Genetics of the Placebo Response: What Can We Learn from the Placebome?

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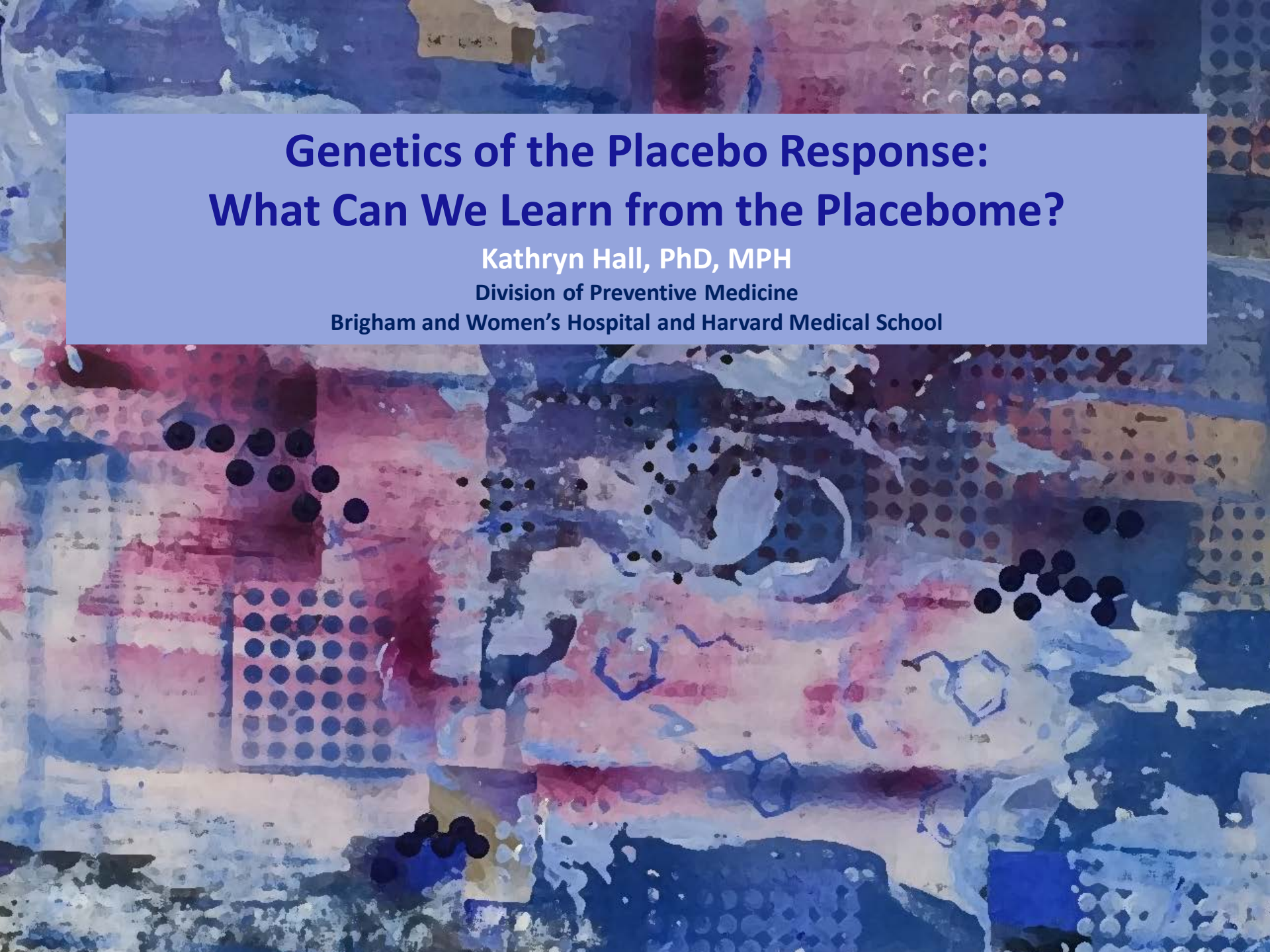
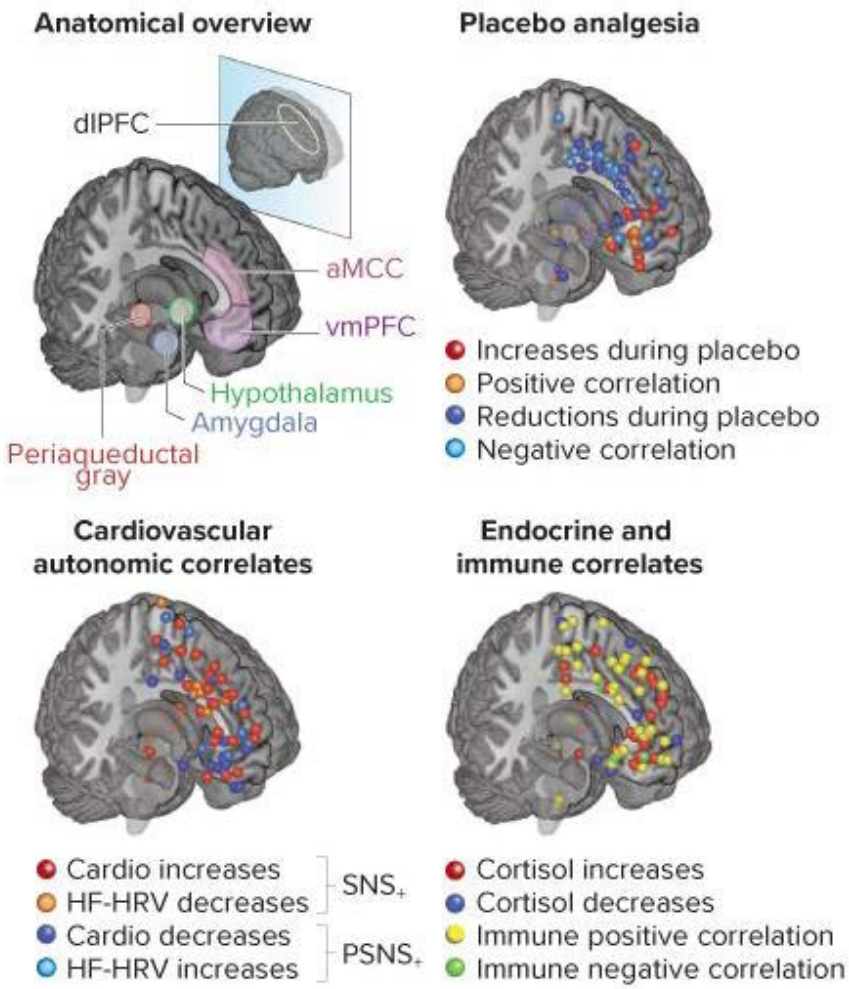


