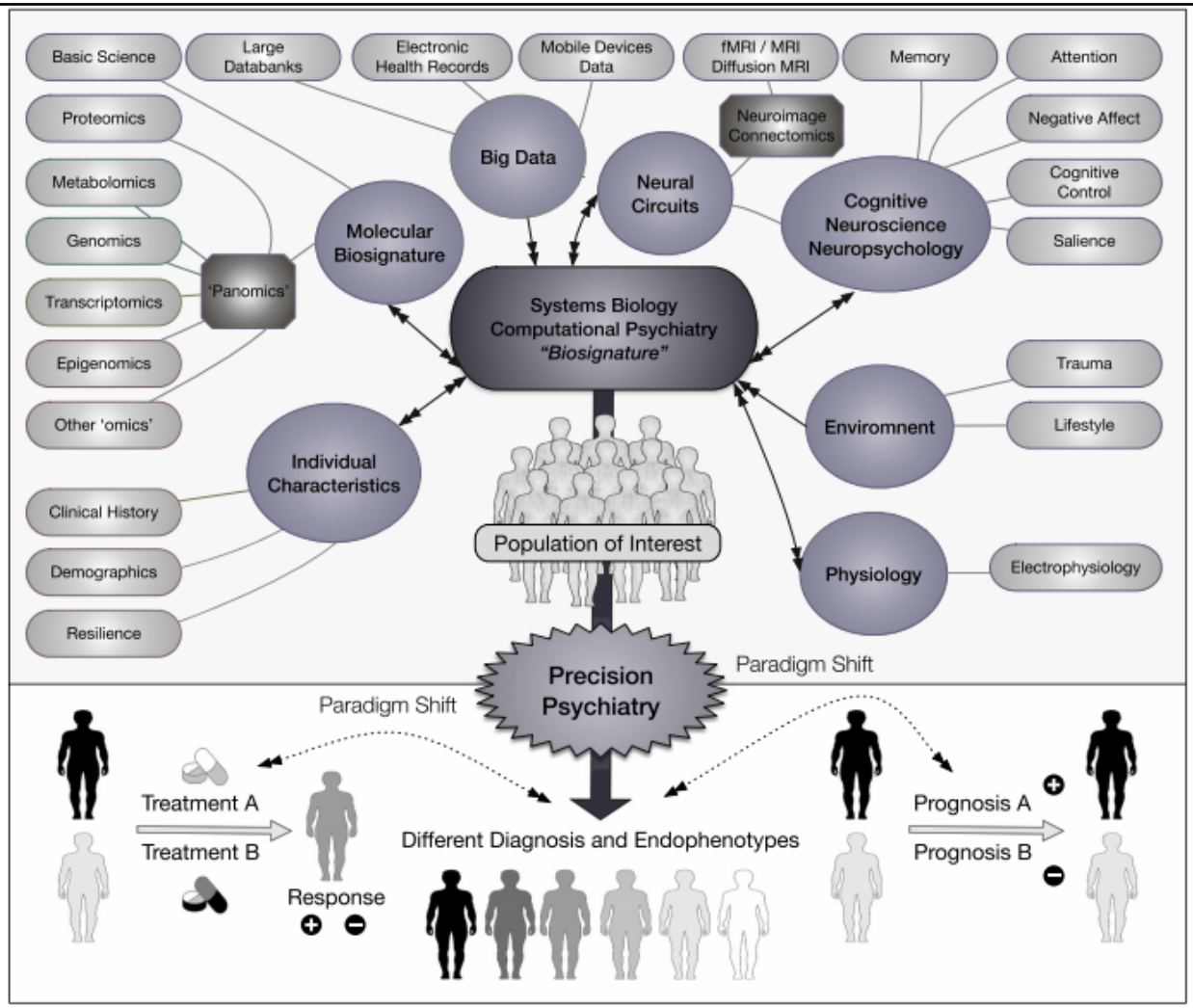
Clinical phenotype

The Neurobiology of Bipolar Disorder: Theoretical Considerations



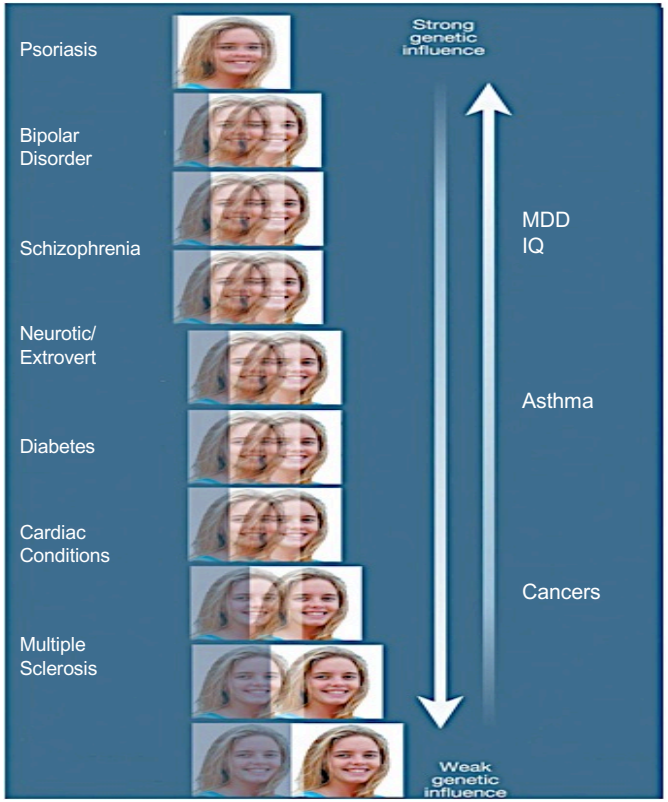
21st Century Medicine





Fernandes BS, et al. *BMC Med*. 2017:15(1):80.

Nature, Nurture, and Human Disease



***"We used to think our fate was in our stars. Now we know, in large measure, our fate is in our genes."* J. D. Watson**

Studies of identical twins have revealed that some conditions, such as psoriasis, have a strong genetic component and are less influenced by environmental and lifestyle factors — identical twins are more likely to share these diseases. But other conditions, such as multiple sclerosis, are only weakly influenced by genetic makeup and therefore twins may show differences depending on their exposure to various environmental factors.

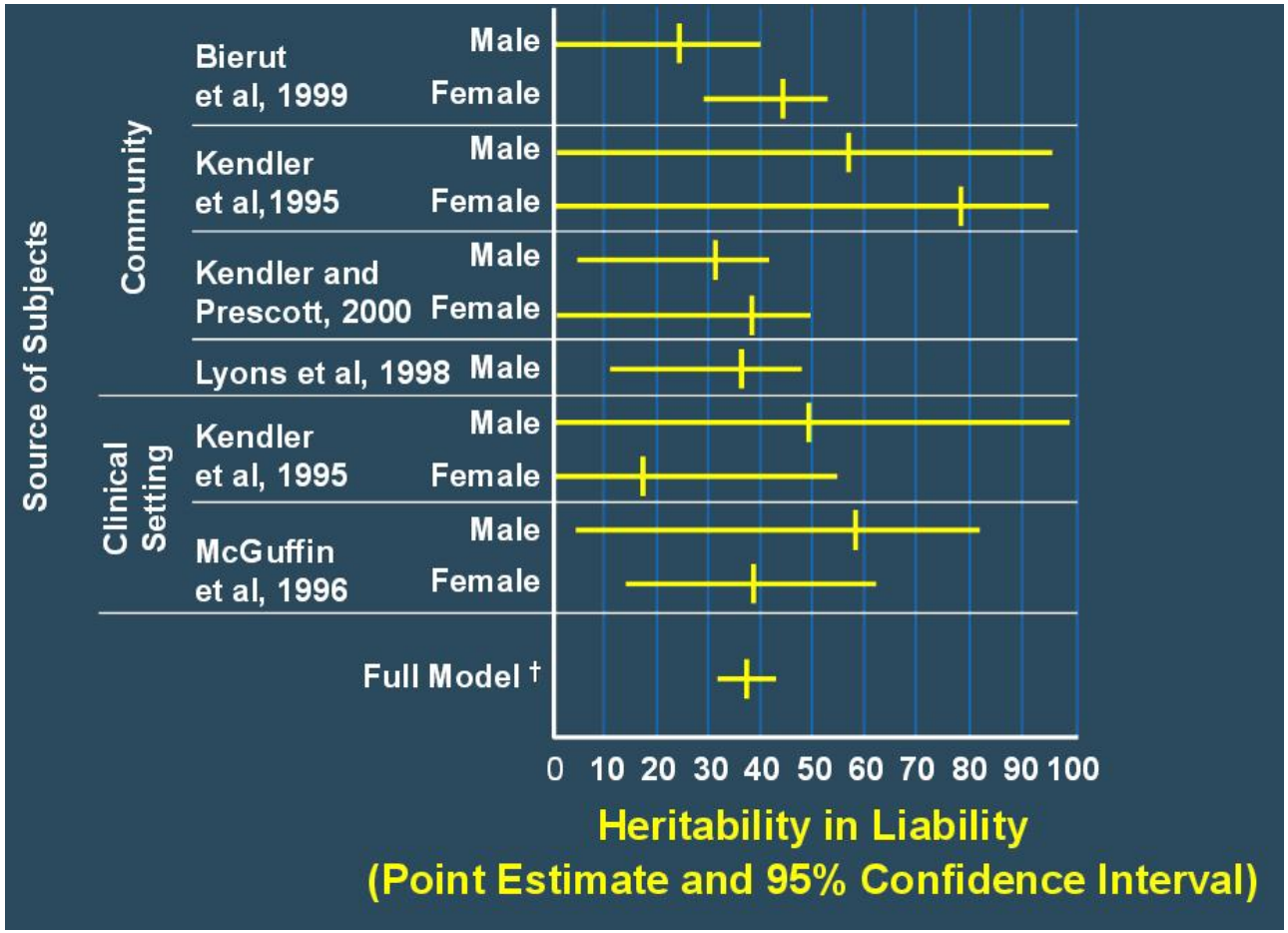
Chakravarti A, et al. *Nature*. 2003;421:412-414.

Concordance Rates (%) for Manic-Depressive Illness in Monozygotic (MZ) and Dizygotic (DZ) Twins

Study	MZ	DZ
Rosanoff et al, 1934	69.9%	16.4%
Kallmann, 1954	92.6%	23.6%
Da Fonseca, 1959	71.4%	38.5%
Harvald, Hauge, 1965	50.0%	2.6%
Kringlen, 1967	33.3%	0.0%
Bertelsen, 1977	58.0%	17.0%
Torgersen, 1986	75.0%	0.0%

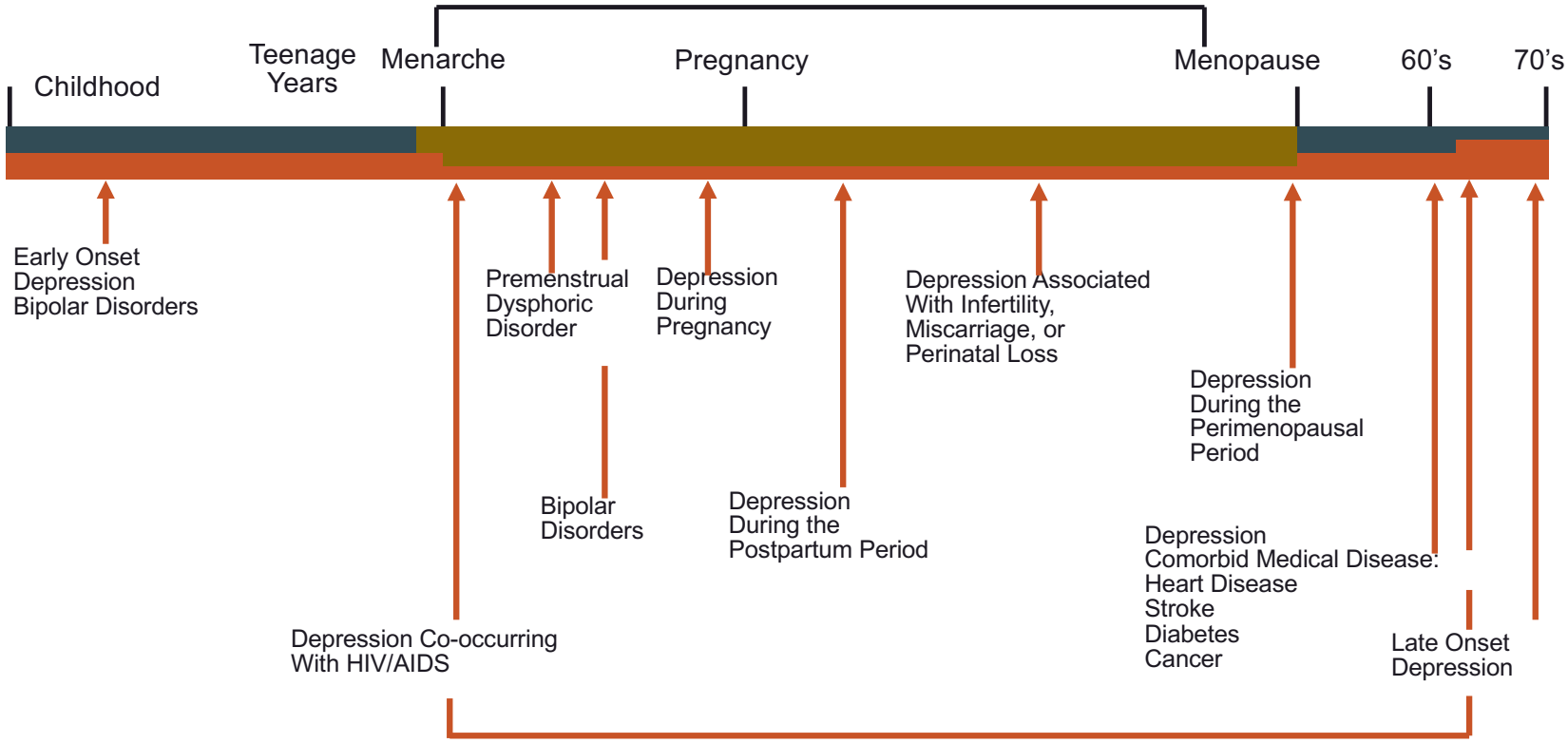
Mendlewicz J. *Br J Psychiatry Suppl*. 1988;(3):16-25.

Genetics of MDD



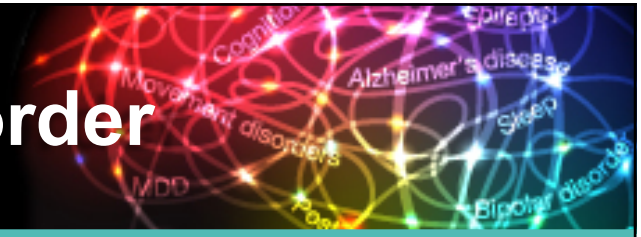
† Aggregate values across studies of heritability in liability to major depression.
Sullivan PF, et al. *Am J Psychiatry*. 2000;157(10):1552-1562. PMID: 11007705.

Mood Disorders Across the Life Cycle



Orange = Women; Blue = Men

Confirmed Linkages in Bipolar Disorder

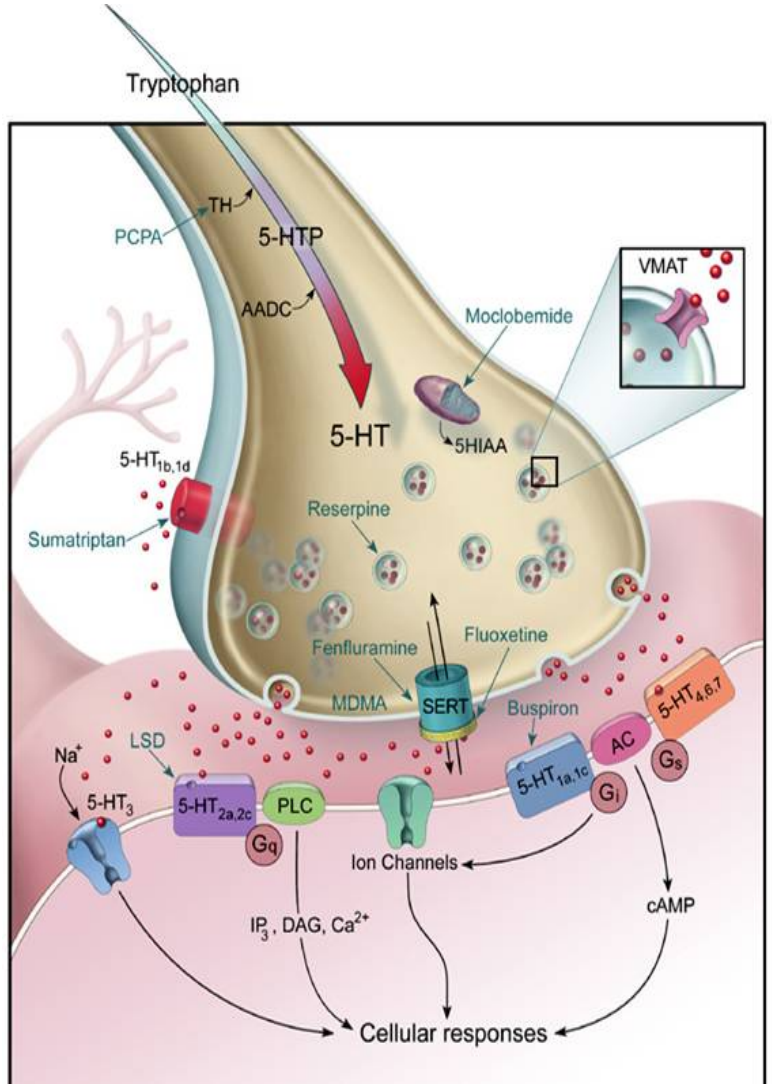


Genomic Location	Principle Report	Independent Confirmations	Comments
18p11.2	Berrettini et al., 1994 and 1997	Stine et al., 1995; Nothen et al., 1999; Turecki et al., 1999	Paternal parent-of-origin effect; see Schwab et al., 1998
21q22	Straub et al., 1994	Detera-Wadleigh et al., 1996; Smyth et al.,1996; Kwok et al.,1999; Morissette et al.,1999	
22q11-13	Kelsoe et al., 2001	Detera-Wadleigh et al., 1997 and 1999	Velocardiofacial syndrome region; possible overlap with a schizophrenia locus
18q22	Stine et al., 1995	McInnes et al., 1996; McMahon et al., 1997; De Bruyn et al., 1996	See Freimer et al., 1996
12q24	Morissette et al., 1999	Ewald et al., 1998; Detera-Wadleigh et al., 1999	Principal report in a Canadian isolate
4p15	Blackwood et al.,1996	Ewald et al., 1998; Nothen et al., 1997; Detera-Wadleigh et al., 1999	See Ginns et al., 1998

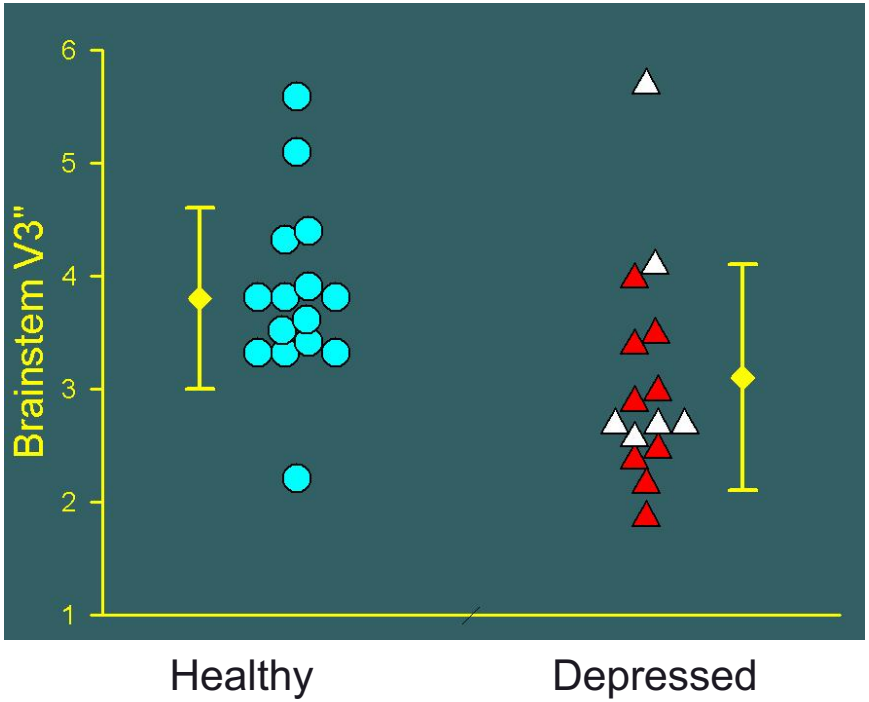
Berrettini. In *Neuropsychopharmacology; The Fifth Generation of Progress* (Davis et al editors) 2002; p1031.

Neurotransmitters and Depression

- There are disturbances in the monoamine systems
  - serotonin (5-hydroxytryptamine, 5-HT)
  - norepinephrine (NE)
  - dopamine (DA)?
- There are also disturbances in other neurotransmitter systems
  - e.g., corticotropin-releasing factor [CRF] and substance P
- Serotonin and norepinephrine have been the most extensively studied in the clinical setting


Tryptophan
TH
PCPA
5-HTP
AADC
VMAT
Moclobemide
5-HT
5HIAA
5-HT1b,1d
Sumatriptan
Reserpine
Fenfluramine
Fluoxetine
MDMA
SERT
Buspiron
5-HT4,6,7
AC
Gs
Na+
LSD
5-HT3
5-HT2a,2c
PLC
Gq
5-HT1a,1c
Gi
Ion Channels
cAMP
IP3, DAG, Ca2+
Cellular responses

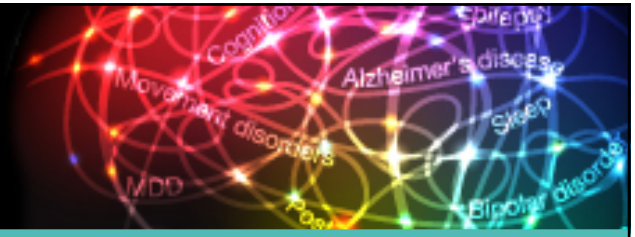
Reduced Brainstem [123I]β-CIT Binding in Depression



*p = 0.03

Malison RT, et al. *Biol Psychiatry* 1998;44(11):1090-1098.