Pharmacogenomics and the placebo response

1. What neuroimaging tells us about placebo response
2. The Placebome
3. Additivity and the placebo response

Three placebo pathways



SOURCE: S. GEUTER *ET AL.* / *ANNUAL REVIEW OF NEUROSCIENCE* 2017 ADAPTED BY G. MAHONEY / KNOWABLE

[placebo response] and [gene] and [SNP]

1. Trials are small
2. Mix of clinical and experimental studies
3. Candidate genes not GWAS
4. Gene selection biased – disease or drug mechanism of action
5. Few no-treatment controls
6. Placebo arm results not always available

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Analysis of 34 candidate genes in bupropion and placebo remission

Arun K. Tiwari, Clement C. Zai, Gautam Sajeev, Tamara Arenovich, Daniel J. Müller and James L. Kennedy

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- 4 clinical trials of major depressive disorder
- bupropion (N=319) vs. placebo (N=257) responders
- Hamilton rating scale for depression (HAMD17)
  - Inclusion $\geq$ 17
  - Responder $\geq$ 50%reduction
  - Remitter $\leq$ 7
- 34 genes 532 tagging SNPs
  - drug mode of action i.e. NE, DA, monamine transporters (NET or SLC6A2, DAT1 or SLC6A3, VMAT1 and VMAT2)
  - Serotonin receptor (5-hydroxytryptamine HTR2A) associated with antidepressant treatment response

Genes that modify placebo remission and response

Table 2. Results of association analysis between SNPs and remission or response during bupropion ($n = 319$) or placebo treatment ($n = 257$) Nyholt, 2004)

	Chr	Gene	SNP	Minor allele	Total N	p value[a]	$p_{corrected}$[b]	OR (CI)
Bupropion remission	13	*HTR2A*	rs2770296	G	317	0.00075	0.0204	1.95 (1.32–2.87)
	13	*HTR2A*	rs985933	T	317	0.00215	0.0587	1.71 (1.21–2.42)
	13	*HTR2A*	rs9526240	T	318	0.00228	0.0620	1.86 (1.25–2.77)
	17	*ACE*	rs8075924	T	319	0.00621	0.0536	0.54 (0.35–0.84)
	9	*DBH*	rs2873804	T	317	0.00378	0.0796	0.61 (0.43–0.85)
	10	*SLC18A2*	rs363226	G	317	0.00410	0.0574	1.74 (1.19–2.55)
	10	*SLC18A2*	rs363225	T	313	0.00632	0.0884	0.61 (0.43–0.87)
Bupropion response	5	*SLC6A3*	rs6347	G	316	0.00119	0.0130	1.85 (1.28–2.69)
	10	*SLC18A2*	rs363225	T	313	0.00427	0.0598	0.59 (0.41–0.85)
	6	*FKBP5*	rs17614642	G	308	0.00713	0.0647	3.14 (1.36–7.24)
Placebo remission	13	*HTR2A*	5-hydroxytryptamine (serotonin) receptor 2A					0.47 (0.29–0.76)
	17	*SLC6A4*	5-Hydroxytryptamine (Serotonin) Transporter					2.73 (1.31–5.68)
	13	*HTR2A*						0.49 (0.31–0.78)
Placebo response	5	*NR3C1*	Glucocorticoid nuclear receptor variant 1					0.45 (0.27–0.76)
	X	*MAOA*	Monoamine oxidase A					1.85 (1.22–2.80)