Dopamine and Depression

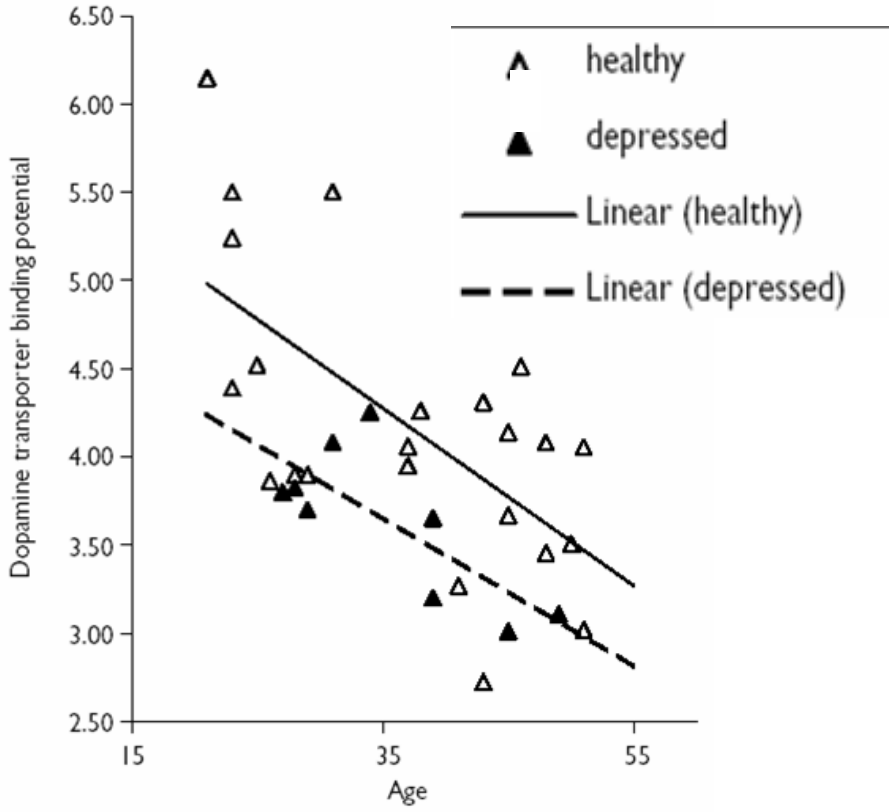


- Role of dopamine neurons in behavioral and physiological areas altered in depression
- High rate of comorbidity of Parkinson's disease and depression
- Pathophysiological involvement of DA systems in depression

Imaging Studies Postmortem Studies Biological Fluids Studies

- Role of DA circuits in the actions of antidepressants
  - MAOIs
  - Effects on the DA transporter

Lower Dopamine Tranporter Binding Potential in Striatum During Depression



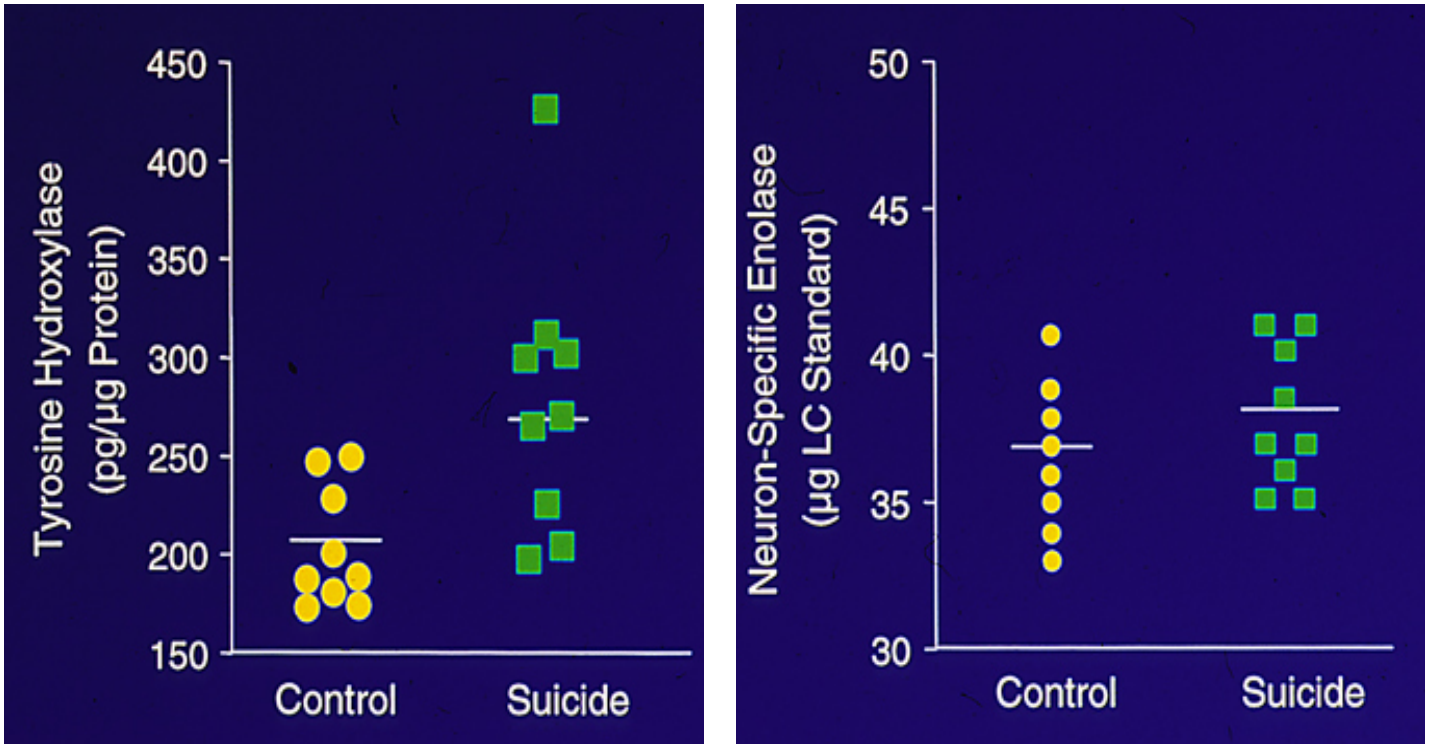
Dopamine transporter binding potential in bilateral striatum is lower in depressed patients. Data was analyzed using analysis of covariance with age as a covariate, examining effect of diagnosis (effect of diagnosis: $F_{1,29} = 7.1$, $p = 0.01$).

Meyer JH, et al. *Neuroreport*. 2001;12(18):4121-4125.

Norepinephrine Alterations

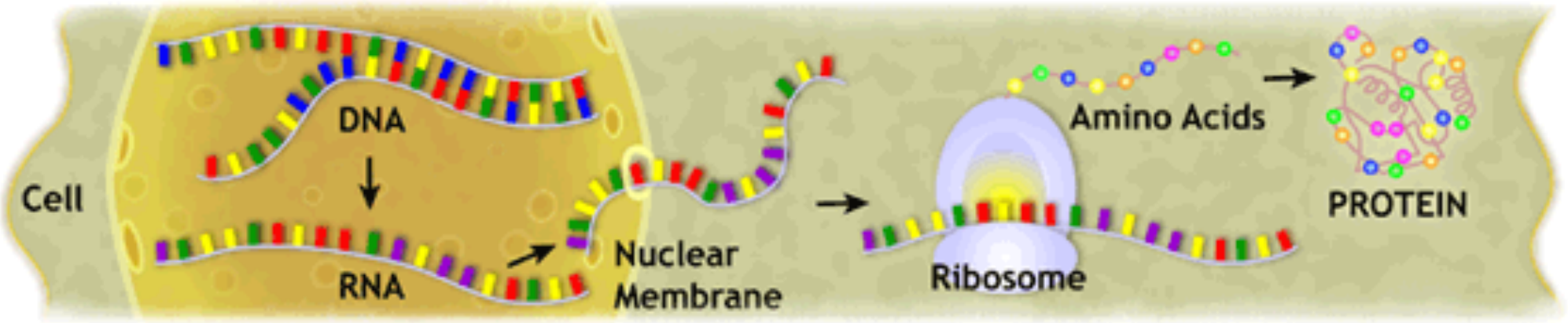
- NE dysfunction is linked to depression
  - Low levels of NE metabolites are found in the urine and CSF of depressed patient
  - Increased density of β-adrenergic receptors is found at postmortem in the cortex of depressed suicide victims
  - NE reuptake inhibitors are effective antidepressants
    - desipramine, reboxetine, maprotiline

TH and NSE Levels in Sections of LC from Control and Suicide Victims



TH = tyrosine hydroxylase, NSE = neuron specific enolase, LC = locus coeruleus

Ordway GA, et al. *J Neurochem*. 1994;62(2):680-685.



Our DNA is our instruction manual !
We can now read the whole manual !!

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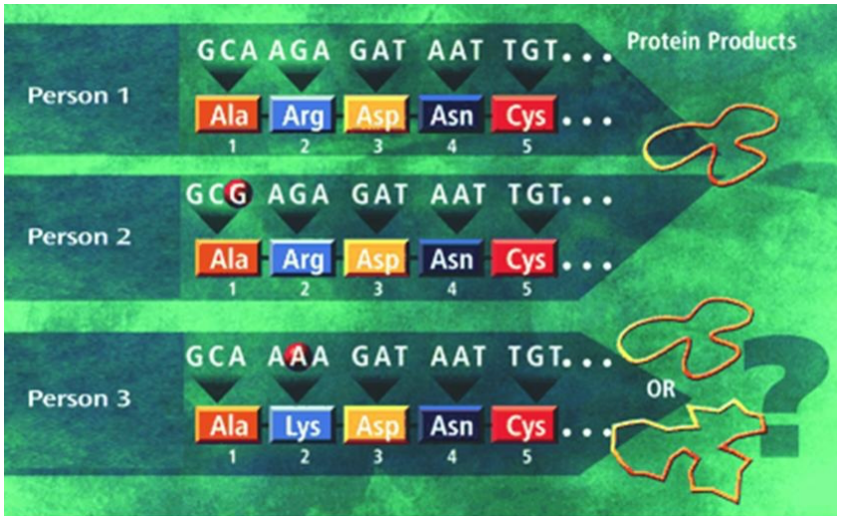
CGATCGTACGACACATATCGTCATCGTACTGCCCTACGGGACTGTCTAGTCTAAACACATCCATCGTACTGACTGCATCGTACTG

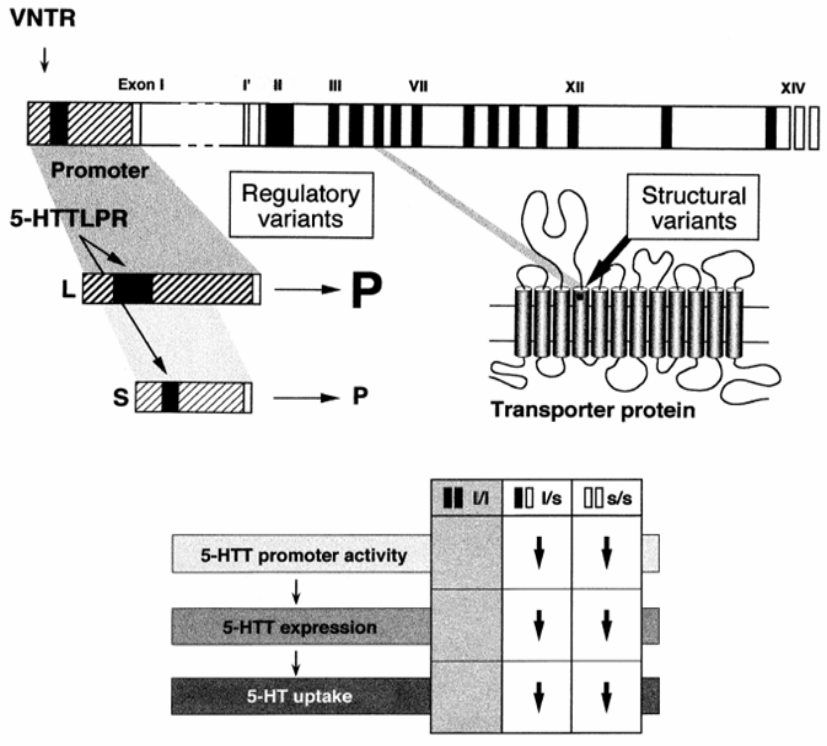
DNA Sequence Variation Can Change the Protein Produced by the Genetic Code



This image shows how DNA sequence variation in a gene can change the protein produced by the genetic code. The nucleotide triplet codon at position 1 in the gene depicted is different in person 1 and person 2, but the codon difference does not change the amino acid sequence. In person 3, the nucleotide triplet codon at position 2 is different from that in person 1 and person 2, and the codon change results in production of a different amino acid at position 2 in person 3.

Tamminga, CA. *Am J Psychiatry*. 2001;158:691.

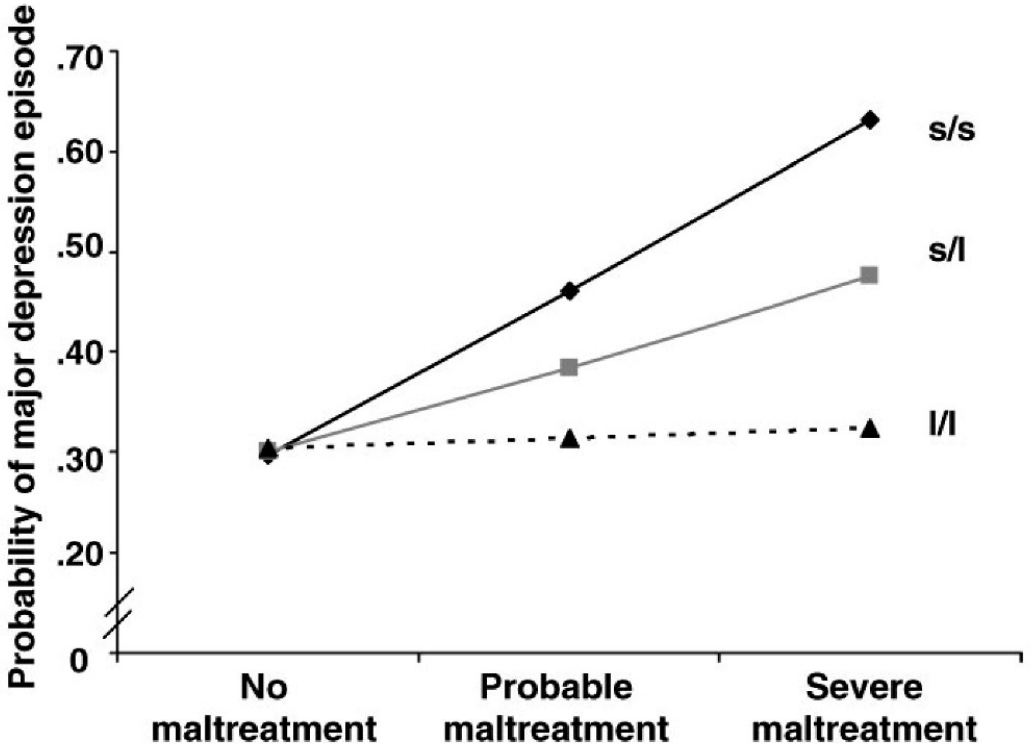
5’-HT Transporter Promoter Polymorphism (SLC6A4, 17q11)



Adapted from Lesch KP, *Mossner R. Biol Psychiatry*. 1998;44(3):179-192.

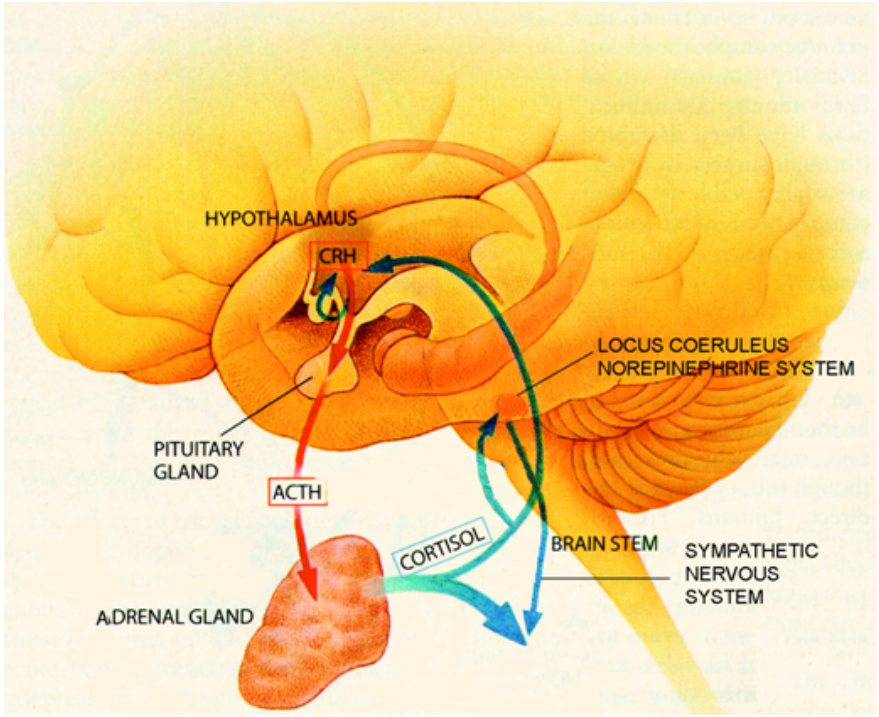
Results of Regression Analysis

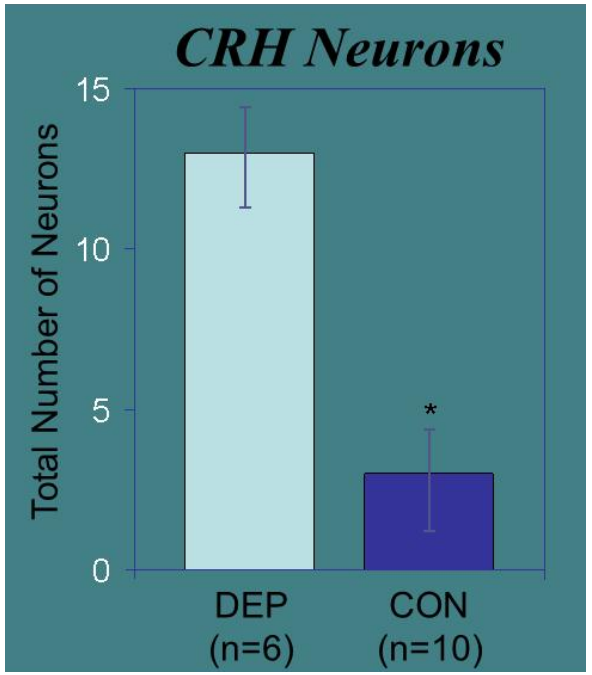
- Estimating the association between childhood maltreatment (between the ages of 3 and 11yrs) and adult depression (ages 18 to 26), as a function of 5-HTT genotype



Caspi A, et al. *Science*. 2003;301(5631):386-389.

Regulation of Stress Response by CRH and HPA Axis



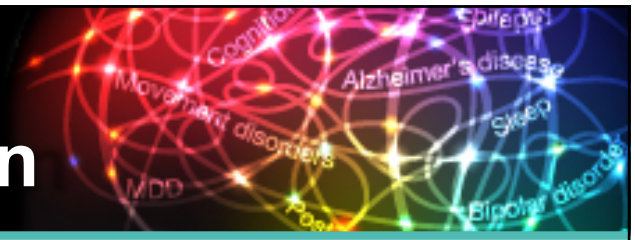


*p < .01; mean ± SEM

HPA = hypothalamic-pituitary-adrenal; ACTH = adrenocorticotropic hormone; DEP = depressed patients; CON = control patients

Purba JS, et al. *Neuroendocrinology*. 1995;62(1):62-70.; Raadsheer FC, et al. *Neuroendocrinology*. 1994;60:436-444.

Central CRH:
A Mediator of Stress and Depression



- CRH CSF concentrations are elevated in depression
- CRH stimulation test shows blunted ACTH response in depression
- Combined dexamethasone/CRH stimulation test is dysregulated in depression
- Increased pituitary/adrenal gland size in depression
- In animals, CRF injections into brain mimic anxiety and chronic depression
- These effects can be blocked by CRHR1 antagonists and a neurokinin-2 (NK2) receptor antagonist
- A principle source of brain CRH is the central nucleus of the amygdala, known to be involved in stress response and depression

Influence of Child Abuse on Adult Depression: Sample Demographics

	N	Percentage
Male	194	39%
Female	303	61%
Self-Identified Race/Ethnicity		
African-American or Black	484	97%
Caucasian or White	4	.8%
Hispanic or Latino	2	.4%
Mixed	5	1%
Other	3	.6%
Education		
< 12th Grade	153	315
High School Graduate or GED	217	44%
Some College or Technical School	78	15%
College Graduate	21	45
Some Graduate School	9	25

Bradley RG, et al. *Arch Gen Psychiatry*. 2008; 65(2):190-200.

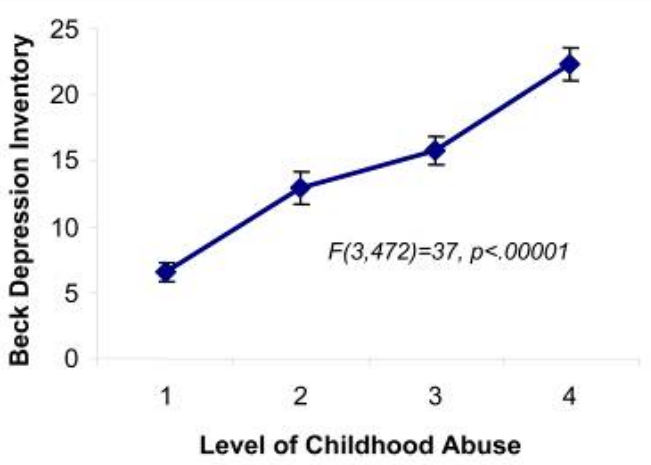
Influence of Child Abuse on Adult Depression: Sample Demographics

	N	Percentage
Employment Status		
Currently Unemployed	338	68%
Currently Employed	162	38%
Caucasian or White	4	.8%
Disability Status		
Not Currently Receiving Disability	394	79%
Currently Receiving Disability	103	21%
Household Monthly Income		
$0 - $249	158	32%
$250 - $499	51	10%
$500 - $999	136	28%
$1000 - $1999	106	21%
$2000 or more	158	%9

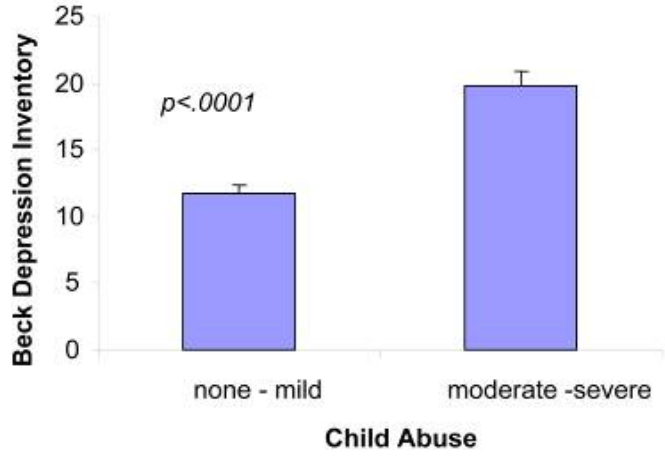
Bradley RG, et al. *Arch Gen Psychiatry*. 2008; 65(2):190-200.

Early Life Stress Significantly Enhances Risk for Depression in Adults

Beck Depression Inventory (BDI) scores are predicted by continuous scores on the childhood trauma questionnaire



Depression is predicted by presence/absence of childhood trauma



Bradley RG, et al. *Arch Gen Psychiatry*. 2008; 65(2):190-200.

CRHR1 Polymorphisms Strongly Interact With Level of Childhood Abuse in the Prediction of Adult Depression

Bradley RG, et al. *Arch Gen Psychiatry*. 2008; 65(2):190-200.

CRHR1 Polymorphism Haplotypes Interact With Level of Childhood Abuse in the Prediction of Adult Depression

A

Block 1 Haplotypes

rs7209436	rs4792887	rs110402	Frequency (%)
C	T	G	34.1
C	C	G	34.0
T	C	A	30.4

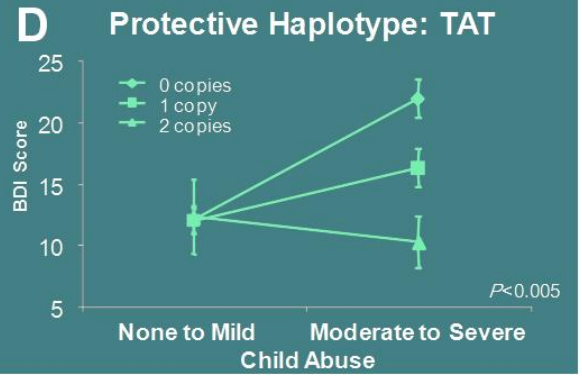
B

C

Most Significant SNP Haplotypes

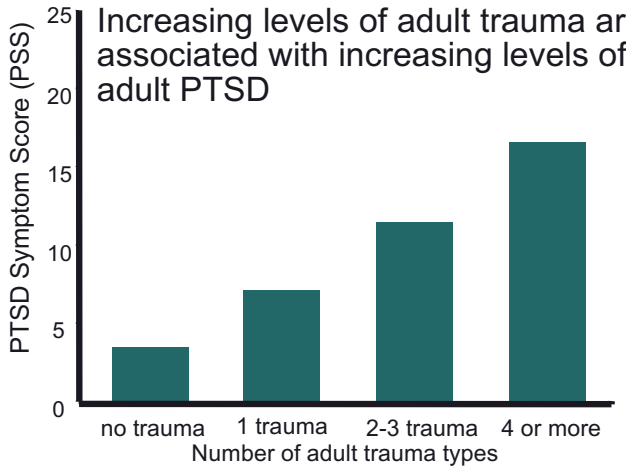
rs7209436	rs110402	rs242924	Frequency (%)
C	G	G	66.5
T	A	T	28.8

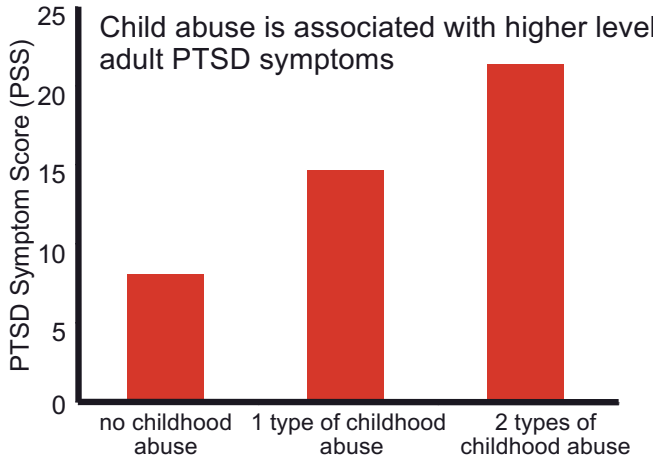
D

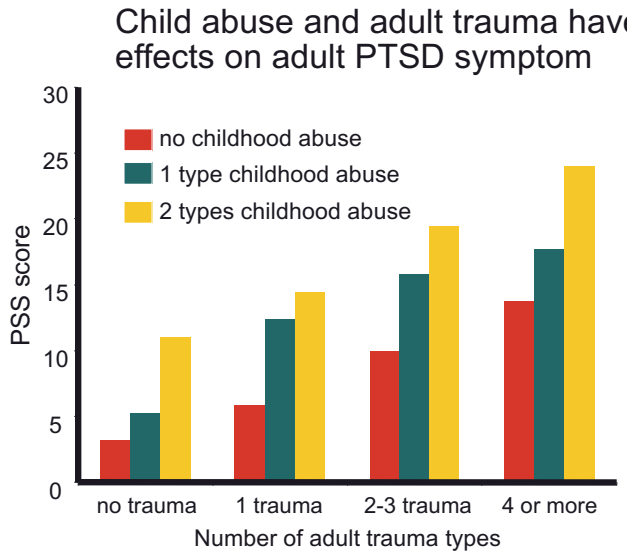


Bradley RG, et al. *Arch Gen Psychiatry*. 2008;65:190-200.

Adult Trauma and Child Abuse Predict PTSD

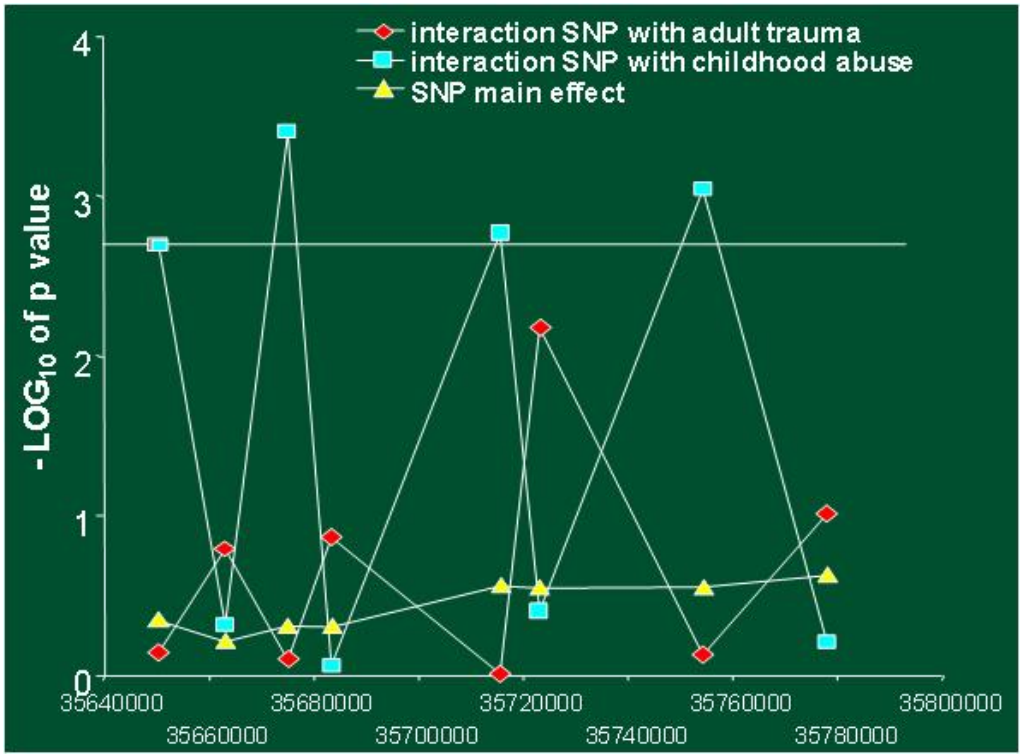


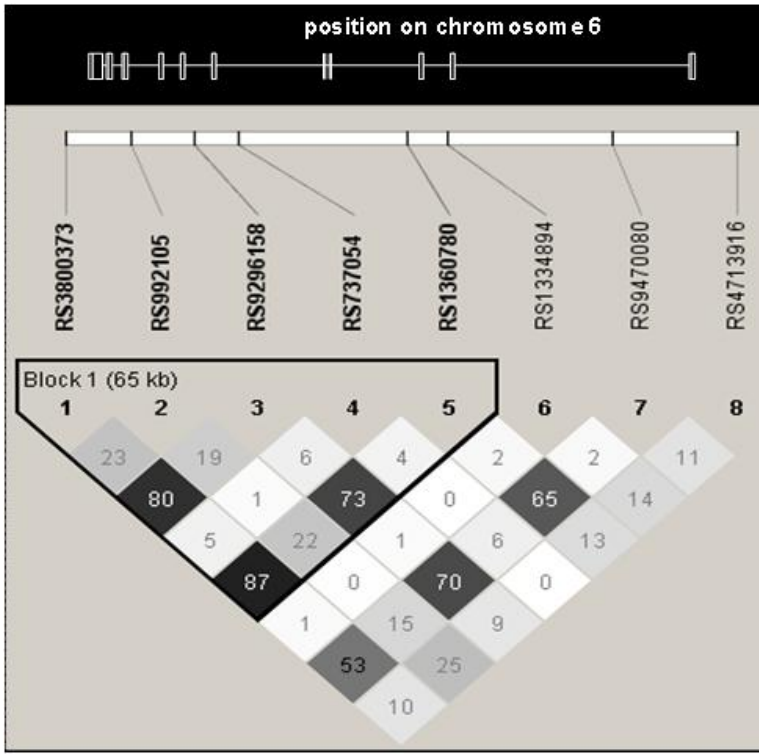




Binder EB, et al. *JAMA*. 2008;299:1291-1305.

FKBP5 SNPs and Main Genetic Effect on PTSD Symptoms and Interaction Effects with Adult Trauma Levels and Child Abuse

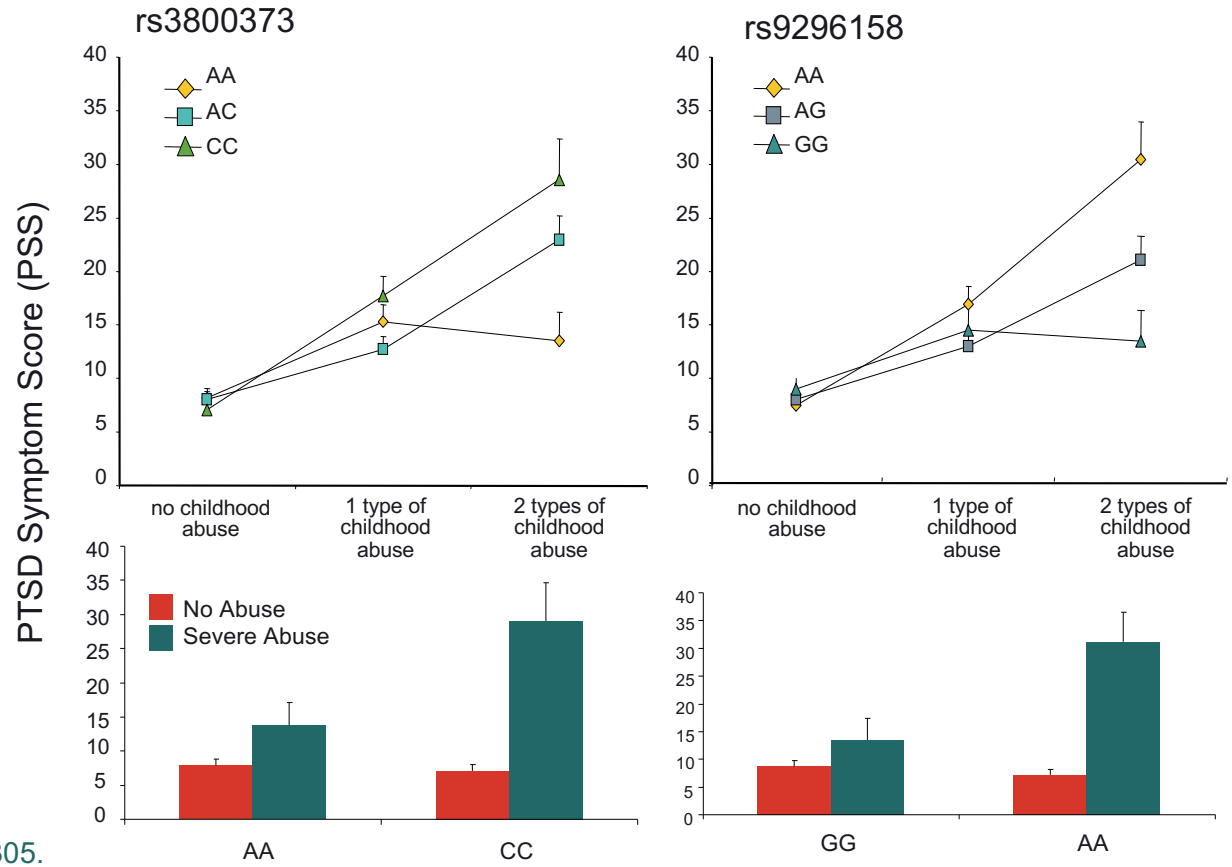




Binder EB, et al. *JAMA*. 2008;299(11):1291-1305.

PTSD Severity, FKBP5 SNP Genotypes and Child Abuse

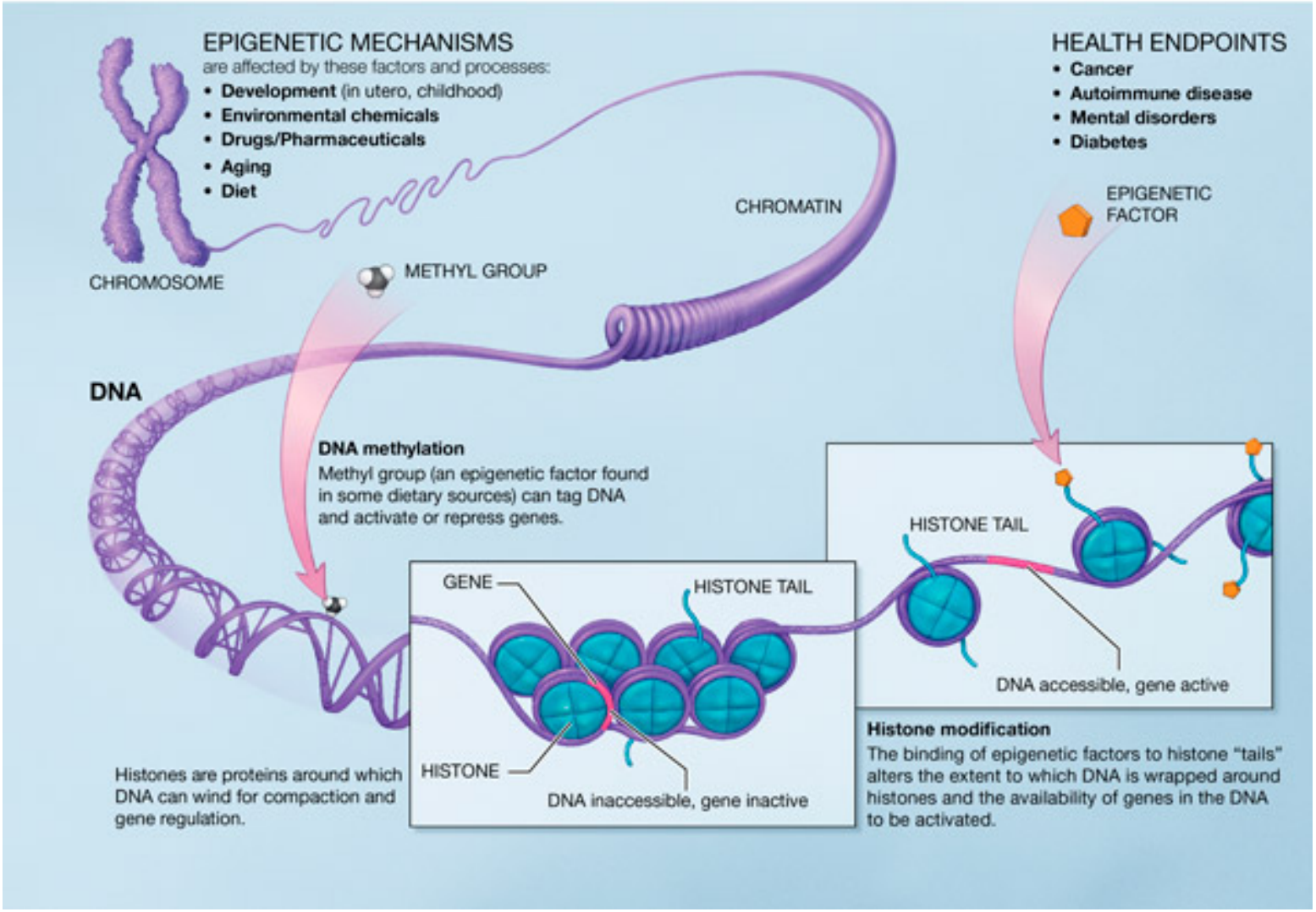
For all 4 SNPs *(rs1360780 and rs9470080 not shown)* an additive interaction effect with child abuse on PSS score is observed



Binder EB, et al. *JAMA*. 2008:299:1291-1305.

Epigenetics

- The phenomenon of heritable (‘metastable’) changes in gene regulation that are governed by non-Mendelian processes, primarily through biochemical modifications to chromatin structure that occur during life.

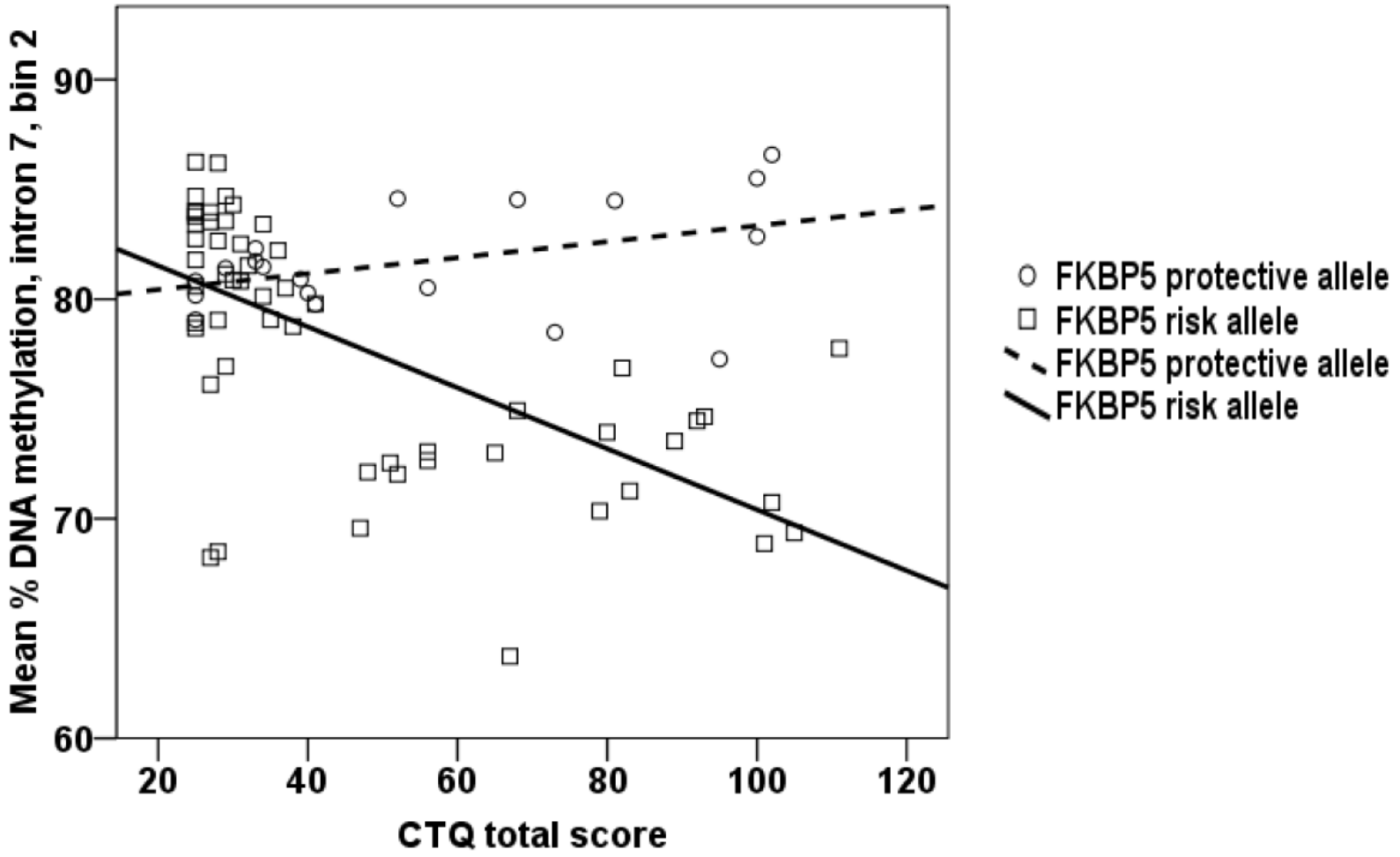

EPIGENETIC MECHANISMS
are affected by these factors and processes:
• Development (in utero, childhood)
• Environmental chemicals
• Drugs/Pharmaceuticals
• Aging
• Diet
HEALTH ENDPOINTS
• Cancer
• Autoimmune disease
• Mental disorders
• Diabetes
CHROMOSOME
CHROMATIN
METHYL GROUP
EPIGENETIC FACTOR
DNA
DNA methylation
Methyl group (an epigenetic factor found in some dietary sources) can tag DNA and activate or repress genes.
GENE
HISTONE TAIL
HISTONE
DNA inaccessible, gene inactive
HISTONE TAIL
DNA accessible, gene active
Histones are proteins around which DNA can wind for compaction and gene regulation.
Histone modification
The binding of epigenetic factors to histone "tails" alters the extent to which DNA is wrapped around histones and the availability of genes in the DNA to be activated.

Allele-Specific DNA Demethylation in FKBP5: A Molecular Mediator of Gene X Childhood Trauma Interactions

Torsten Klengel, Divya Mehta, Christoph Anacker, Jens C. Pruessner, Carmine M. Pariante, Thaddeus W.W. Pace, Kristina B. Mercer, Helen S. Mayberg, Bekh Bradley, Charles B. Nemeroff, Florian Holsboer, Christine M. Heim, Kerry J. Ressler, Theo Rein, and Elisabeth B. Binder

A polymorphism in the FK506 binding protein 5 (*FKBP5*) gene, an important regulator of the stress hormone system, increase the risk of developing stress-related psychiatric disorders in adulthood by allele-specific, childhood trauma-dependent DNA demethylation in functional glucocorticoid response elements (GREs) of *FKBP5*. This demethylation is linked to increased stress-dependent gene transcription followed by a long-term dysregulation of the stress hormone system and a global impact on the function of immune cells and brain areas associated with stress regulation.

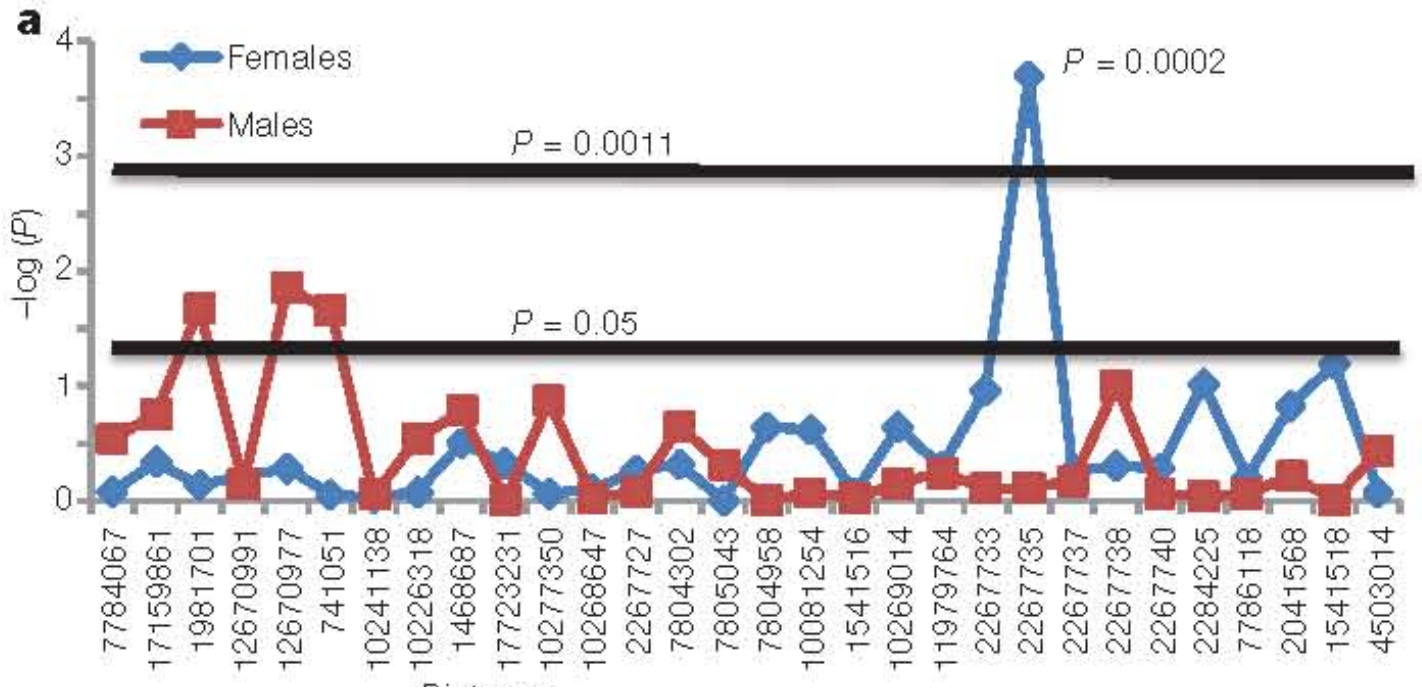
Klengel T, et al. *Nat Neurosci*. 2013;16(1):33-41.



Klengel T, et al. *Nat Neuroci*. 2013;16(1):33-41.

ADCYAP1R1 Associated with PTSD in Females

Only the *ADCYAP1R1* receptor SNP rs2267735 remained significant after experiment correction for sex and 44 independent tests



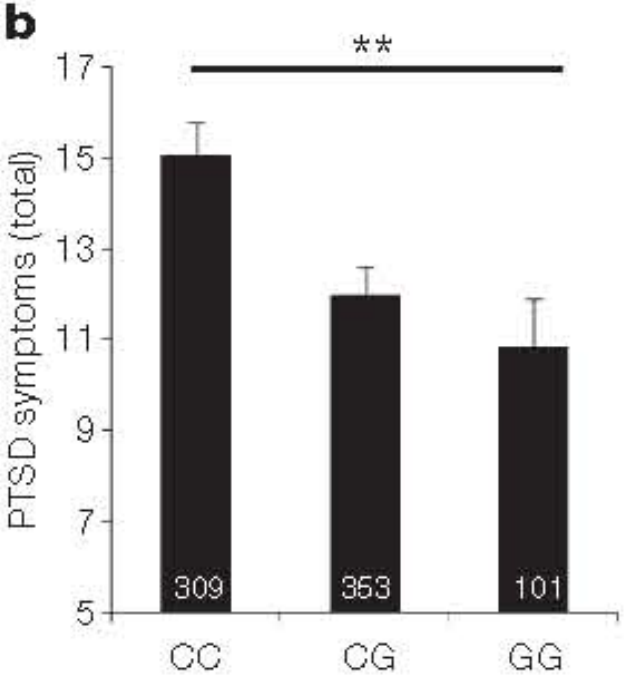
Ressler KJ, et al. *Nature*. 2011;470(7335):492-497.