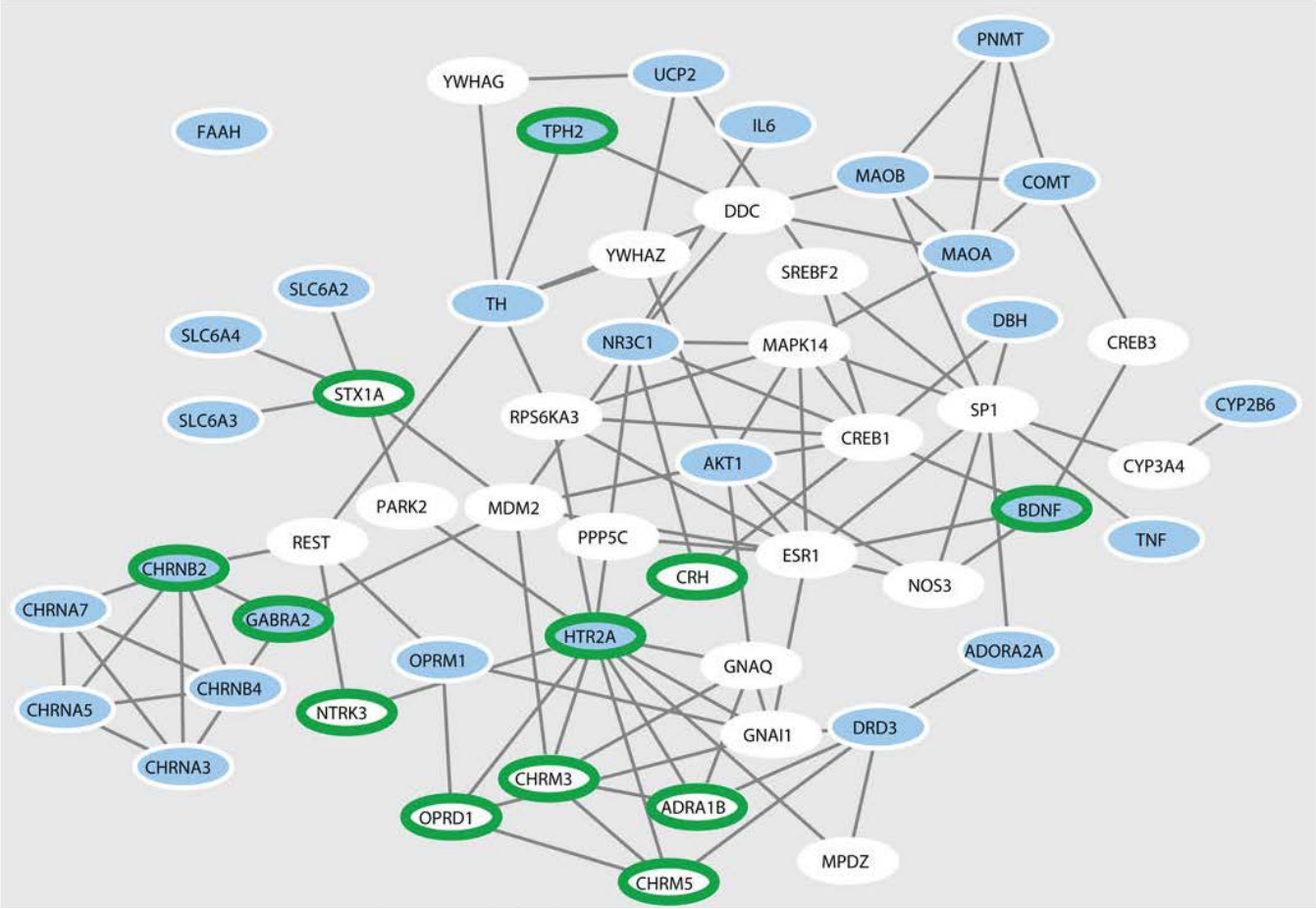
Placebome Seeds

Gene symbol	Gene name	SNP	Associated placebo outcomes
ADORA2A	Adenosine A2a receptor	rs5751876	Borderline significant differences in caffeine-associated anxiety (46)
AKT1	v-akt murine thymoma viral oncogene homolog 1	rs1130233	Associated with sham-induced cannabis motor impairments (47)
BDNF	Brain-derived neurotrophic factor	rs6265	Indirectly related through dopamine-related stress and reward responses (48, 49)
CHRNA3	Cholinergic receptor, nicotinic, α3	rs16969968	Differential craving and abstinence outcomes related to smoking abstinence (50, 51)
CHRNA5	Cholinergic receptor, nicotinic, α5	rs680244	Differential craving and abstinence outcomes related to smoking abstinence (50, 51)
CHRNA7	Cholinergic receptor, nicotinic, α7	rs2337980	Differential cognitive performance in placebo treatment arms (52)
CHRNB2	Cholinergic receptor, nicotinic, β2	rs2072661	Differential craving and abstinence outcomes related to smoking abstinence (53–55)
CHRNB4	Cholinergic receptor, nicotinic, β4	rs3813567	Differential craving and abstinence outcomes related to smoking abstinence (50, 51)
COMT	Catechol-O-methyltransferase	rs4680	Reduction in IBS-SSS and pain rating; reduction in depression scale rating (11, 56, 57)
CYP2B6	Cytochrome P450 2B6	CYP2B6*1	Smoking cessation (54, 58)
DBH	Dopamine β-hydroxylase	rs1611115	Improvement in alcoholism (59)
DRD3	Dopamine receptor D3	rs6280	Improvement in schizophrenia scale (60)
FAAH	Fatty acid amide hydrolase	rs324420	Improved analgesia and affective state (49)
GABRA2	γ-Aminobutyric acid (GABA) A receptor, α2	rs279871	Subjective outcomes in response to placebo alcohol (61–63);
HTR2A	5-Hydroxytryptamine (serotonin) receptor 2A	rs2296972, rs622337	Remission from major depressive disorder (64)