Association of ADCYAP1R1 with PTSD Symptoms and Physiological Fear Response

a

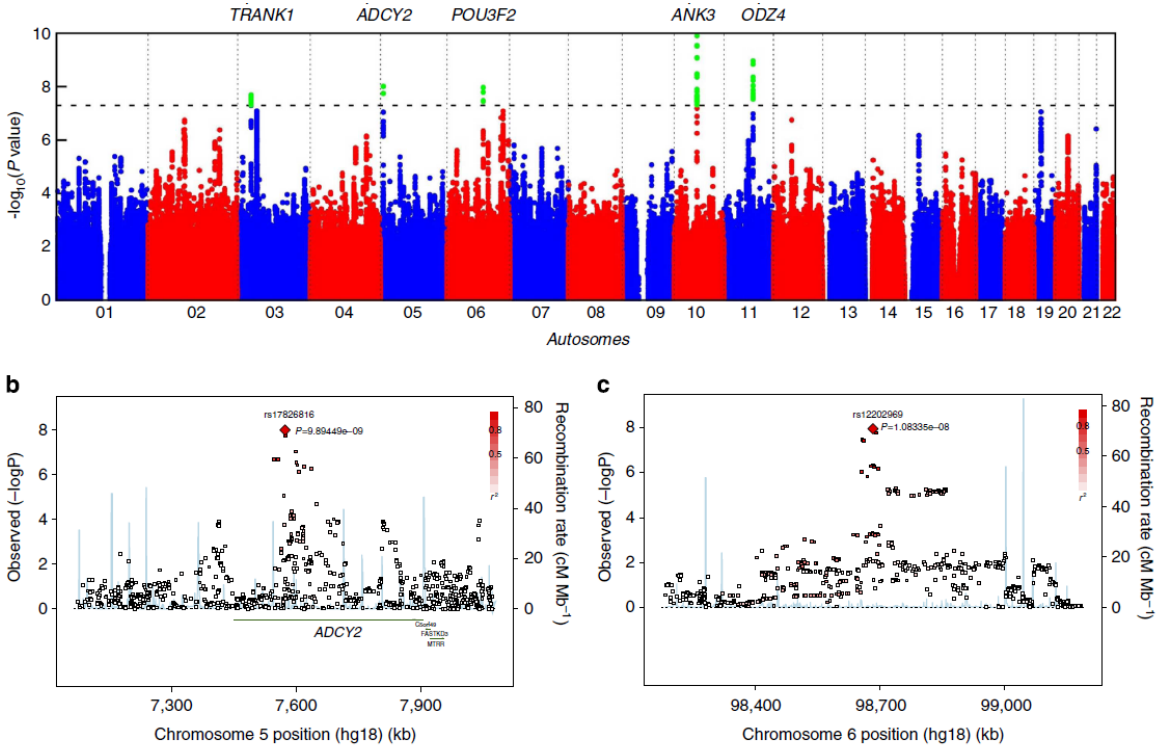
rs2267735–PTSD	*N* (1,237)	*Wald* χ^2	OR (CI)	*P*-value
Male original	295	0.036	1.03 (0.71–1.49)	0.85
Male replication	179	0.57	0.83 (0.52–1.33)	0.45
Male combined	474	0.123	0.95 (0.71–1.27)	0.73
Female original	503	13.7	1.72 (1.29–2.28)	**0.00021**
Female replication	260	4.8	1.54 (1.04–2.29)	**0.029**
Female combined	763	18.4	1.66 (1.32–2.09)	**0.000018**

b



Ressler KJ, et al. *Nature*. 2011;470(7335):492-497.

Association Results for the MooDS-PGC GWAS and 2 New Risk Loci for Bipolar Disorder



a) Manhattan plot for all analyzed SNPs

b,c) Regional association plots for the SNPs analysed at *ADCY2* (5p15.31) and *MIR2113-POU3F2* (6q16.1)

Red = Data for LD

Blue = Recombination frequency

Mühleisen TW, et al. *Nat. Commun*. 2014;5:3339.

Genetic Effect Sizes for the New Loci Identified Through the MooDS-PGC GWAS of Bipolar Disorder

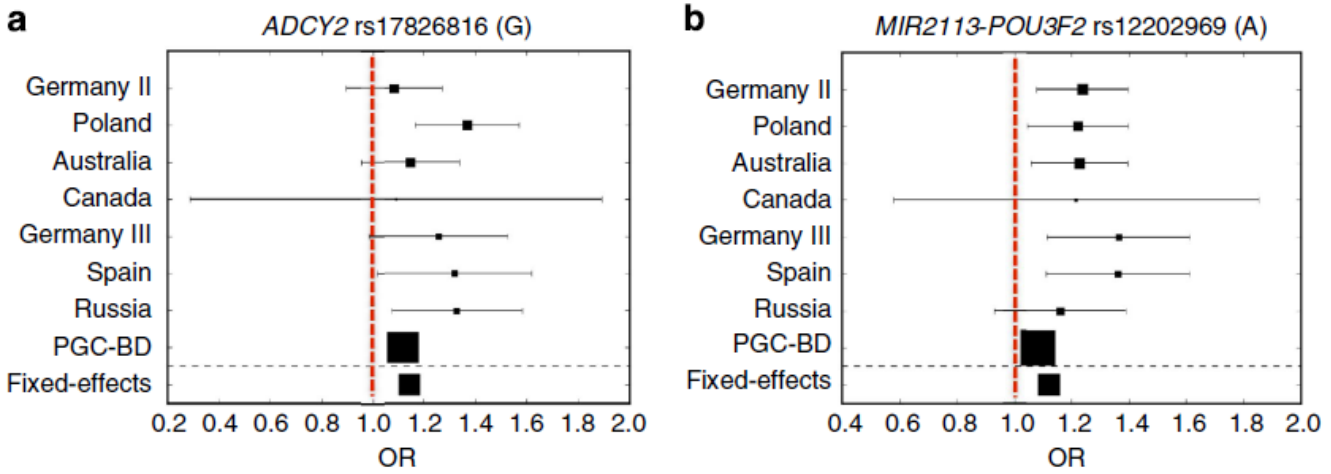
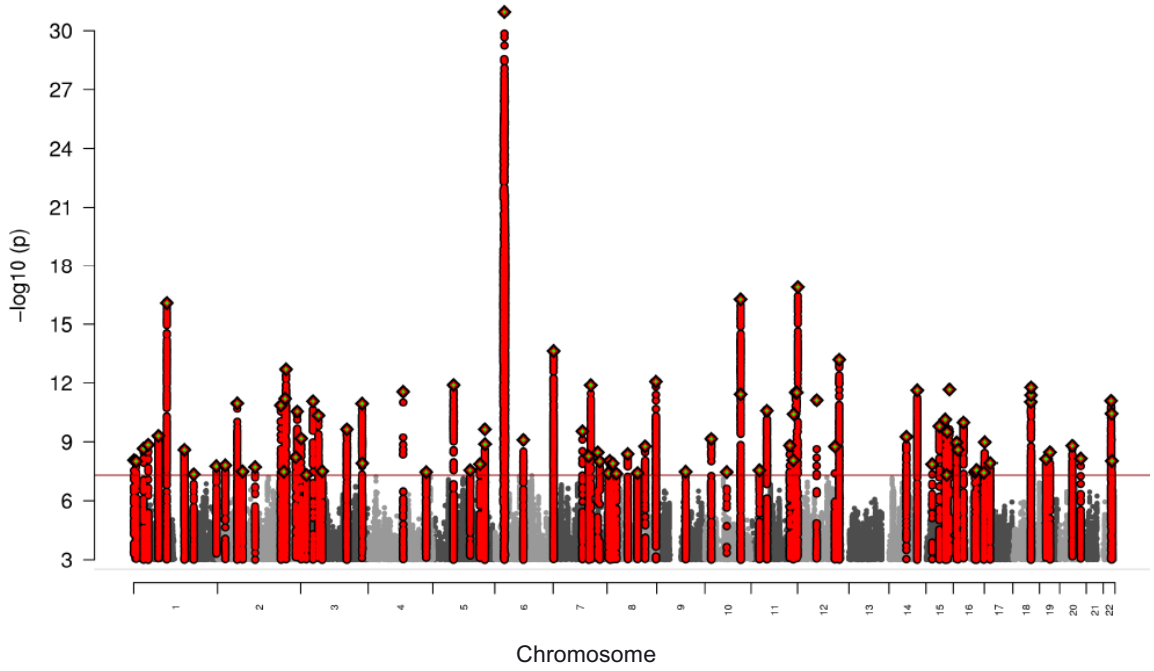


Figure 3 | Genetic effect sizes for the two new risk loci identified through the MooDS-PGC GWAS of BD. (**a**,**b**) Forest plots displaying the most significant SNP's odds ratio (OR, full square) and their 95% confidence interval (horizontal continuous lines) for the gene *ADCY2* (5p15.31) as well as the region between the genes *MIR2113* and *POU3F2* (6q16.1). The overall OR was calculated using a fixed-effects meta-analysis based on the weighted *z*-score method[51]. The effect allele of each SNP is given in brackets. The area of a square reflects the statistical power of the respective study sample. Areas were calculated by the reciprocal value of the standard deviations.

Mühleisen TW, et al. *Nat. Commun*. 2014;5:3339.

PGC 2 –150,000 Subjects, 108“GWAS Significant” Loci



Polygene risk score based on all independent SNPs p < .05, explains ≈ 7% of trait liability

Schizophrenia Working Group of the Psychiatric Genomics Consortium. *Nature* 2014;511(7510):421-427.

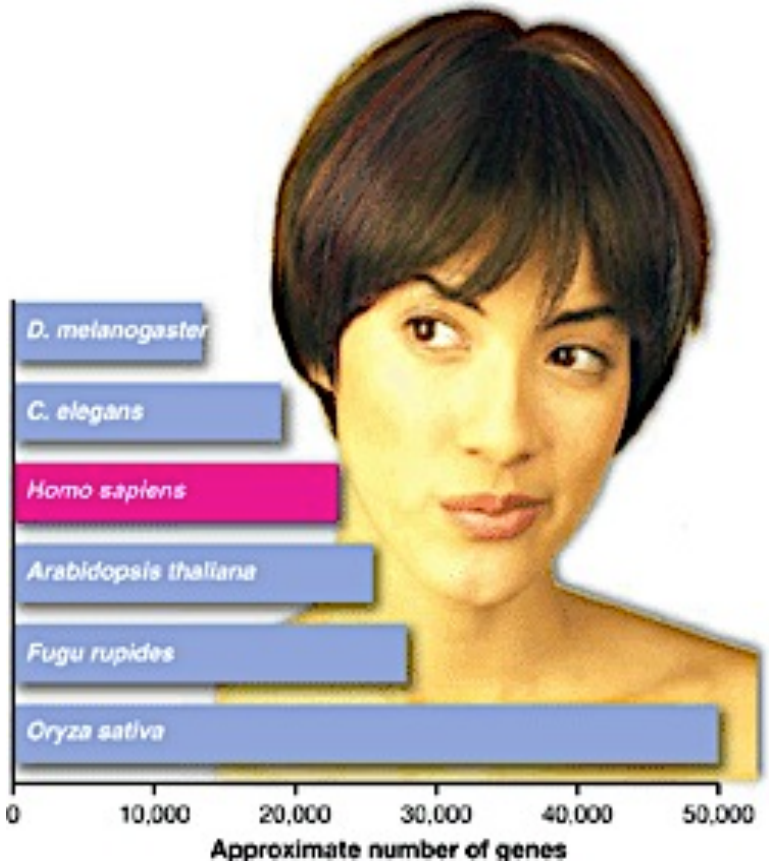
The Schizophrenia GWAS "Success Story" Strong Statistics, (Weak Effects)

128 Genome-Wide Significant Associations for Schizophrenia

Rank	Index SNP	A12	Frq_{case}	$Frq_{control}$	Chr	Position	Combined		Discovery		Replication	
							OR (95% CI)	P	OR	P	OR	P
54	rs4648845	TC	0.533	0.527	1	2,372,401-2,402,501	1.072 (1.049-1.097)	8.7e-10	1.071	4.03e-9	1.088	8.85e-2
57	chr1_8424984_D	I2D	0.319	0.301	1	8,411,184-8,638,984	1.071 (1.048-1.095)	1.17e-9	1.071	2.03e-9	1.057	2.96e-1
65	rs1498232	TC	0.311	0.296	1	30,412,551-30,437,271	1.069 (1.046-1.093)	2.86e-9	1.072	1.28e-9	0.999	9.88e-1
50	rs11210892	AG	0.659	0.677	1	44,029,384-44,128,084	0.934 (0.914-0.954)	3.39e-10	0.933	4.97e-10	0.949	3.08e-1
22	rs12129573	AC	0.377	0.358	1	73,766,426-73,991,366	1.078 (1.056-1.101)	2.03e-12	1.072	2.35e-10	1.217	6.25e-5
107	rs76869799	CG	0.959	0.964	1	97,792,625-97,834,525	0.846 (0.798-0.897)	2.64e-8	0.850	1.44e-7	0.779	5.34e-2
2	rs1702294	TC	0.175	0.191	1	98,374,984-98,559,084	0.887 (0.865-0.911)	3.36e-19	0.891	2.79e-17	0.831	1.35e-3
52	rs140505938	TC	0.151	0.164	1	149,998,890-150,242,490	0.914 (0.888-0.940)	4.49e-10	0.913	9.34e-10	0.928	2.53e-1
120	rs6670165	TC	0.196	0.184	1	177,247,821-177,300,821	1.075 (1.047-1.103)	4.45e-8	1.074	1.16e-7	1.090	1.46e-1
121	rs7523273	AG	0.695	0.685	1	207,912,183-208,024,083	1.063 (1.040-1.087)	4.47e-8	1.062	1.61e-7	1.092	8.85e-2
101	rs10803138	AG	0.232	0.238	1	243,503,719-243,612,019	0.933 (0.911-0.956)	2.03e-8	0.932	1.79e-8	0.968	5.56e-1
68	rs77149735	AG	0.0225	0.0191	1	243,555,105-243,555,105	1.317 (1.202-1.444)	3.73e-9	1.329	4.4e-9	1.173	3.66e-1
119	rs14403	TC	0.207	0.222	1	243,639,893-243,664,923	0.934 (0.911-0.957)	4.42e-8	0.935	1.31e-7	0.920	1.53e-1
78	chr1_243881945_I	I2D	0.638	0.619	1	243,690,945-244,002,945	1.068 (1.045-1.092)	6.53e-9	1.066	3.11e-8	1.107	6.17e-2

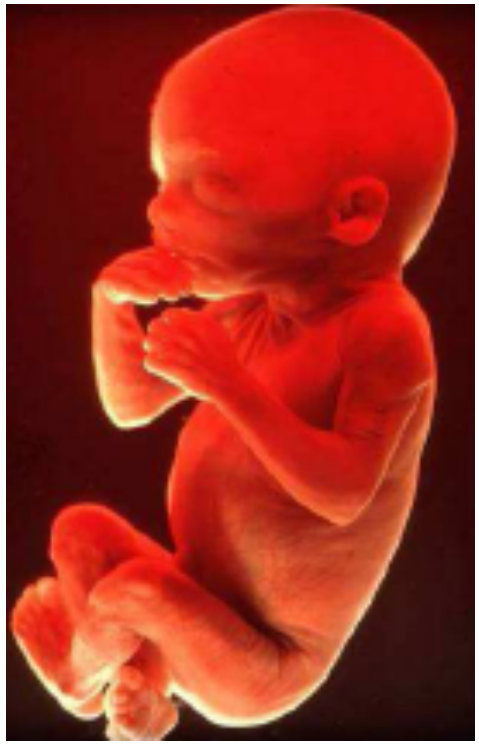
Schizophrenia Working Group of the Psychiatric Genomics Consortium. *Nature* 2014;511(7510):421-427.

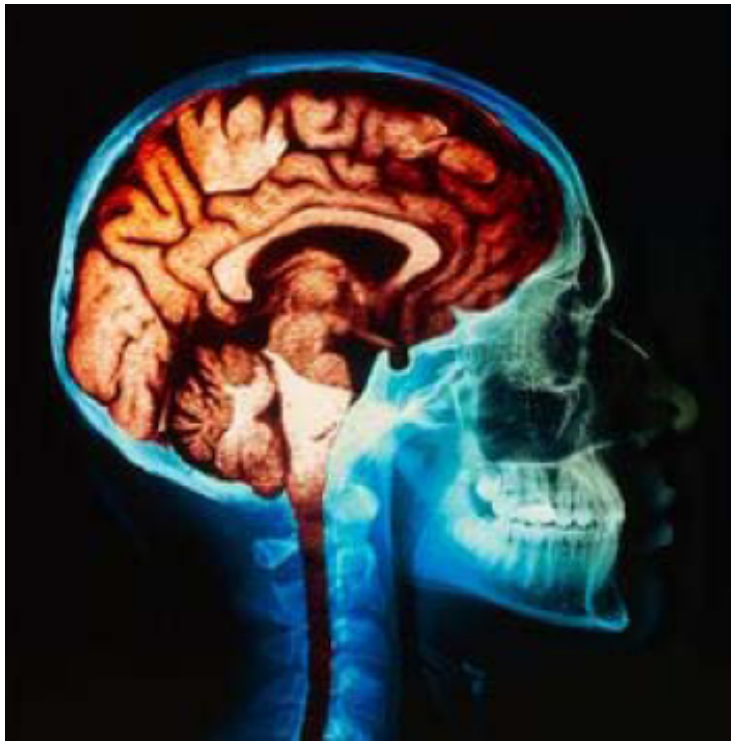
Biggest Surprise From the Genome Projects: Number of Conventional Genes Do Not Scale with Complexity



Daiger, SP. *Science*. 2005;362-364.

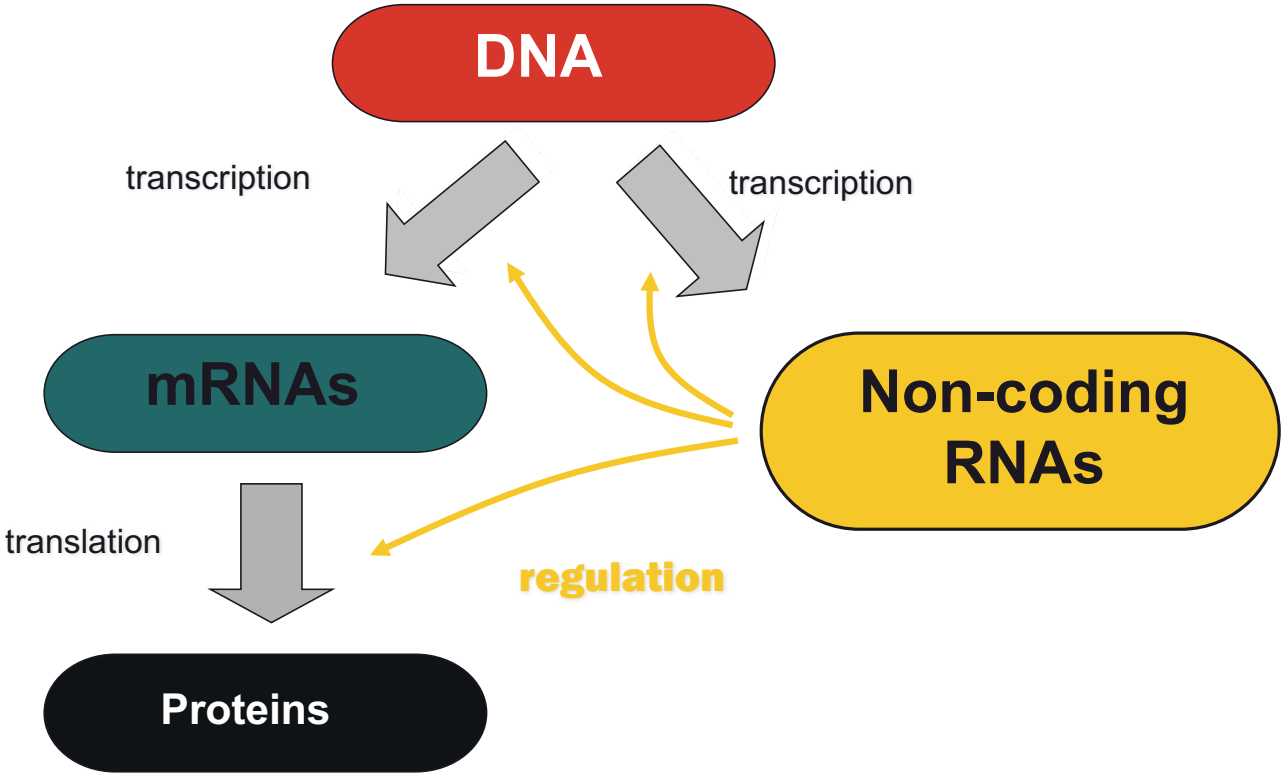
Where is the Information That Programs Our Complexity?





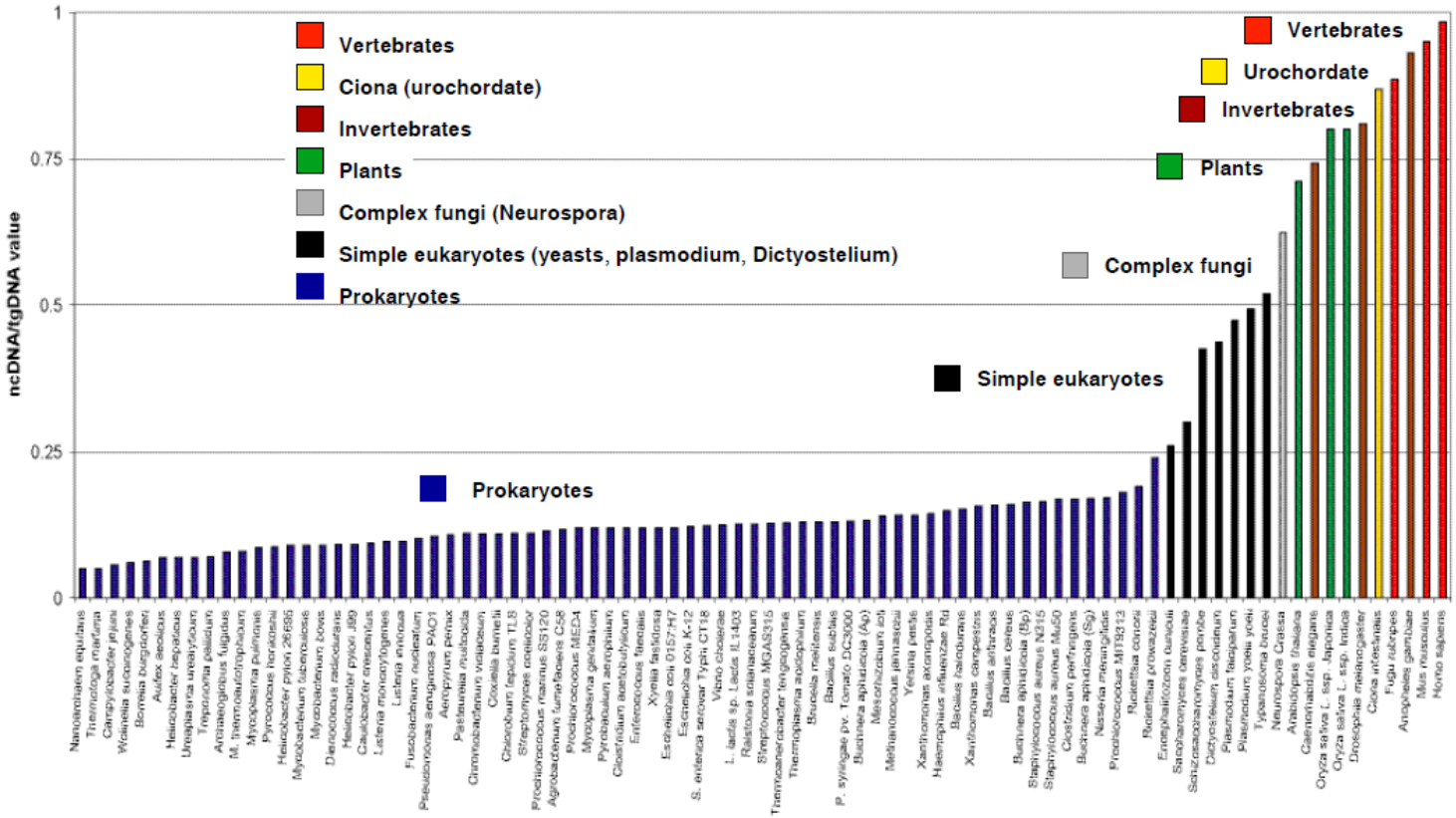
Modified “Central Dogma”

F. Crick

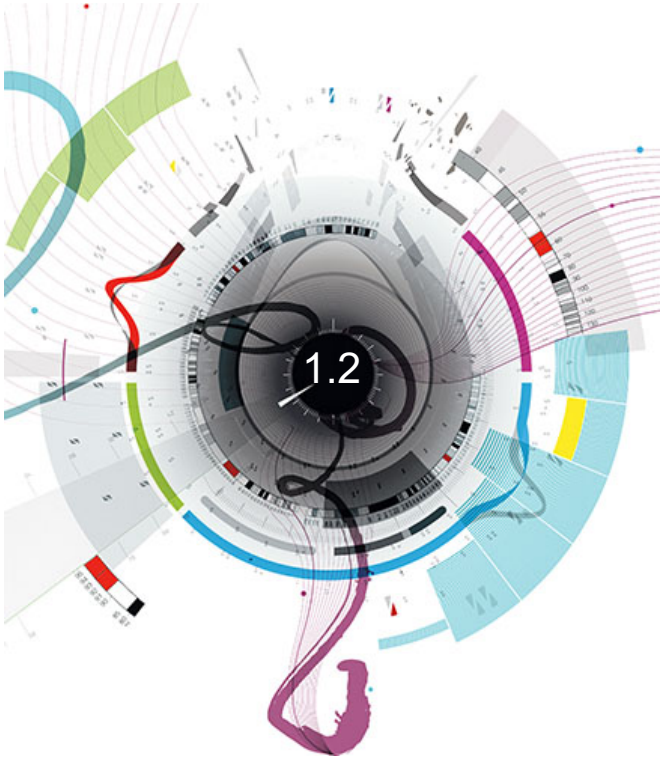


The Proportion of Nancoding DNA Broadly Increases with Developmental Complexity

J. Mattick



Only 1.2% of the Genome is Made Up of Conventional Genes…



…but most of the genome is transcribed.