IL6	Interleukin 6	rs2066992	Associated with placebo response in major depression (65)
MAOA	Monoamine oxidase A	rs6323, rs6609257, rs2235186	Reduction in depression scale rating (56, 64)
MAOB	Monoamine oxidase B	rs736944, rs4824574	Reduction in depression scale rating (64)
NR3C1	Glucocorticoid nuclear receptor variant 1	rs1048261	Reduction in depression scale ratings (64)
OPRM1	Opioid receptor, μ1	rs1799971	Activation of mood response and neurotransmission (66, 67)
PNMT	Phenylethanolamine N-methyltransferase	G-182A, G-387A	Associated with response to placebo in depression (US patent US 2002/0187474 A1)
SLC6A2	Norepinephrine transporter	rs1861647, rs36017	Modulated feelings of elation in response to placebo amphetamine (68)
SLC6A3	Dopamine transporter	9 and 10 VNTRs[A]	Modulated responses to placebo alcohol (69, 70)
SLC6A4	5-Hydroxytryptamine (serotonin) transporter	rs4251417	Remission from major depressive disorder (64)
TH	Tyrosine hydroxylase	N/A	Tyrosine hydroxylase induced in response to placebo treatment (43).
TNF	Tumor necrosis factor	rs1800629	Differential TNF-α production in placebo treatment arms (71)
TPH2	Tryptophan hydroxylase 2	rs4570625	Reduced stress-related activity and anxiety symptoms (72)
UCP2	Uncoupling protein 2 (mitochondrial, proton carrier)	rs659366	Weak effects on weight loss in placebo treatment arms (73)

Network analysis of the genomic basis of the placebo effect

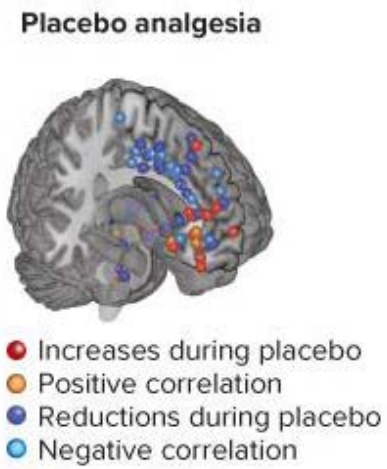
JCI insight

- 42 studies + 6 studies that known to us
- Seed genes = 28
- Seed connector algorithm – connect the seed genes with as few extra nodes as possible
- Seed connectors = 26
- Placebome module = 54



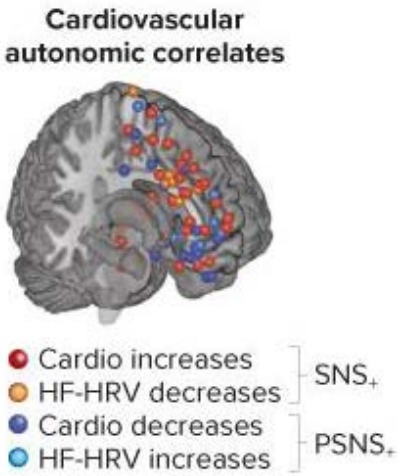
Rui-Sheng Wang,[1] Kathryn T. Hall,[1,2] Franco Giulianini,[1,2] Dani Passow,[3] Ted J. Kaptchuk,[3] and Joseph Loscalzo[1]