Zimmer C. *New York Times*, November 10, 2008. http://www.nytimes.com/2008/11/11/science/11gene.html?_r=0.

New View of the Human Genome

- Islands of (conventional) protein-coding genes in a sea of regulatory information
- “Genes” are not discrete entities
- Regulation is orchestrated by RNA as well as proteins
- Theory: Complexity is achieved primarily by RNA

Why Study microRNAs in Psychiatric Disease?

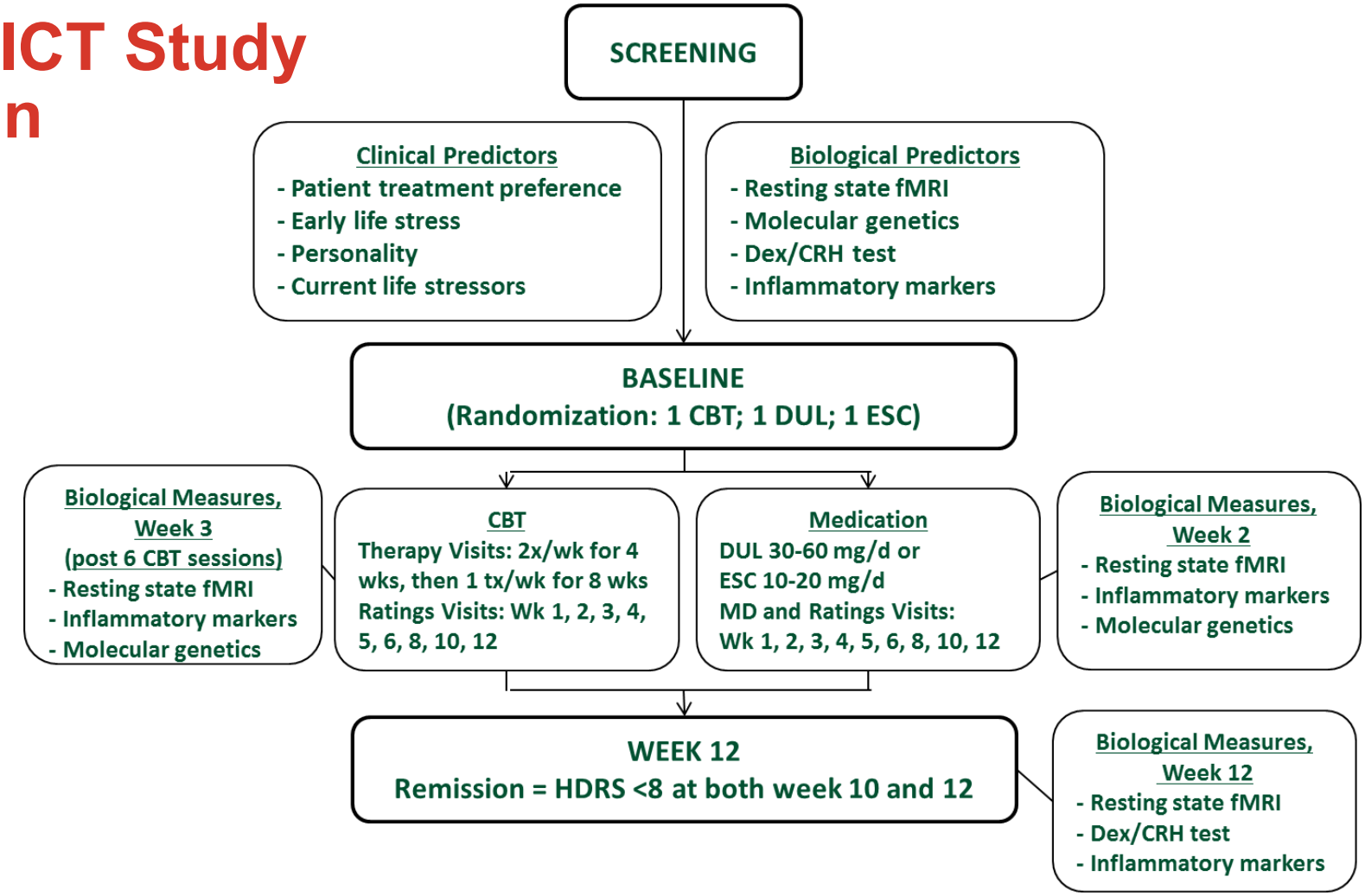
- MicroRNAs are predicted to regulate up to hundreds of genes each (‘master regulators’)
- At least half of protein-coding genes may be regulated by microRNAs
- Single microRNAs may target multiple genes within a biological pathway
- MicroRNAs evolve easily and their number increases with organismal complexity
- Major role in neurodevelopment and cell differentiation
- Regulatory layer that may account for missing genetic/epigenetic variability in the etiology of disease

Predictors of Remission in Depression to Individual and Combined Treatments [PReDICT]

- PReDICT study aimed to identify clinical and biological factors predictive of treatment outcomes in major depressive disorder (MDD) among treatment naïve adults.
- The authors evaluated the efficacy of cognitive behavioral therapy (CBT) and 2 antidepressant medications (escitalopram and duloxetine) in patients with major depression and examined the moderating effect of patients' treatment preferences on outcomes.

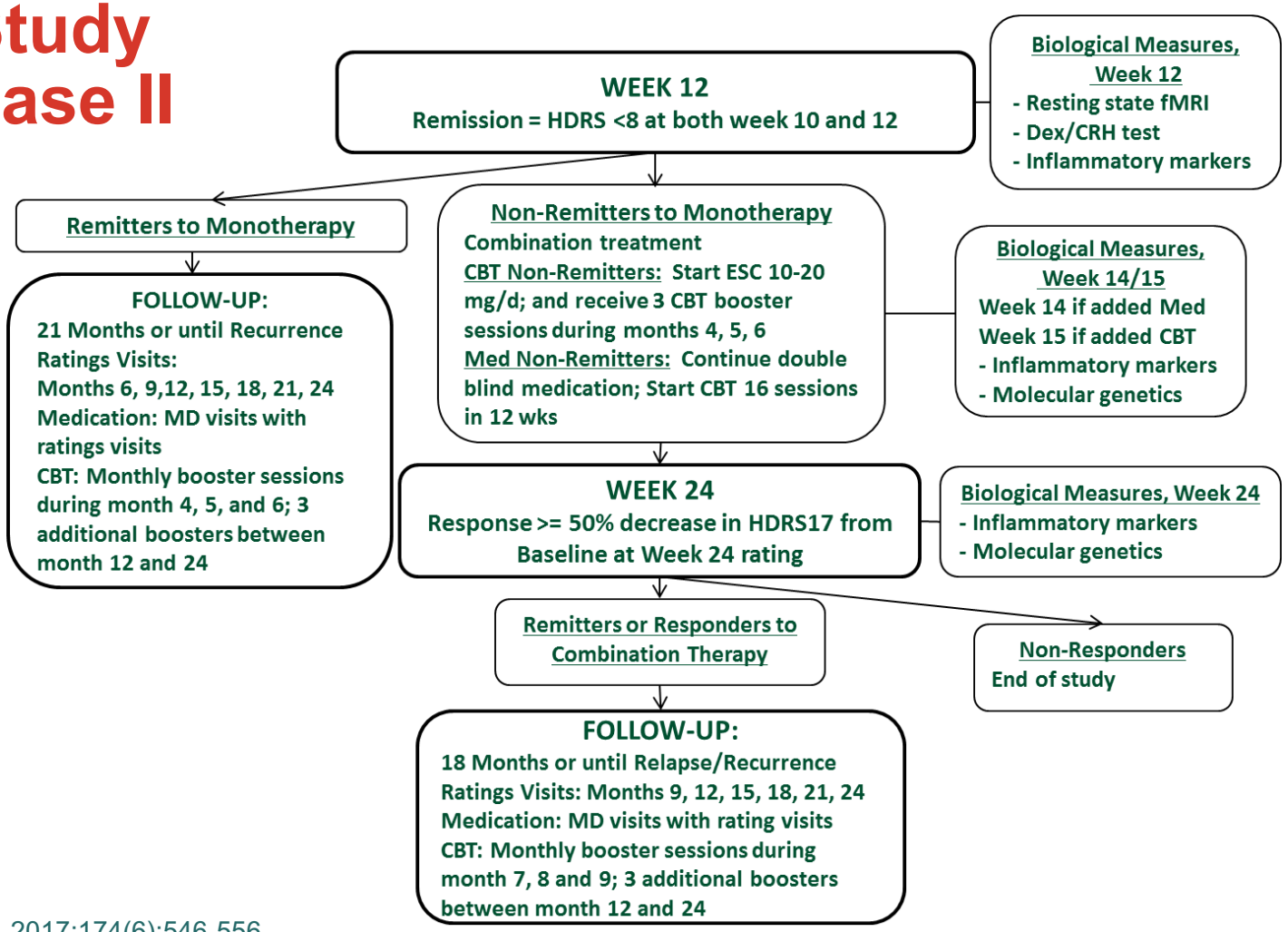
Dunlop B, et al. *Am J Psychiatry*. 2017;174(6):546-556.

PReDICT Study Design



Dunlop B, et al. *Am J Psychiatry*. 2017;174(6):546-556.

PReDICT Study Design, Phase II



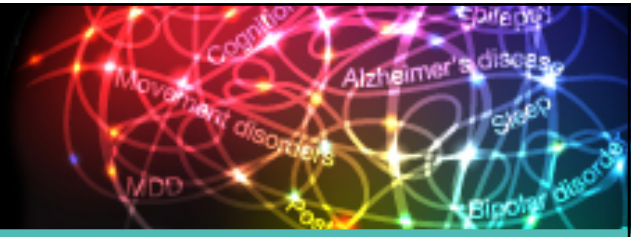
Dunlop B, et al. *Am J Psychiatry*. 2017;174(6):546-556.

PReDICT Methods

- Adults aged 18-65 with treatment-naïve MDD were randomly assigned with equal likelihood to 12 weeks of treatment with escitalopram (10-20 mg/day), duloxetine (30-60 mg/day), or CBT (16 x 50-minute sessions).
- Prior to randomization, patients indicated whether they preferred medication or CBT or had no preference
- The primary outcomes was change in the 17-item Hamilton Depression Rating Scale (HAM-D), administered by raters blinded to treatment.

Dunlop B, et al. *Am J Psychiatry*. 2017;174(6):546-556.

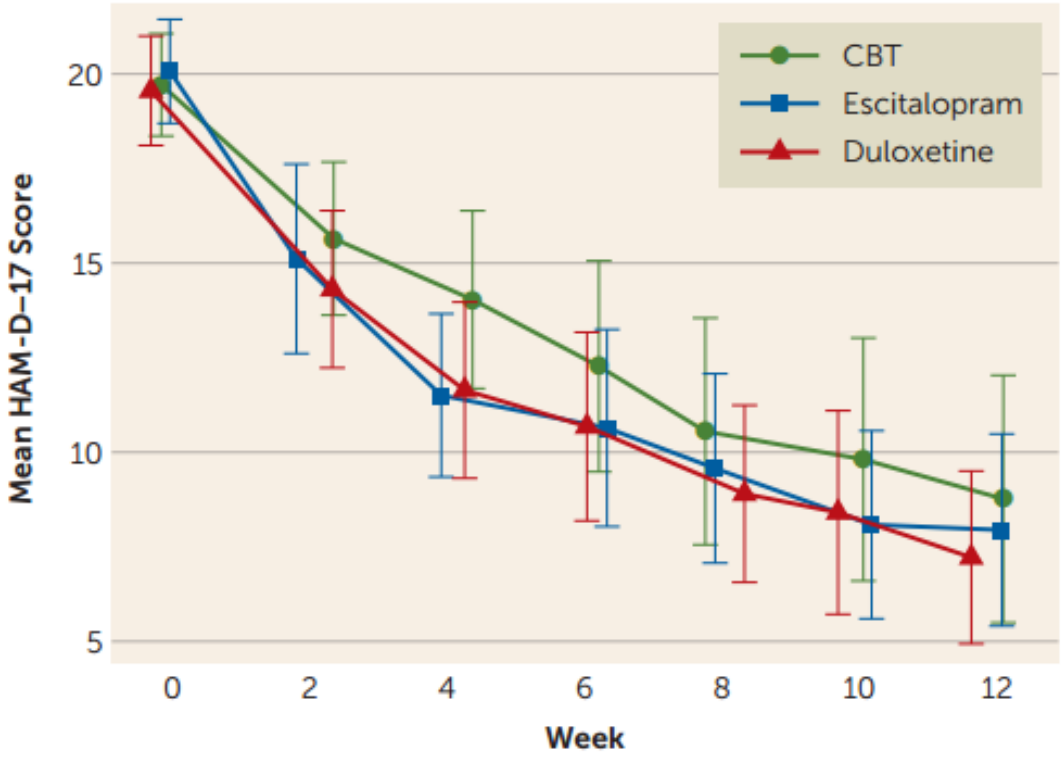
PReDICT Results



- A total of 344 patients were randomly assigned, with a mean baseline HAM-D score of 19.8 (SD = 3.8)
- The mean estimated overall decreases in HAM-D score did not significanty differ between treatments
  - CBT: 10.2
  - Escitalopram: 11.1
  - Duloxetine: 11.2
- Last observation carried forward remission rates did not significantly differ between treatments
  - CBT: 41.9%
  - Escitalopram: 46.7%
  - Duloxetine: 54.7%
- Patients matched to their preferred treatment were more likely to complete the trial but not more likely to achieve remission

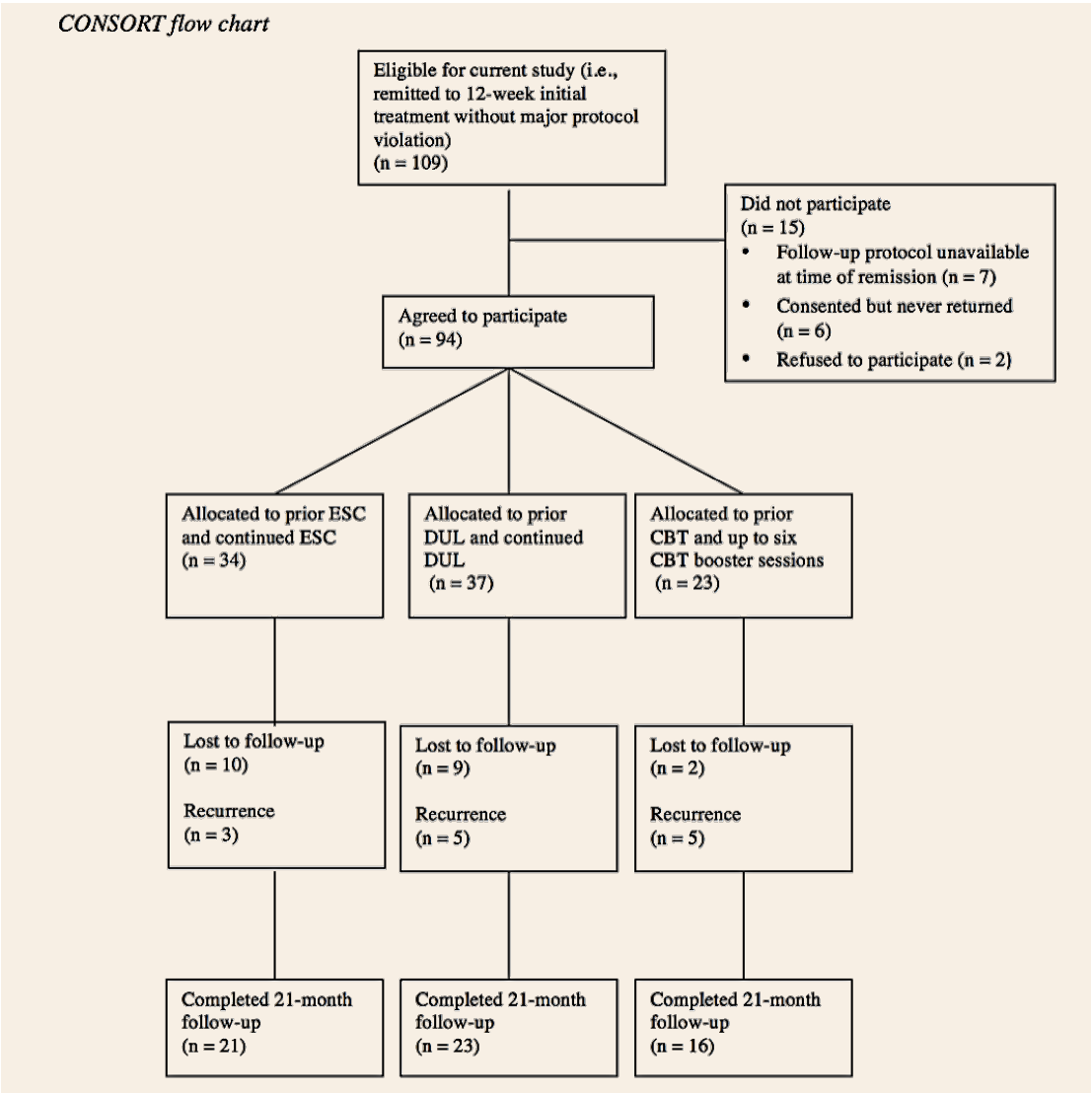
Dunlop B, et al. *Am J Psychiatry*. 2017;174(6):546-556.

Modeled Change in the Mean Hamilton Depression Rating Scale (HAM-D) Score by Week



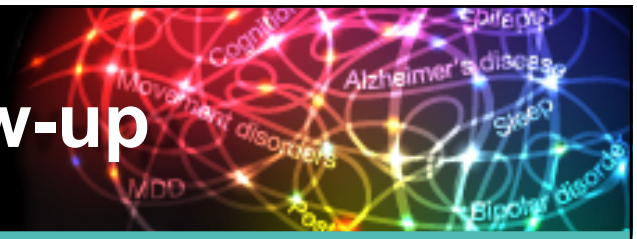
Error bars represent 95% confident intervals

Dunlop B, et al. *Am J Psychiatry*. 2017;174(6):546-556.



Kennedy et al. 2017

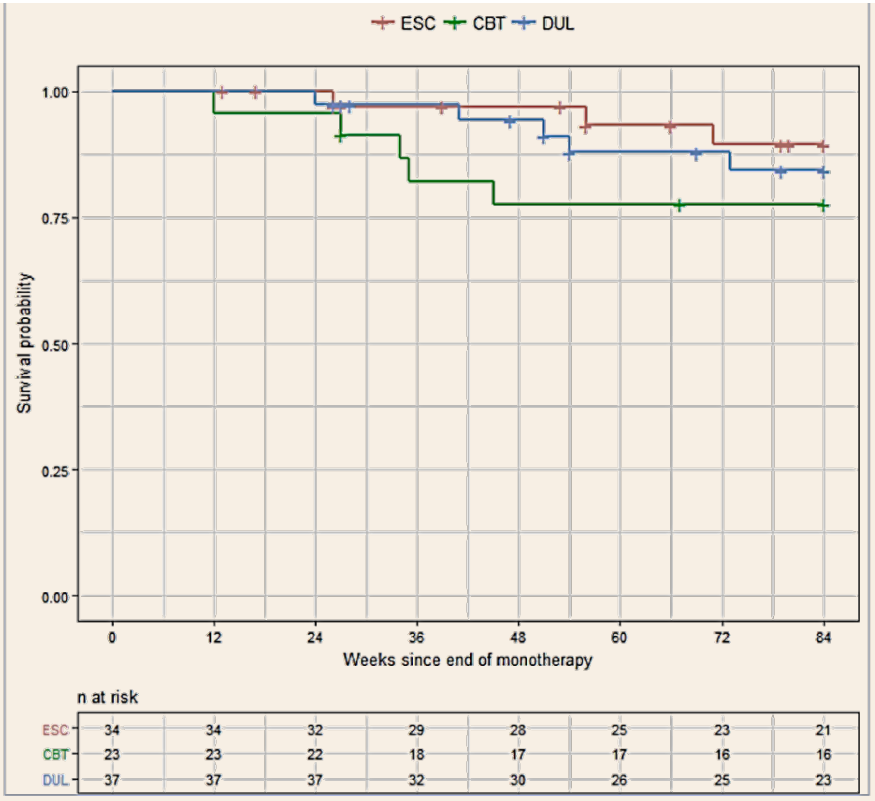
Monotherapy Remitter 2-Year Follow-up



- No differences in three treatments for 94 (109) who remitted to monotherapy
- Relapse rate was ~15%
- Two variables predicted relapse
  - Residual symptoms of depression
  - Baseline diagnosis of comorbid anxiety
- Will be investigating biomarkers of recurrence.

Kennedy et al., 2017.

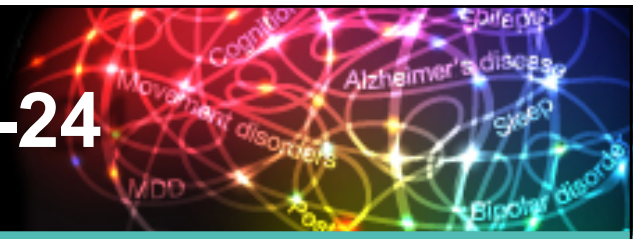
Cumulative Proportion of Participants Surviving Without Depressive Relapse/Recurrence Over 21 Months of Follow-up



Note. ESC = escitalopram; CBT = cognitive behavior therapy; DUL = duloxetine

Kennedy et al., 2017.

Combination Treatment – Weeks 12-24



- No differences at 24 weeks in three combination treatments for non-remitters at 12 weeks
- In total, about 70% of patients remitted
- No differences in order (sequencing) of treatment
- Currently analyzing 2-year recurrence rates (18 months after end of combination treatment)

Kennedy et al., 2017.

Striatal Serotonin Transporter (5-HTT) Occupancy in Depressed Subjects After 4 Weeks of Treatment at Minimum Therapeutic Doses of 5 SSRIs

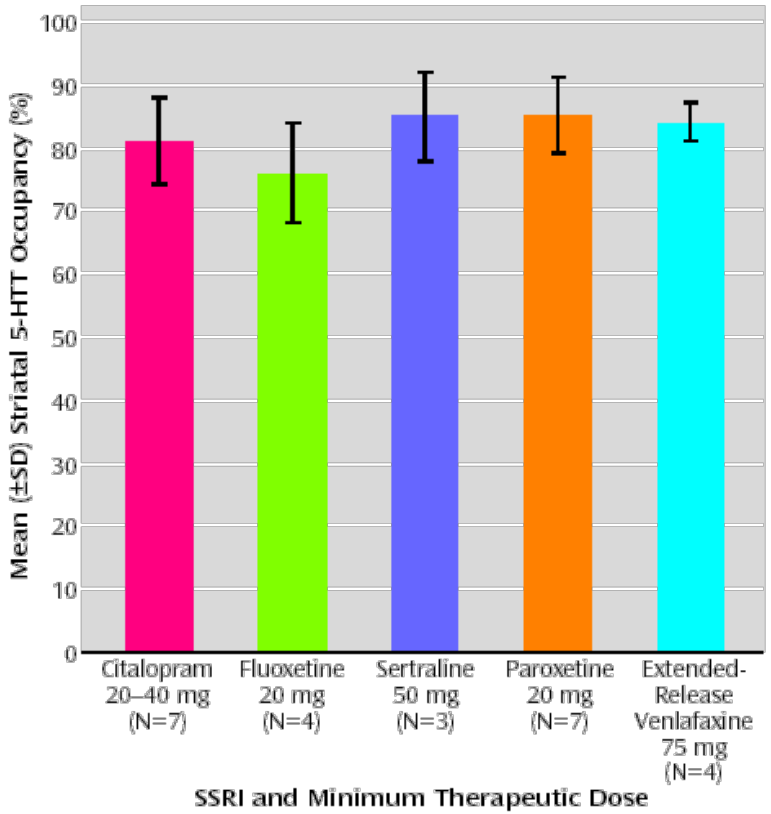
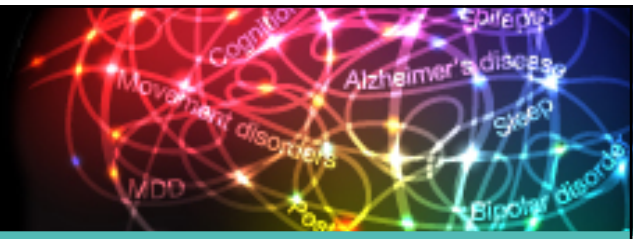


TABLE 1. Estimated Dose (ED_{50}) and Plasma Concentration (EC_{50}) Needed to Obtain 50% Serotonin Transporter Striatal Occupancy for Five SSRIs Administered to 77 Healthy and Depressed Subjects for 4 Weeks

SSRI	ED_{50} (mg/day)	EC_{50} (µg/liter)
Citalopram	3.4	11.7
Fluoxetine	2.7	14.8
Sertraline	9.1	1.1
Paroxetine	5.0	2.7
Extended-release venlafaxine	5.8	3.4

Meyer J, et al. *Am J Psychiatry*. 2004;161(5):826-835.