Modulating placebo analgesia



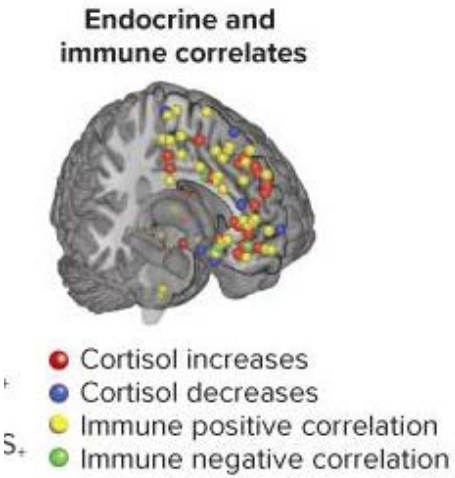
BDNF	brain-derived neurotrophic factor
CHRM3	cholinergic receptor, muscarinic 3
CHRNA3	cholinergic receptor, nicotinic, alpha 3
CHRNA5	cholinergic receptor, nicotinic, alpha 5
CHRNA7	cholinergic receptor, nicotinic, alpha 7
CHRNB2	cholinergic (acetylcholine) receptor, nicotinic, beta 2 (neuronal)
CHRNB4	cholinergic receptor, nicotinic, beta 4
FAAH	fatty acid amide hydrolase
GABRA2	gamma-aminobutyric acid (GABA) A receptor, alpha 2
HTR2A	5-hydroxytryptamine (serotonin) receptor 2A
NTRK3	neurotrophic tyrosine kinase, receptor, type 3
OPRD1	opioid receptor, delta 1
OPRM1	opioid receptor, mu 1
PNMT	phenylethanolamine N-methyltransferase
SLC6A3	solute carrier family 6 (neurotransmitter transporter, dopamine), member 3
SLC6A4	solute carrier family 6 (neurotransmitter transporter, serotonin), member 4

Cardiovascular and autonomic correlates



ADORA2A	adenosine A2a receptor
ADRA1B	adrenergic, alpha-1B-, receptor
COMT	catechol-O-methyltransferase
CREB1	cAMP responsive element binding protein 1
DBH	dopamine beta-hydroxylase (dopamine beta-monooxygenase)
DDC	dopa decarboxylase (aromatic L-amino acid decarboxylase)
DRD3	dopamine receptor D3
ESR1	estrogen receptor 1
MAOA	monoamine oxidase A
MAOB	monoamine oxidase B
NOS3	nitric oxide synthase 3 (endothelial cell)
NR3C1	nuclear receptor subfamily 3, group C, member 1 (glucocorticoid receptor)
PPP5C	protein phosphatase 5, catalytic subunit hormone and cellular stress response
SLC6A2	solute carrier family 6 (neurotransmitter transporter, noradrenalin), member 2
SREBF2	sterol regulatory element binding transcription factor 2
TH	tyrosine hydroxylase
TPH2	tryptophan hydroxylase 2
YWHAG	tyrosine 3-monooxygenase/tryptophan 5-monooxygenase activation protein
YWHAZ	tyrosine 3-monooxygenase/tryptophan 5-monooxygenase activation protein
CREB3	cAMP responsive element binding protein 3

Endocrine and Immune correlates



IL6 interleukin 6 (interferon, beta 2)
MDM2 Mdm2 p53 binding protein homolog (mouse)
TNF tumor necrosis factor

Network proximity between placebome and disease modules

Diseases	Placebo response (S: strong, W: weak)	Placebome seeds		Placebome module	
		Proximity	*P*	Proximity	*P*
Schizophrenia	S	0.11	3.4×10^{-22}	0.35	2.4×10^{-22}
Anxiety disorders	S	0.25	8.5×10^{-29}	0.54	4.2×10^{-27}
Alcoholism	S	0.29	3.5×10^{-26}	0.46	1.4×10^{-28}
Depression	S	0.39	1.3×10^{-21}	0.57	3.9×10^{-22}
Parkinson disease	S	0.50	7.5×10^{-18}	0.67	1.3×10^{-16}
Eating disorders	S	0.54	3.8×10^{-20}	0.65	5.7×10^{-26}
Migraine disorders	S	0.79	6.8×10^{-18}	0.87	1.1×10^{-18}
Asthma	S	0.96	7.3×10^{-7}	0.89	1.8×10^{-5}
Epilepsy	S	0.96	1.6×10^{-9}	1.04	1.2×10^{-8}
Fibromyalgia	S	1.14	2.6×10^{-11}	1.11	1.9×10^{-12}
Irritable bowel syndrome	S	1.11	5.3×10^{-9}	1.07	4.6×10^{-12}
Restless leg syndrome	S	1.32	1.6×10^{-7}	1.24	1.4×10^{-9}
Diabetic neuropathies	S	1.50	2.1×10^{-3}	1.41	5.1×10^{-4}
Crohn's disease	S	1.50	0.68	1.39	0.52
Ulcerative colitis	S	1.68	1.00	1.48	1.00
Duodenal ulcer	S	1.71	0.25	1.63	0.48
Osteoarthritis	S	1.75	1.00	1.61	1.00
Pancreatitis, chronic	S	1.79	0.67	1.78	1.00
Infertility	W	1.25	2.6×10^{-3}	1.09	1.2×10^{-5}
Bacterial infections	W	1.32	0.22	1.17	0.022
Carcinoma, hepatocellular	W	1.50	0.52	1.28	0.019
Carcinoma, renal cell	W	1.68	0.46	1.44	4.8×10^{-3}
Viremia	W	1.75	1.00	1.57	0.64
Uremia	W	2.04	1.00	2.00	1.00
Pneumothorax	W	2.32	1.00	2.04	0.21

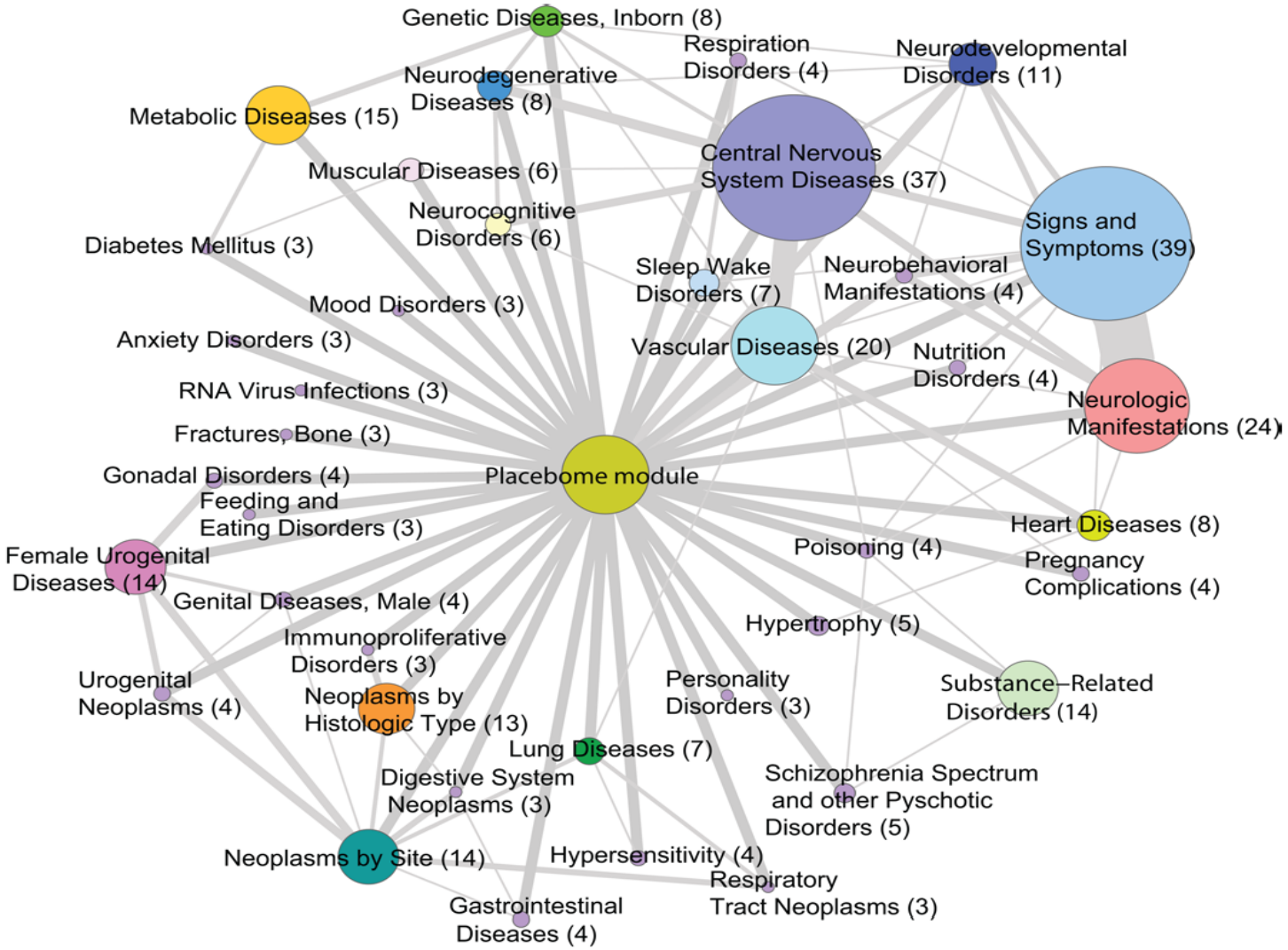
Genes associated with benchmark diseases were taken from Phenopedia