Potency of SSRIs

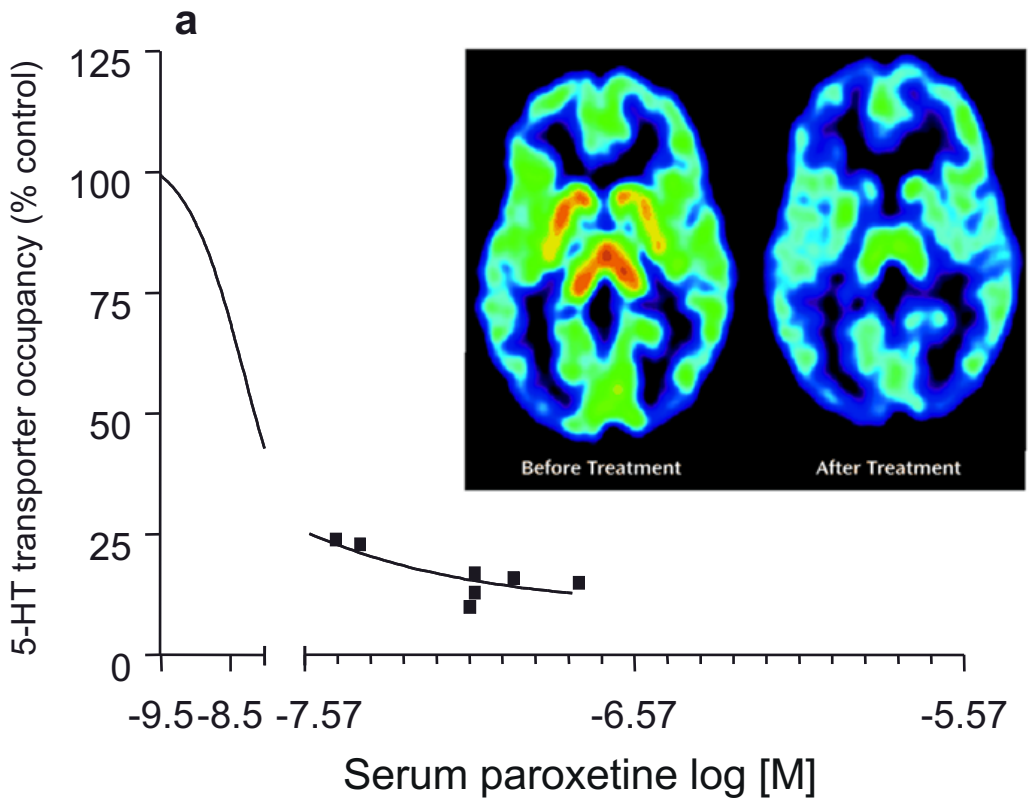


Human Monoamine Transporter Binding and Uptake Inhibition

	Transporter Binding K_i (nmol/L)			Uptake Inhibition K_i (nmol/L)		
	5-HT	NE	DA	5-HT	NE	DA
Escitalopram	1.10	7,841	27,410	2.5	6,514	>100,000
Citalopram	1.60	6,190	16,540	9.6	5,029	>100,000
Fluoxetine	1.10	599	3,764	5.7	599	5,960
Fluvoxamine	2.30	1,427	16,790	11	1,119	32,240
Paroxetine	0.10	45	268	0.34	156	963
Sertraline	0.26	714	22	2.8	925	315

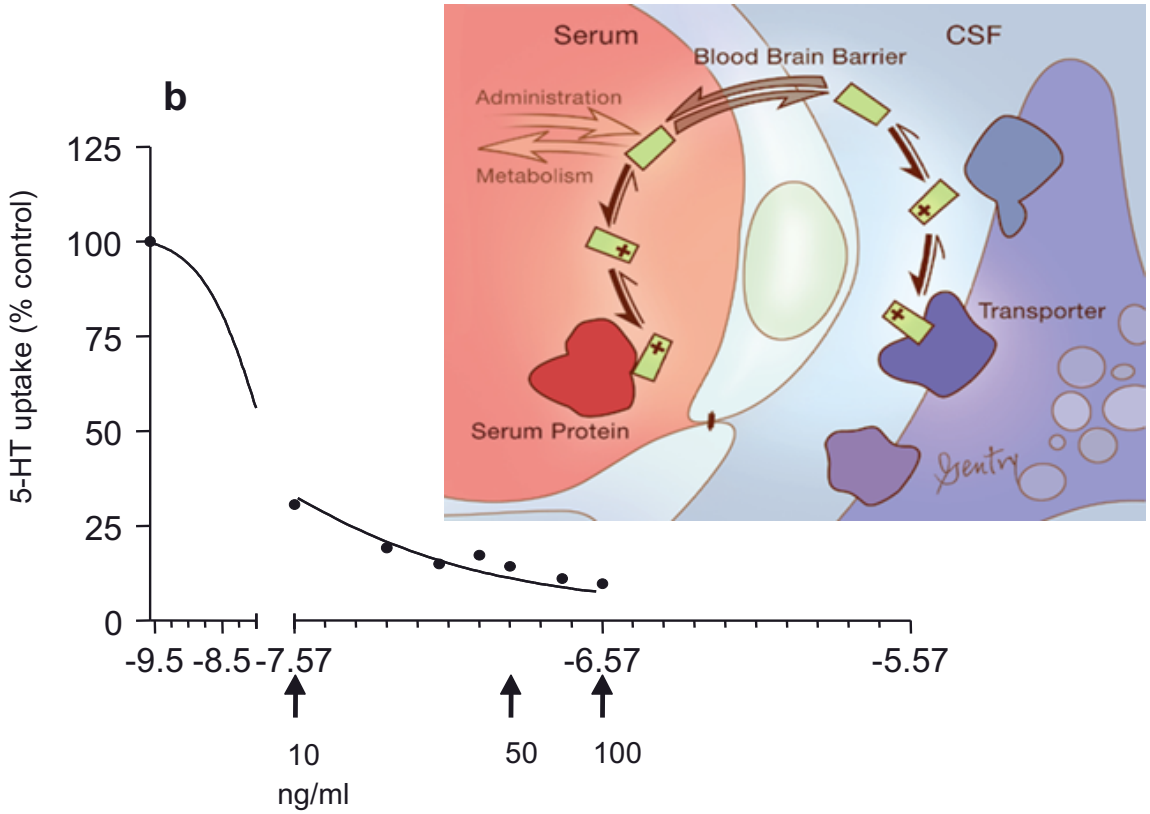
Coplan JD, et al. *Biol Psychiatry*. 2001;50(3):200-204.

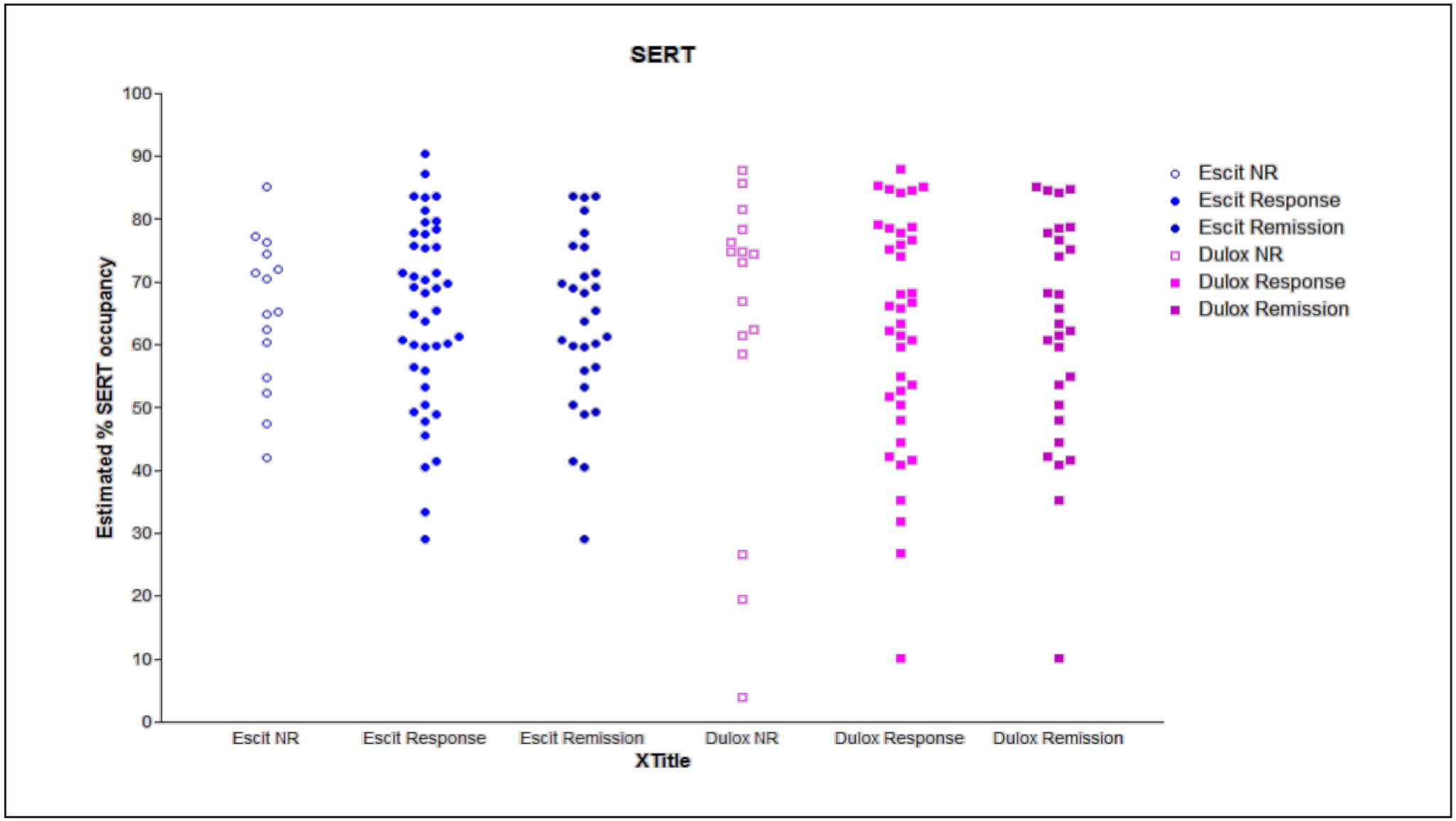
Estimates Of 5-HT Transporter Occupancy Using PET Imaging. Inset Is Representative PET Image From A Patient Before And After 4 Week Treatment With Citalopram

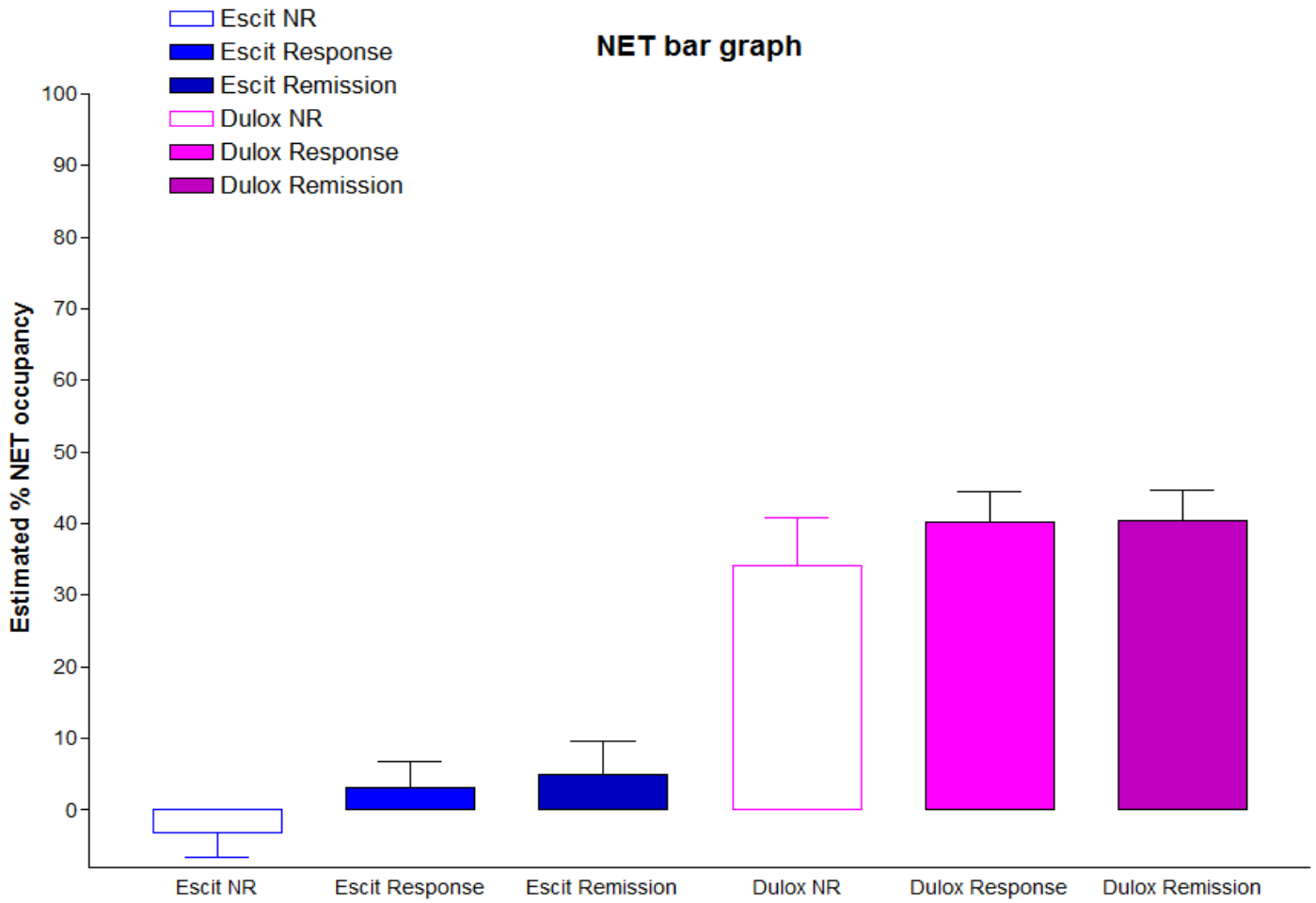


Meyer JH, et al. *Am J Psychiatry*. 158(11):1843-1849.

Inhibition Of 5-HT Uptake Ex Vivo Using Human Serum Equilibrated With Increasing Concentrations Of Paroxetine. Inset Depicts Equilibrium Between Total and Free Paroxetine In Serum and Shows that Only Unbound ('Free') Paroxetine Has Access to the CNS

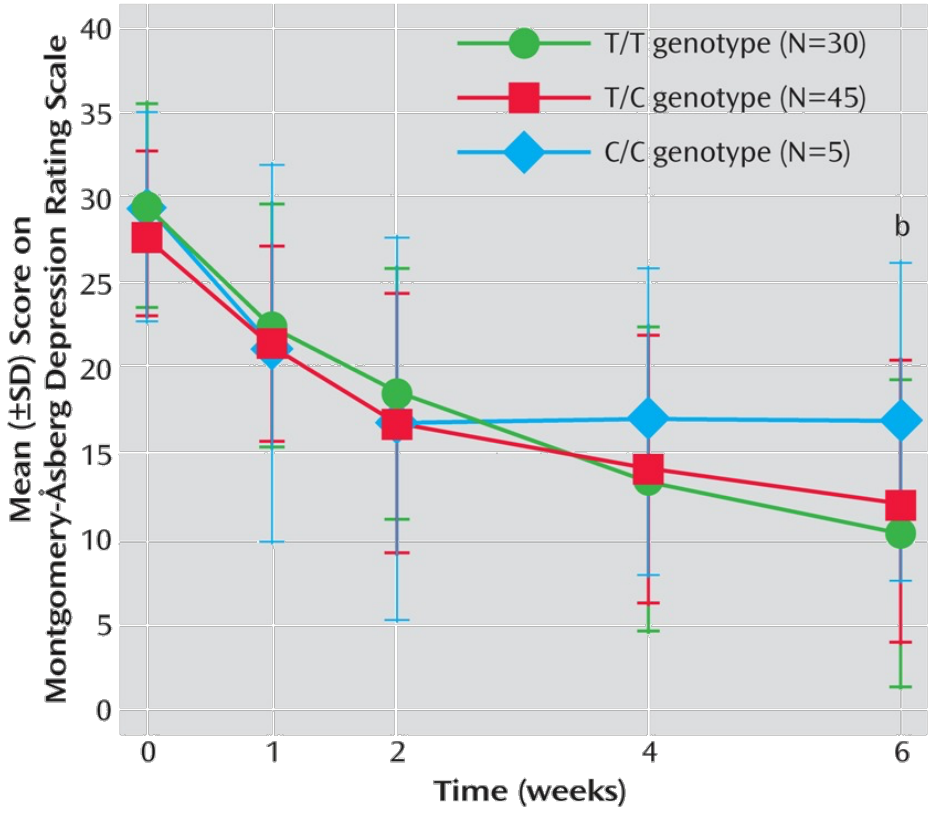



SERT
Estimated % SERT occupancy
100
90
80
70
60
50
40
30
20
10
0
Escit NR
Escit Response
Escit Remission
Dulox NR
Dulox Response
Dulox Remission
XTitle
Escit NR
Escit Response
Escit Remission
Dulox NR
Dulox Response
Dulox Remission



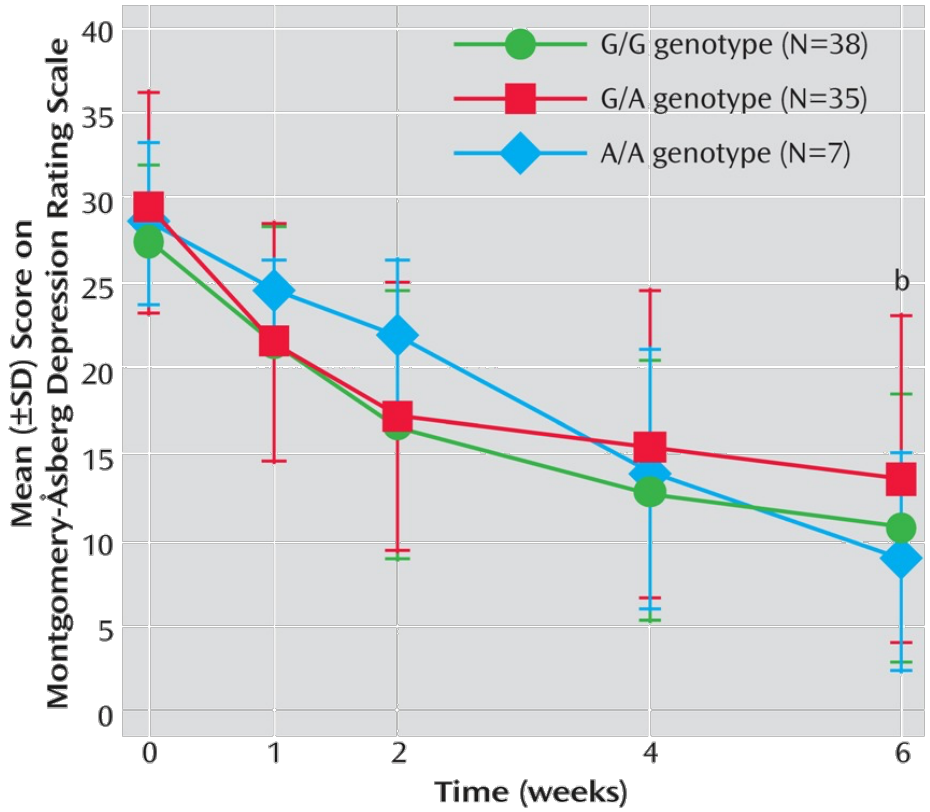
Estimated NET occupancy (mean ± SEM) at week 12 did not predict treatment response. ESC = escitalopram; DUL = duloxetine; NR = no response or worsening; PR = partial response but not meeting criteria for Response. NR+PR = the "Nonresponse" group.

Montgomery-Åsberg Depression Scores During 6 Week Treatment in Relation to the NET T-128C Polymorphism



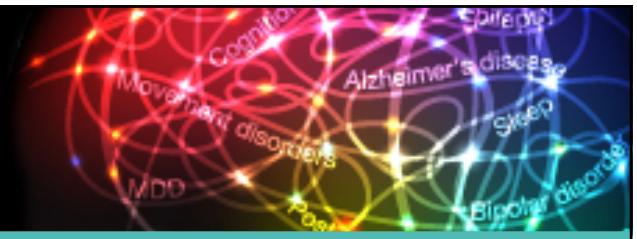
Yoshida K, et al. *Am J Psychiatry.* 2004:161:1575-1580.

Montgomery-Åsberg Depression Scores During 6 Week Treatment in Relation to the Polymorphism



Yoshida K, et al. *Am J Psychiatry*. 2004:161:1575-1580.

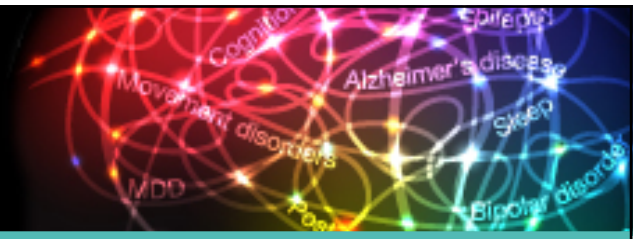
Objective and Method



- **Objective:** Investigate 5 putatively functional variants of the norepinephrine transporter (*SLC6A2, NET*) serotonin transporter (*SLC6A4, SERT*) genes and remission in depressed older adults treated with venlafaxine. Secondary objective was to analyze 17 other variants in serotonergic system genes (*HTR1A, HTR2A, HTR1B, HTR2C, TPH1, TPH2)* potential involved in the mechanisms of action of venlafaxine.
- **Methods:** 350 adults age 60 or older with *DSM-IV*-defined MDD and a score of at least 15 on the Montgomery-Asberg Depression Rating Scale (MADRS). Participants received protocolized treatment with open-label venlafaxine, up to 300 mg/day for approximately 12 weeks, as part of a 3-site clinical trial. Each individual was genotyped for 22 polymorphisms in 8 genes, which were tested for association with venlafaxine remission (MADRS score ≤ 10) and changes in MADRS score during treatment.

Marshe VS, et al. *Am J Psychiatry*. 2017;174:468-475.

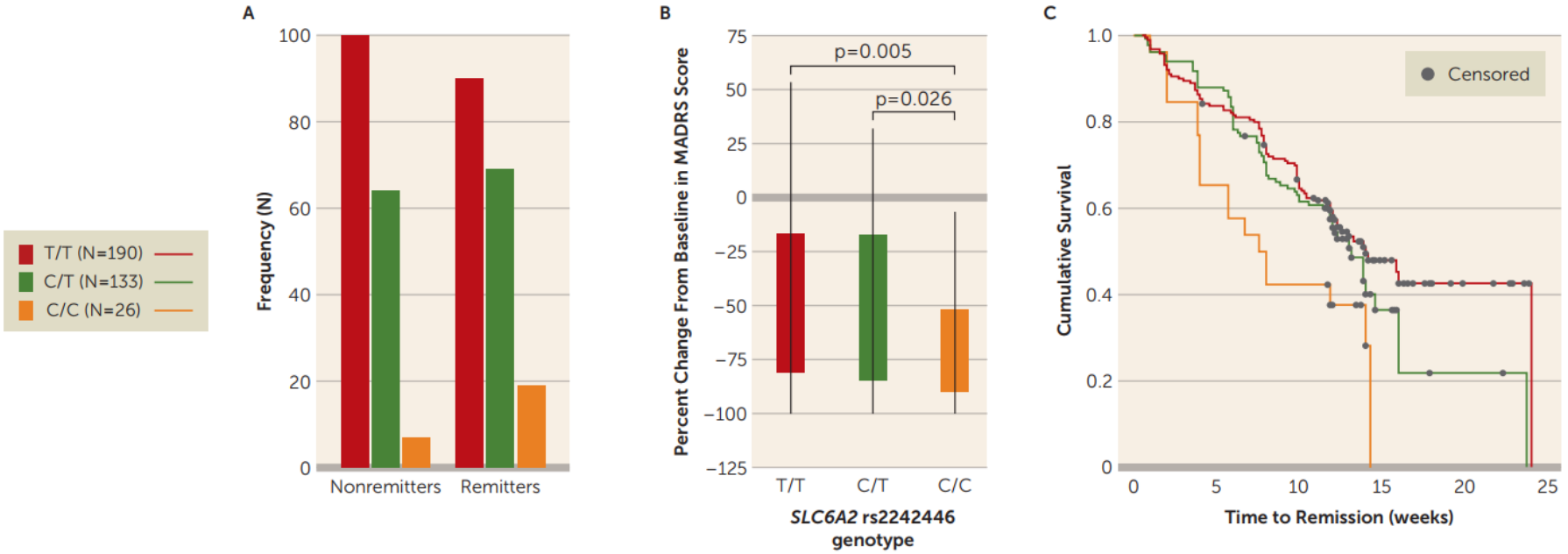
Results



- **Results:** After adjusting for multiple comparisons, *NET* variant rs2242446 (T-182C) was significantly associates with remission (odds ratio = 1.66, CI = 1.13, 2.42). Individuals with the rs2242446 C/C genotype were more likely to remit &73.1%) than those with either the C/T (51.8%) or the T/T genotype (47.3%). Individuals with the C/C genotype also had a shorter time to remission than those with the C/T or T/T genotypes and had a greater percentage change in MADRS score from baseline to end of treatment (up to week 12).

Marshe VS, et al. *Am J Psychiatry*. 2017;174:468-475.

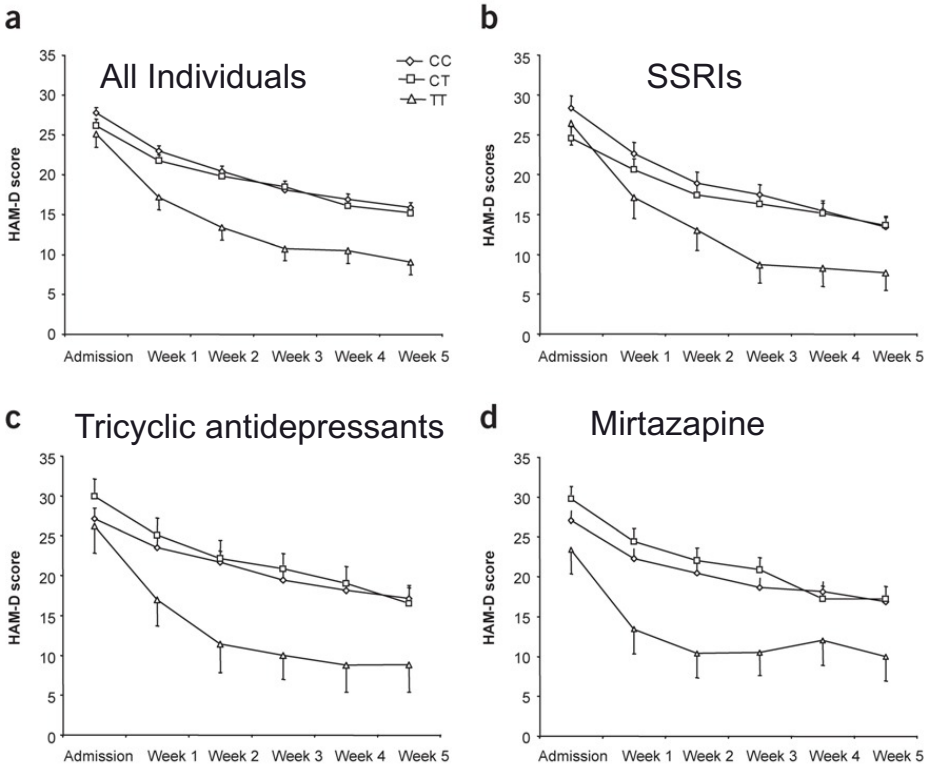
Association of *SCL6A2* Variant re2242446 with Remission, % Change from Baseline to End of Treatment in MADRS Score, and Time to Remission in the Total Sample (n = 350)



[a] In panel A, there was a significant association between remission status and *SLC6A2* rs2242446 genotype (odds ratio=1.67, 95% CI=1.13, 2.42, p=0.009). Panel B is a box-and-whisker plot showing the first quartile (25%, lower end), the median, and the third quartile (75%, upper end) for the variable percentage change in MADRS score. There was a significant association between percentage change in MADRS score and rs2242446 (partial eta squared, η^2=0.03, p=0.006). Panel C illustrates time to remission by rs2242446 status. There was a significant association between time to remission and rs2242446 (Mantel-Cox χ^2=9.47, df=2, p=0.009). MADRS=Montgomery-Åsberg Depression Rating Scale.

Marshe VS, et al. *Am J Psychiatry*. 2017;174:468-475.

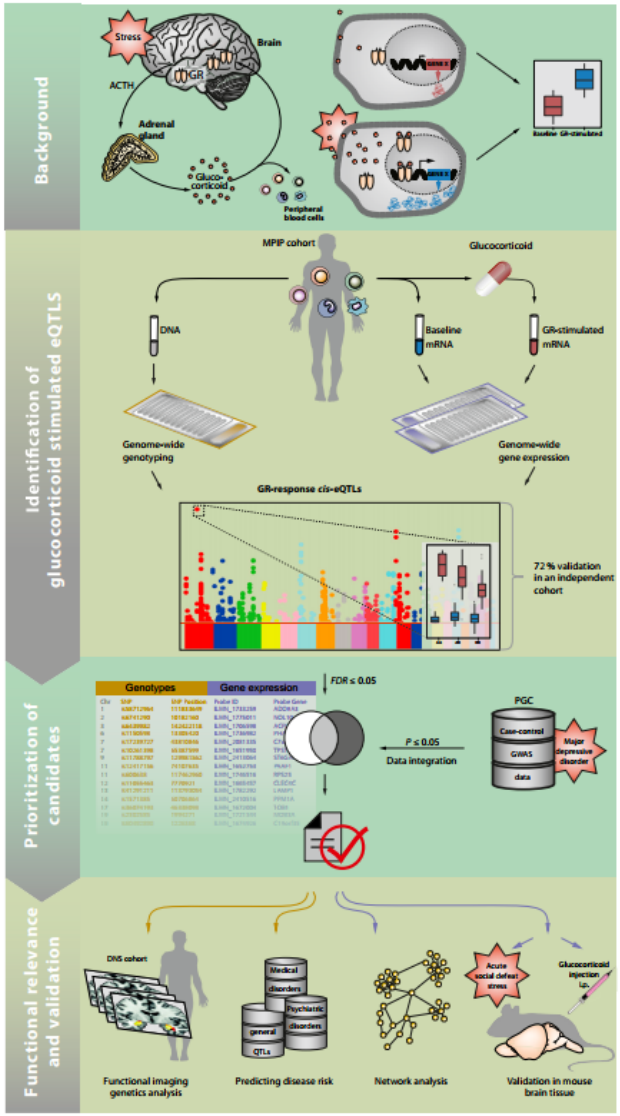
Polymorphisms in FKBP5 are Associated with Rapid Response to Antidepressant Treatment



Binder EB, et al. *Nature Genetics*. 2004;36(12):1319-1325.

Summary Figure Illustrating the Sequence of Experiments and Analyses

The main hypothesis tested in this study is that common genetic variants that after the short-term transcriptional response to GR activation also after the risk for stress-related psychiatric disorders and related neural endophenotypes.



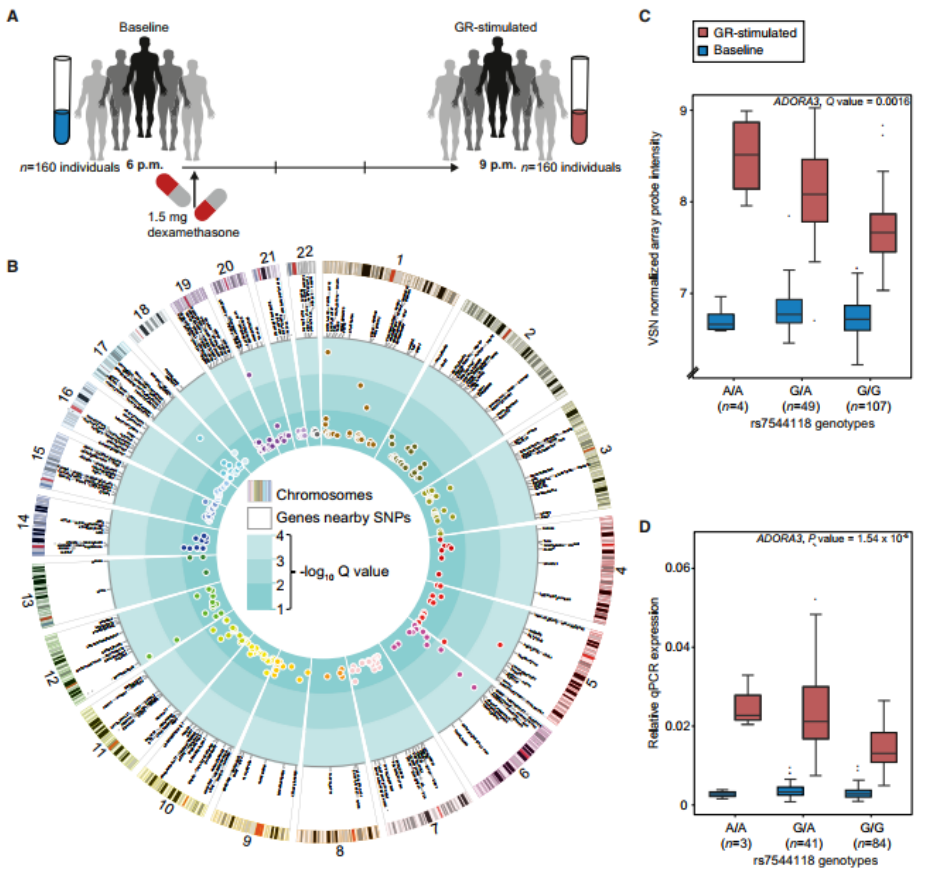
Arloth J, et al. *Neuron.* 2015;86(5):1189-1202.

GR-Response-Modulating *cis*-*e*QTLs

(A) Study design of GR-stimulated gene expression in whole blood of 160 male individuals from the Max Planck Institute of the Psychiatry cohort

(B) Circularized Manhattan plot displaying *cis*-associations for GR-response *e*QTL bins (n = 320) and their respective significance (-$\log_{10}$ Q values). Displayed from the outer to the inner circle are the number of chromosomes, the ideograms for the human karyotype (hg18), genes nearby *e*SNPs and Manhattan plot for the *e*QTL bins that survived correction for multiple testing.

(C and D) Boxplots of human gene expression values for *ADORA3.* Baseline (6 pm) measures are displayed in blue and GR-stimulated measures (9 pm) in red. Microarrays data are displayed in (C) and their *q*PCR validation in (D). Q value in (C) is derived from GR-response *cis*-*e*QTL analysis and the p value in (D) from the *q*PCR linear regression model.

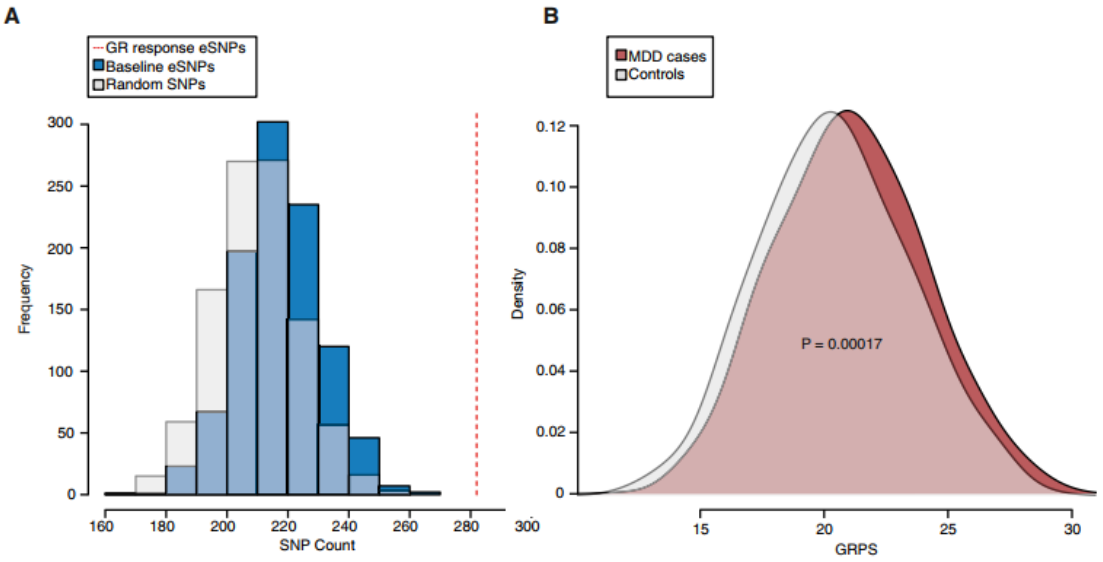


Arloth J, et al. *Neuron*. 2015;86(5):1189-1202.

GR-Response eSNPs are Enriched Among Variants Associated with MDD

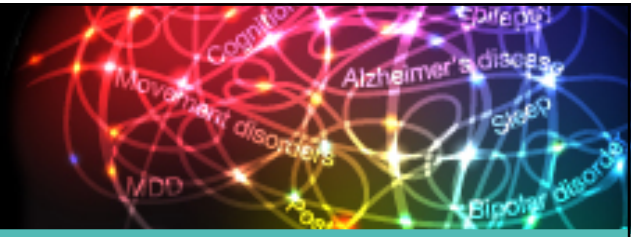
A. The dotted red line shows the enriched number of GR-response *e*SNPs that overlap with SNPs in our meta-analysis for MDD (= MDD-related GR *e*SNPs; 8,864 cases and 8,982 controls). The distribution of the observed overlap for sets of 1,000 random SNPs (gray) and 1,000 random baseline *e*SNPs (blue) are represented as histograms (null distributions). Both permuted data sets never reached the same overlap with MDD-associated SNPs as the GR-response *e*SNPs

B. The distribution of the MDD-related GR *e*SNPs genetic risk profile scores (GRPSs) for an independent sample of MDD cases (n = 1,005 cases; red) and controls (n = 478; gray) are represented as density plots. Individuals with MDD display higher GRPSs (p = 0.00017). P value by logistic regression model.



Arloth J, et al. *Neuron*. 2015;86(5):1189-1202.

Study Objective and Method



- **Objective**: The purpose was to inform the first-line treatment choice between CBT or an antidepressant medication for treatment-naïve adults with MDD by defining a neuroimaging biomarker that differentially identifies the outcomes of remission and treatment failure.
- **Method:** Functional MRI resting-state functional connectivity analyses using a bilateral subcallosal cingulate cortex (SCC) seed was applied to 122 patients from PReDICT study who completed 12 weeks of randomized treatment with CBT or antidepressant medication. Of the 122 participants, 58 achieved remission (HAM-D scored ≤ 7 at weeks 10 and 12), and 24 had treatment failure (< 30% decrease from baseline in HAM-D score). A 2 x 2 analysis of variance using voxel-wise subsampling permutation tests compared the interaction of treatment and outcomes. Receiver operating characteristic curves constructed using brain connectivity measures were used to determine possible classification rates for differential treatment outcomes.

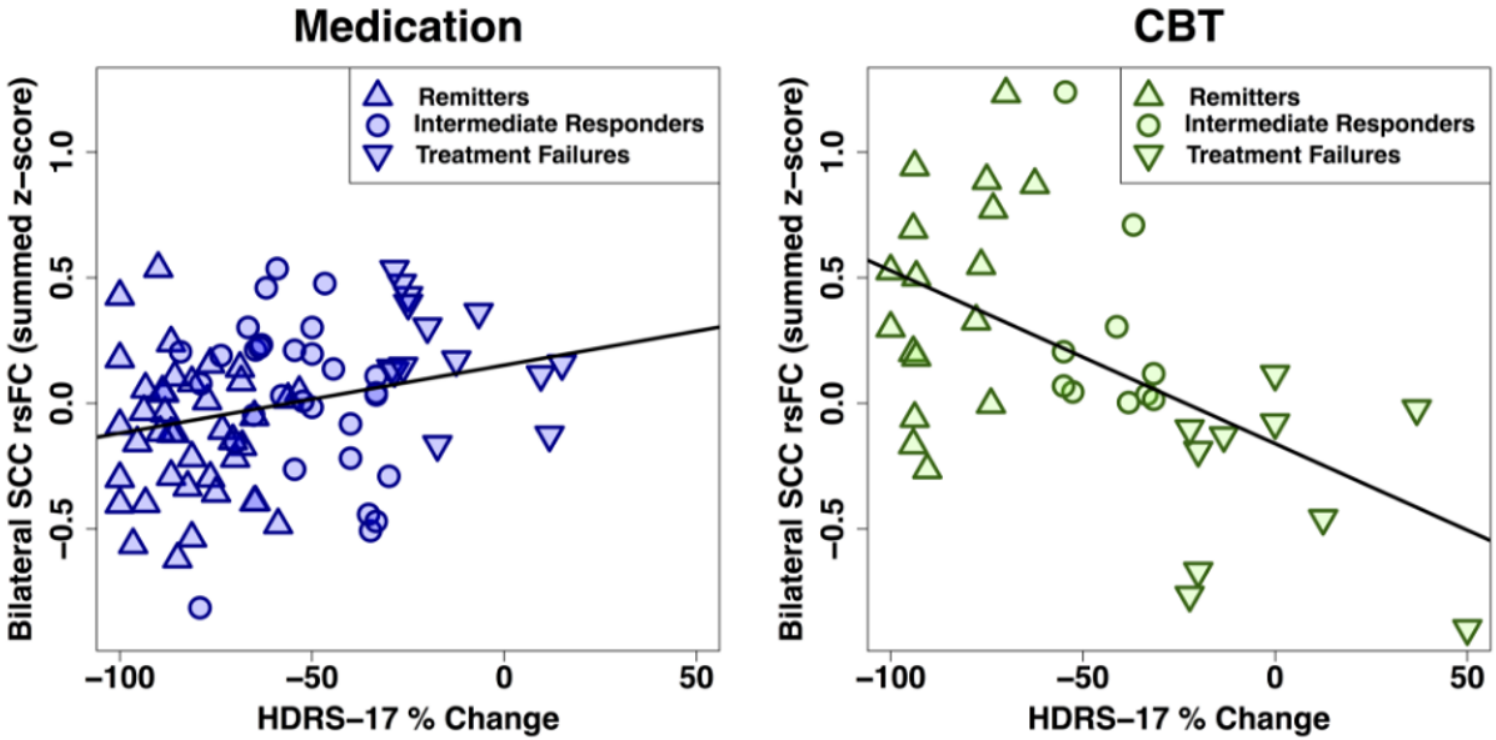
Dunlop BW, et al. *Am J Psychiatry*. 2017;174(6):533-545.

Results and Conclusions

- **Results:** Resting-stated functional connectivity of the following 3 regions with the SCC was differentially associated with outcomes of remission and treatment failure to CBT and antidepressant medication and survived application of the subsample permutation tests: dorsal midbrain, and left ventromedial prefrontal cortex. Using the summed SCC functional connectivity scores for these 3 regions, overall classification rates of 72%-78% for remission and 75%-89% for treatment failure was demonstrated. Positive summed functional connectivity was associated with remission with CBT and treatment failure with medication, whereas negative summed functional connectivity scores were associated with remission to medication and failure with CBT.
- **Conclusions**: Imaging-based depression subtypes defined using resting-state functional connectivity differentially identified an individual's probability of remission or treatment failure with first-line treatment options for MDD. This biomarker should be explored in future research through prospective testing and as a component of multivariate treatment prediction models.

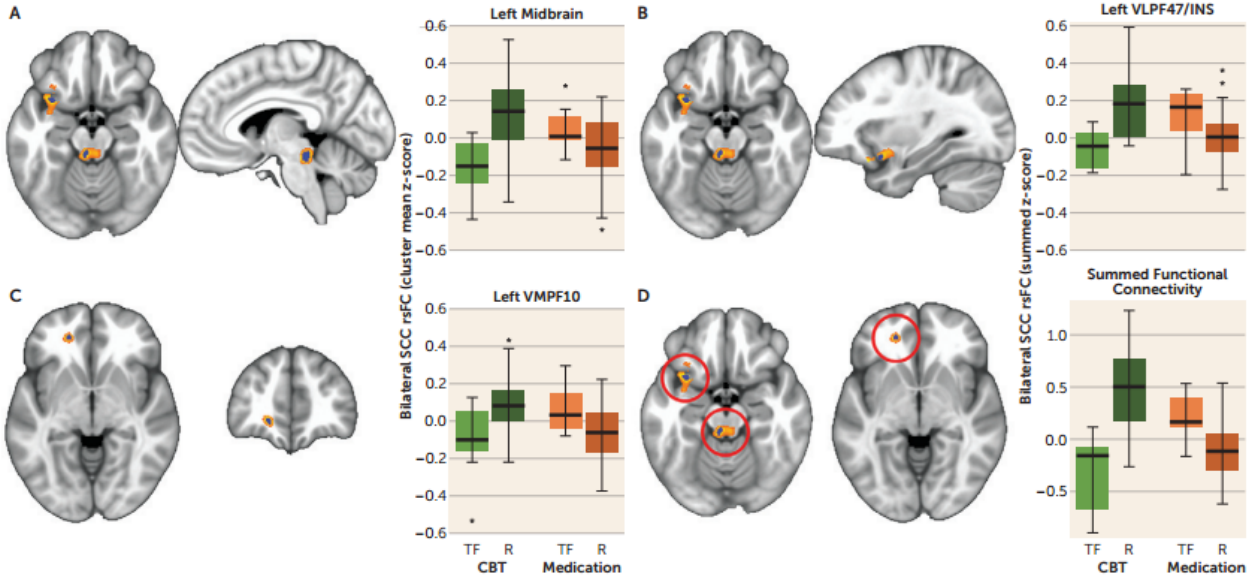
Dunlop BW, et al. *Am J Psychiatry*. 2017;174(6):533-545.

Medication vs. CBT



Dunlop BW, et al. *Am J Psychiatry*. 2017;174(6):533-545.