Network proximity between placebome and symptom modules

		Placebome seeds		Placebome module	
Symptoms	**Placebo response (S: strong, W: weak)**	**Proximity**	***P***	**Proximity**	***P***
Pain	S	0.36	1.6×10^{-20}	0.54	9.2×10^{-22}
Nausea	S	1.11	1.8×10^{-11}	1.06	1.0×10^{-14}
Headache	S	1.11	1.8×10^{-10}	1.04	4.4×10^{-14}
Fatigue	S	1.07	3.2×10^{-11}	1.06	2.7×10^{-12}
Hot flashes	S	1.68	6.9×10^{-4}	1.52	6.3×10^{-5}
Fever	W	1.71	1.00	1.59	1.00

P values were adjusted using the Bonferroni procedure.

The placebome-disease network



- 252/859 diseases were significantly proximate to the placebome
- CNS disorders = Parkinson's, AD, migraine, epilepsy
- Proximity of diseases like cancer suggests a subgroup of diseases in which the PR has no efficacy

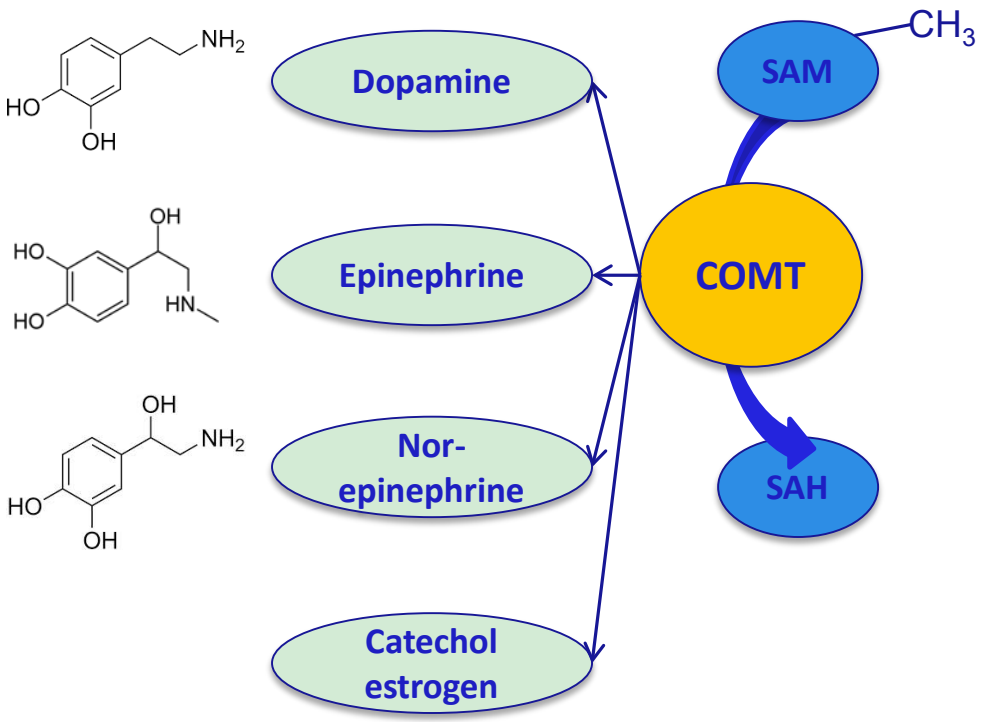
Overlap between the placebome and drug targets

Gene sets	Drug targets	Drug targets in TYPE 1 random gene sets	Drug targets in TYPE 2 random gene sets
Placebome seeds	26 out of 28	4.1 ± 1.9 ($P < 1.0 \times 10^{-16}$)	
Placebome module	40 out of 54	7.9 ± 2.6 ($P < 1.0 \times 10^{-16}$)	29.8 ± 1.8 ($P = 8.2 \times 10^{-9}$)