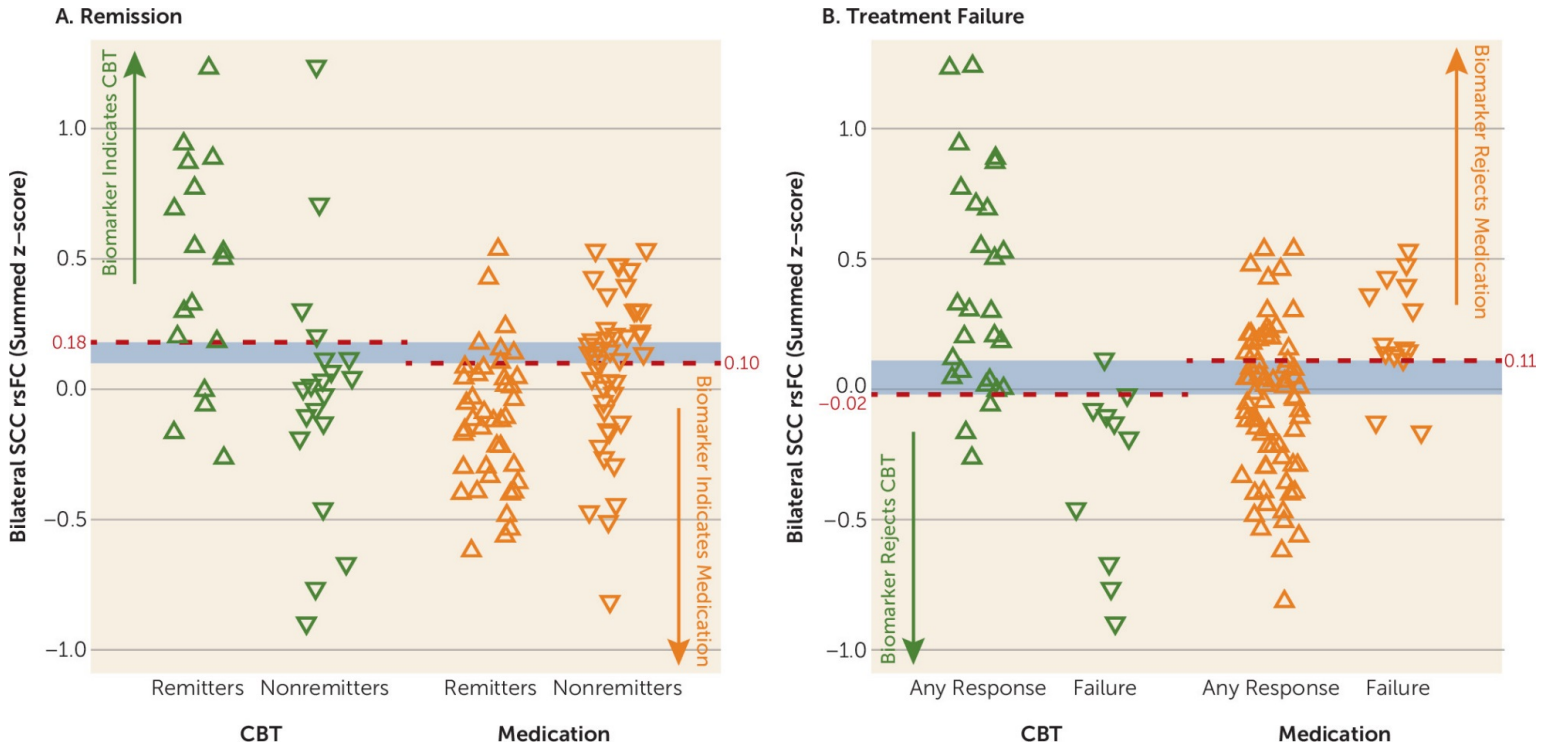
Differential Functional Connectivity of Subcallosal Cingulate Cortex Between Remitters and Treatment Failures With Antidepressant Medication or CBT[a]



[a] The figure shows A–C) the representative brain region and box plot of the z-score of the resting-state functional connectivity (rsFC) with the subcallosal cingulate cortex (SCC) between remitters (R) and treatment failures (TF) with each treatment type. The voxels identified by the subsample permutation testing (blue) are shown superimposed over voxels identified by the original analysis of variance (orange; see the Methods section in the article text). Box plots reflect contrasts using the permuted data. In all regions, the functional connectivity with the SCC seed is positive in CBT remitters and anticorrelated in CBT-treatment failures, whereas the inverse is true for antidepressant medication remitters and treatment failures. The images are as follows: A) dorsal midbrain; B) ventrolateral prefrontal cortex Brodmann area (BA) 47/insula (VLPF47/INS); C) ventromedial prefrontal cortex BA 10 (VMPF10); and D) box plots of the z-scores of the sum of the functional connectivity of the SCC with the three regions. The treatment-by-response interaction was significant at p=5e−10.

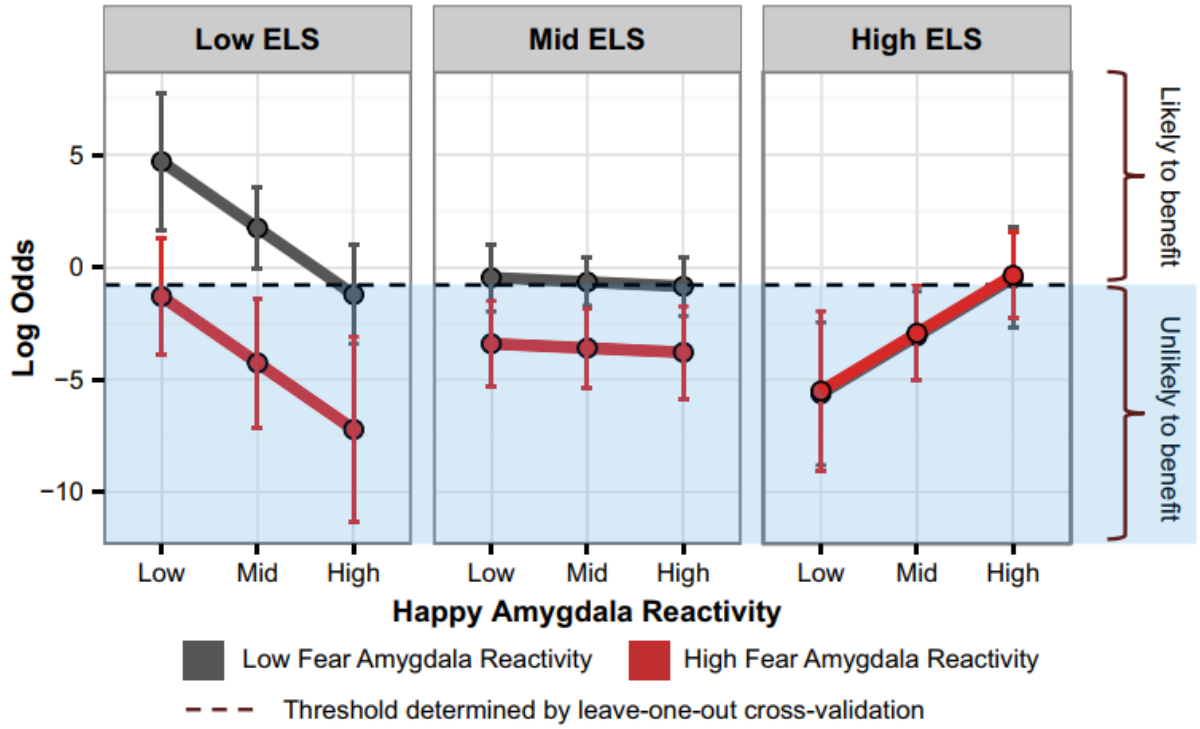
Dunlop BW, et al. *Am J Psychiatry*. 2017;174(6):533-545.

Individual Participants' Summed Functional Connectivity Scores Grouped by Treatment Outcome



Dunlop BW, et al. *Am J Psychiatry*. 2017;174(6):533-545.

Happy Amygdala Reactivity

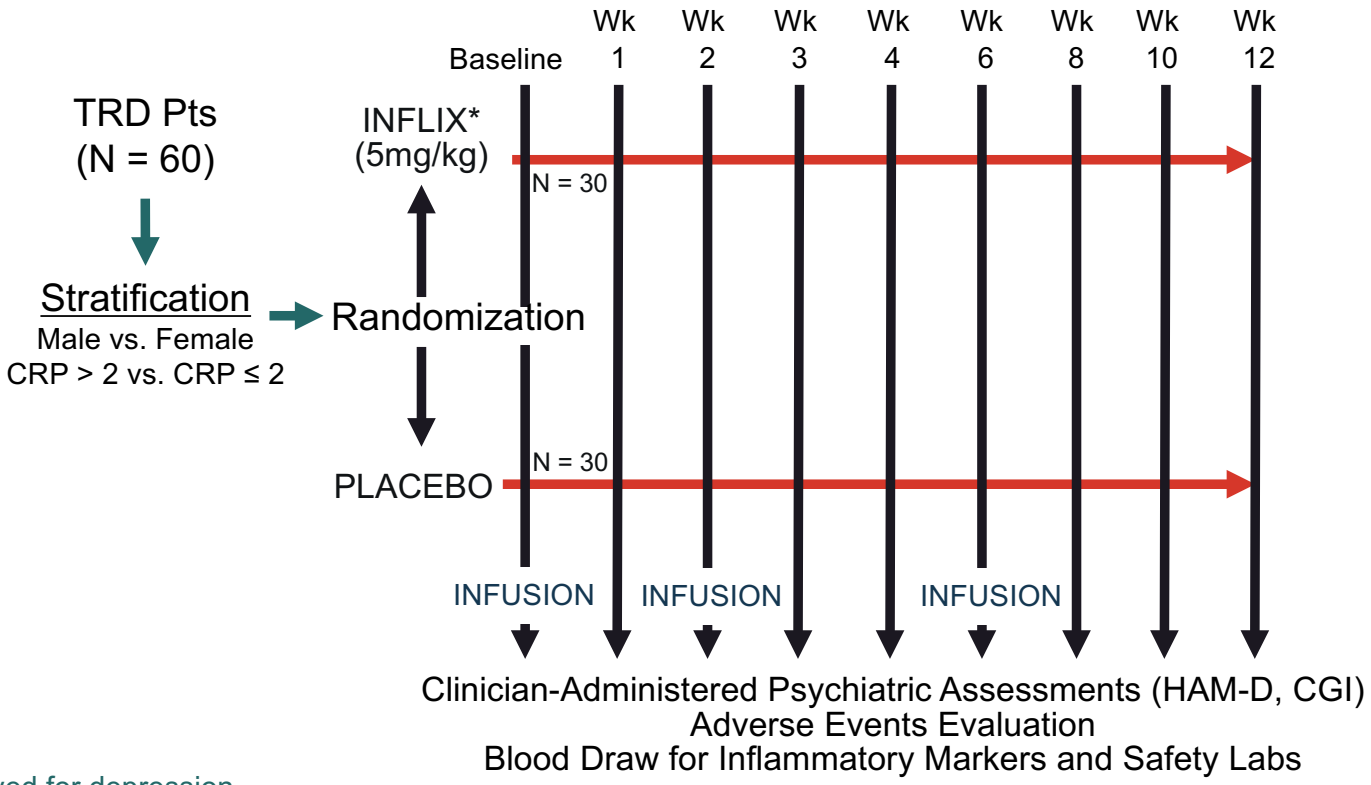


Goldstein-Piekarski AN, et al. *Proc Natl Acad Sci U.S.A.* 2016;113(42):11955-11960.

Basis for the Hypothesis that Inflammation and an Activated Innate Immune Response may Play a Role in Depression

- Patients with depression (both medically ill and medically healthy) have been found to exhibit all the cardinal features of inflammation.
  - increased peripheral blood and csf innate immune cytokines (IL-6 and TNF-alpha most reliable)
  - increased acute phase reactants (CRP most reliable)
  - increased chemokines
  - increased cellular adhesion molecules
- In the majority of studies, inflammatory markers decrease with successful antidepressant therapy ("state marker").

Double-Blind, Parallel-Group, Randomized Design



*Not FDA approved for depression

Raison CL, et al. *Arch Gen Psychiatry*. 2012;3:1-11.

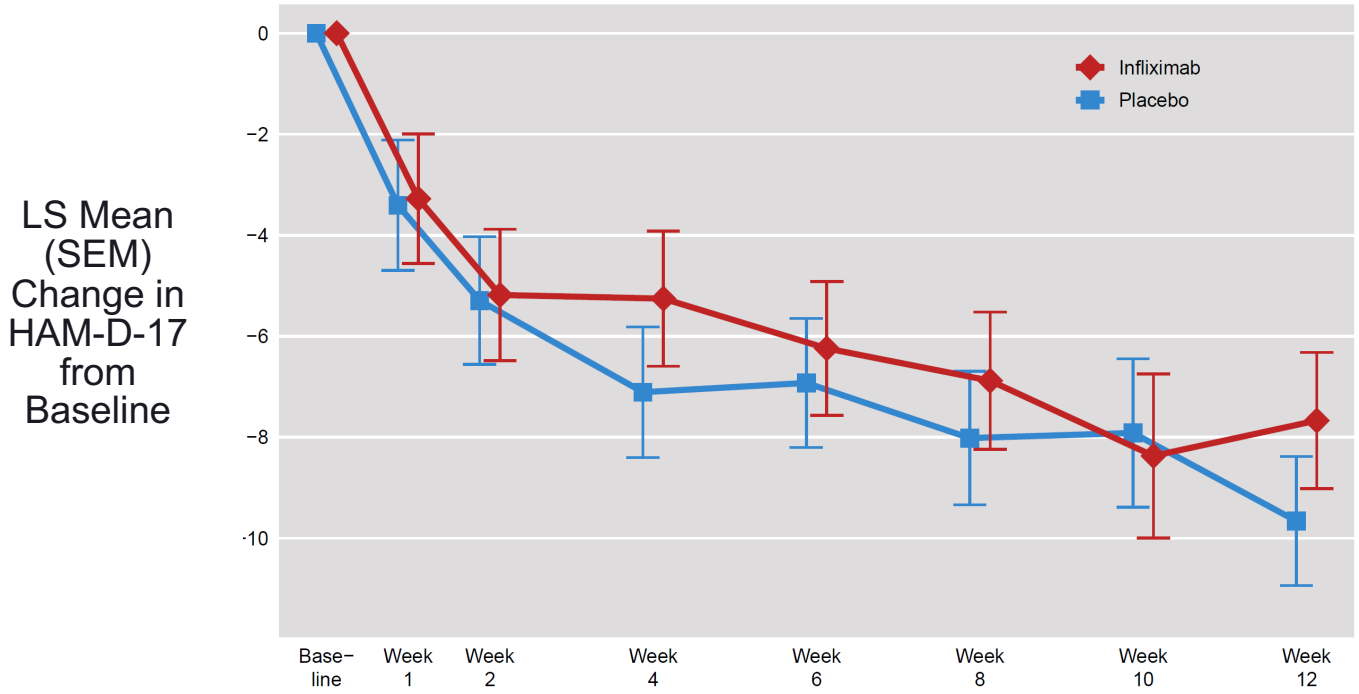
Demographic Characteristics of Study Sample

	Infliximab* (n = 30)	Placebo (n = 30)
Age (yrs.) – mean (SD)	42.5 (8.2)	44.3 (9.4)
Sex (female) – no. (%)	20 (66%)	20 (66%)
Ethnic Origin - no. (%) - Caucasian - Black - Other	 23 (77%) 6 (20%) 1 (3%)	 23 (77%) 5 (17%) 2 (6%)
Education (Highest Degree) – no. (%) - Graduate Degree - College Graduate - Partial College - High School Graduate	 8 (27%) 13 (43%) 8 (27%) 1 (3%)	 7 (23%) 13 (43%) 9 (30%) 1 (3%)
Unemployed – no. (%)	12 (40%)	12 (40%)

*Not FDA approved for depression

Raison CL, et al. *Arch Gen Psychiatry*. 2012;3:1-11.

Change in HAM-D-17 in Infliximab* vs. Placebo-Treated TRD Patients

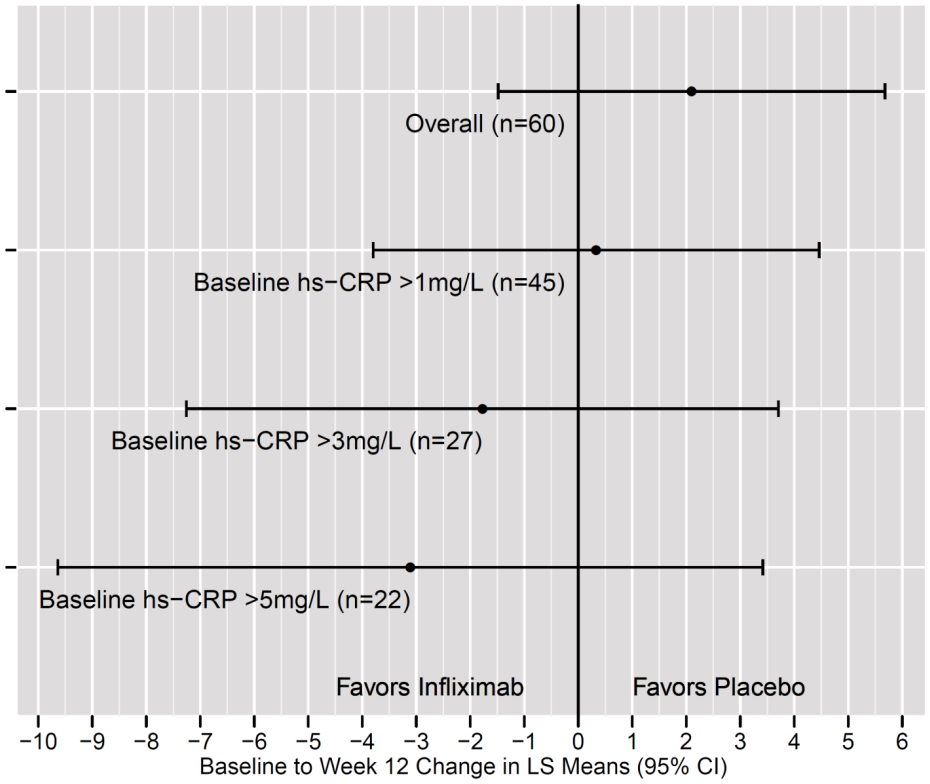


*Not FDA approved for depression

Significant interaction among treatment, time and log hs-CRP (t = 2.65, df = 302, p = .01)

Raison CL, et al. *Arch Gen Psychiatry*. 2012;3:1-11.

Change in HAM-D-17 Score from Baseline to Week 12 (Infliximab*-Placebo) in TRD Patients Subgrouped By Baseline Plasma hs-CRP



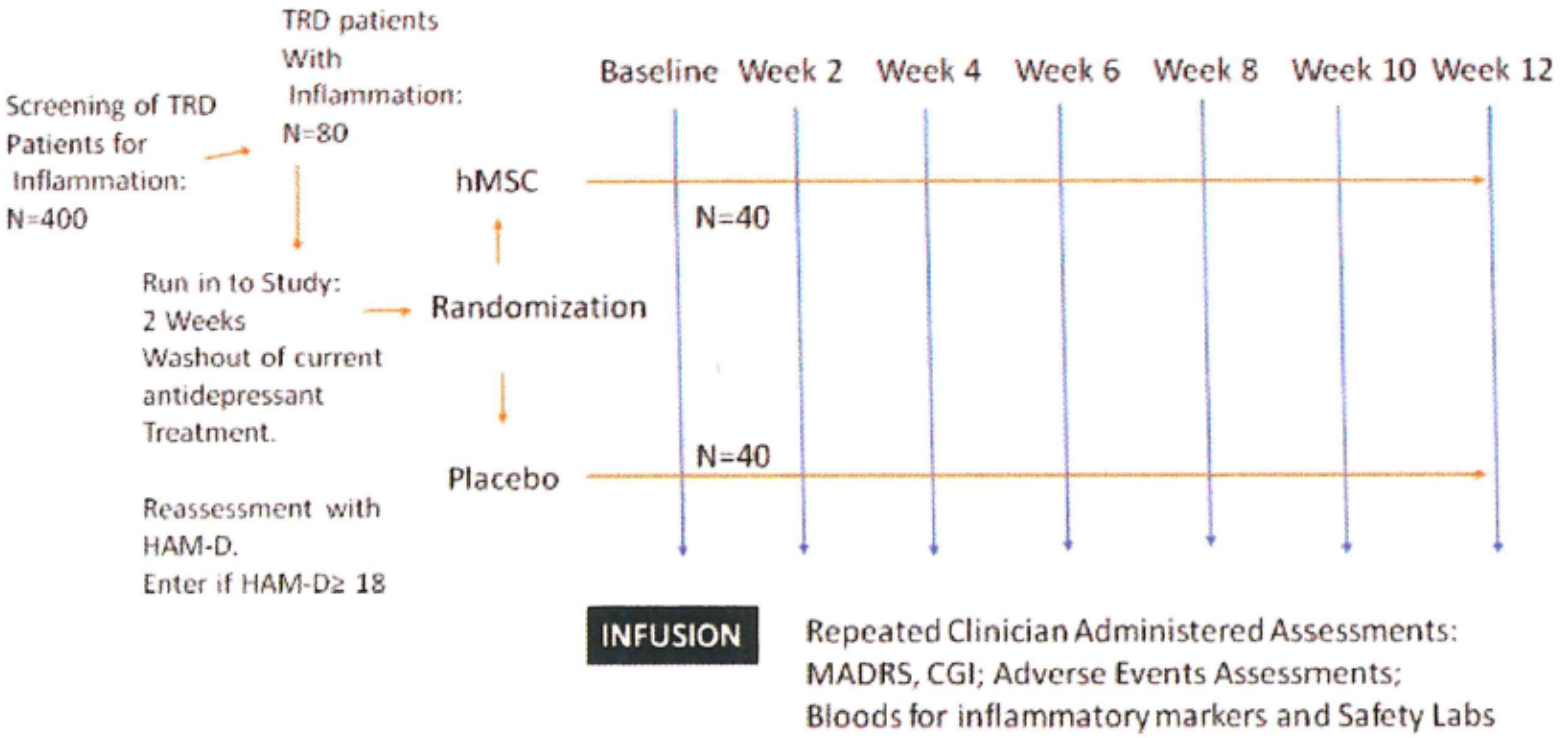
*Not FDA approved for depress...

Standardized Effect Size = 0.41 favoring infliximab* at CRP > 5mg/L

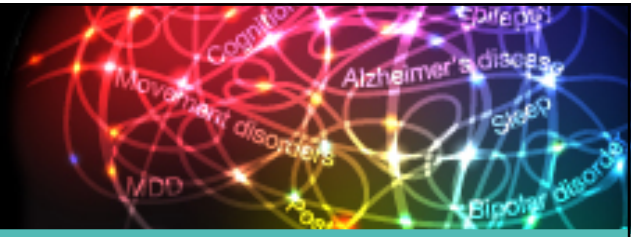
Raison CL, et al. *Arch Gen Psychiatry*. 2012;3:1-11.

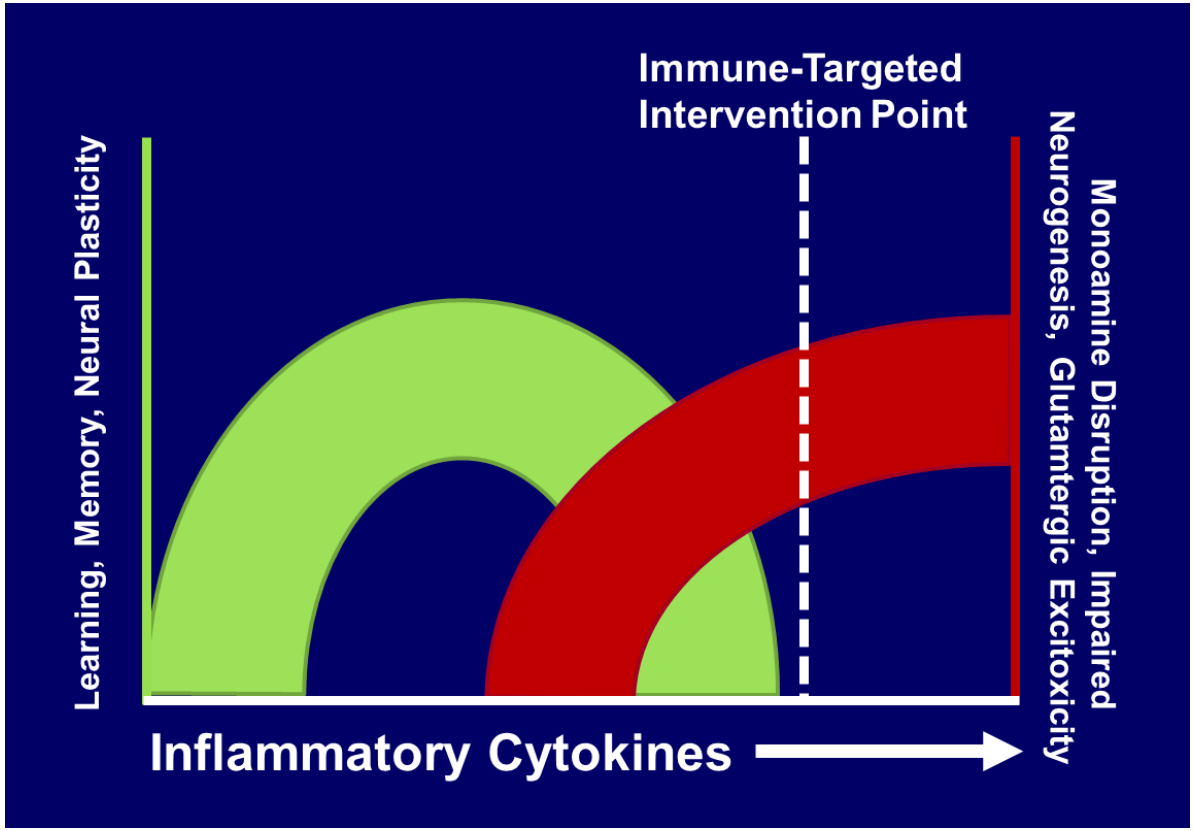
We propose the first study of mesenchymal stem cell therapy for the treatment of refractory depression.

Double-Blind Parallel Group Randomized Design



Hitting the Sweet Spot





Call to Action

- When evaluating a patient for major depression, make sure to get a thorough history to identify both genetic and environmental risk factors
- Engage patients in determining their preferred treatment plan as it may increase ability to achieve remission