		Placebome module	
Drug categories	**Size of the targets**	**Proximity**	***P***
Analgesics, non-narcotic	142	0.96	3.5×10^{-10}
Appetite depressants	88	1.04	1.78×10^{-12}
Antidepressive agents	262	1.04	8.6×10^{-5}
Sympathomimetics	165	1.07	2.6×10^{-6}
Antiparkinson agents	179	1.07	6.0×10^{-6}
Cardiotonic agents	72	1.09	1.2×10^{-11}
Serotonin uptake inhibitors	140	1.11	6.5×10^{-7}
Central nervous system depressants	78	1.13	6.1×10^{-9}
Antioxidants	116	1.19	1.4×10^{-5}
Dopamine agents	78	1.22	6.5×10^{-7}
Excitatory amino acid antagonists	99	1.22	1.5×10^{-5}
Dopamine uptake inhibitors	74	1.30	1.7×10^{-5}
Adrenergic α-agonists	126	1.30	9.1×10^{-3}
Neuroprotective agents	43	1.31	2.5×10^{-7}
Adrenergic β-agonists	28	1.50	3.1×10^{-4}

P values were adjusted using the Bonferroni procedure.

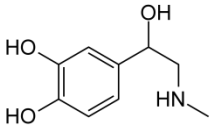
Catechol-O-methyltransferase (*COMT*) metabolizes catecholamines



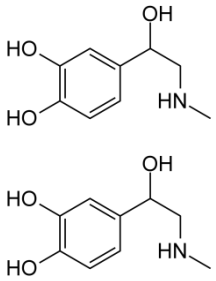
COMT val158met rs4680

G = valine → **A = methionine**

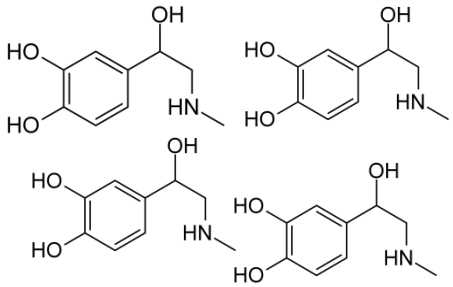
high-activity → low-activity



val/val
high-activity
***less* dopamine**
epinephrine and
norepinephrine



val/met

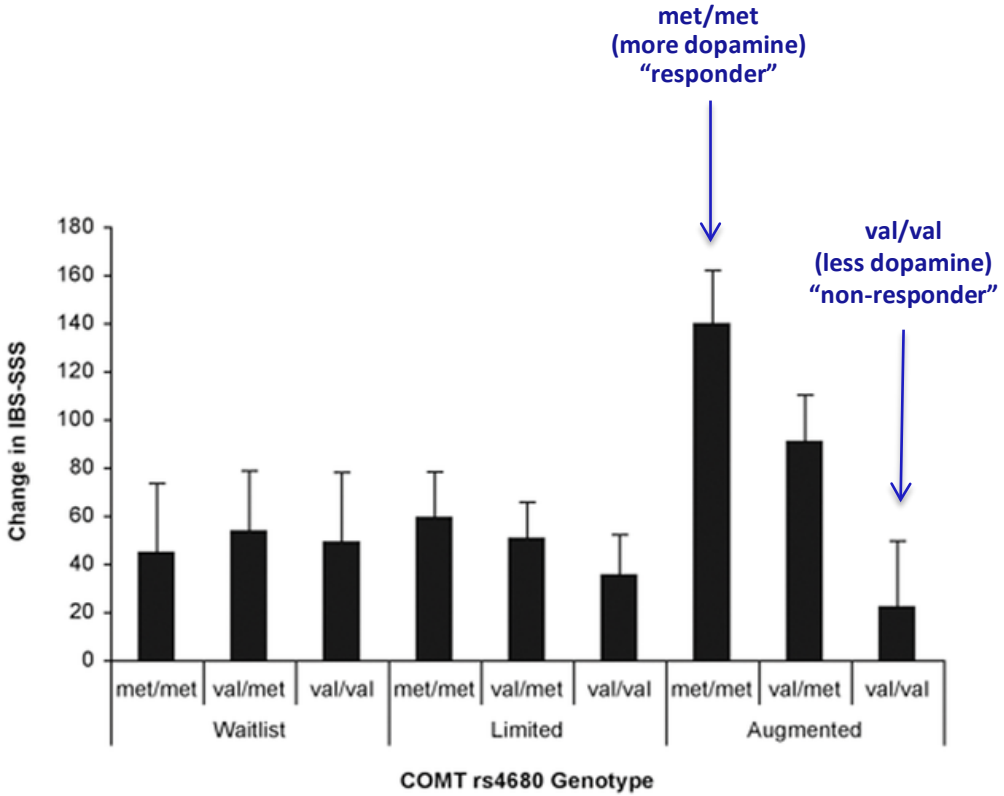


met/met
low-activity
***more* dopamine**
epinephrine and
norepinephrine

OPEN ACCESS Freely available online PLOS ONE

Catechol-O-Methyltransferase val158met Polymorphism Predicts Placebo Effect in Irritable Bowel Syndrome

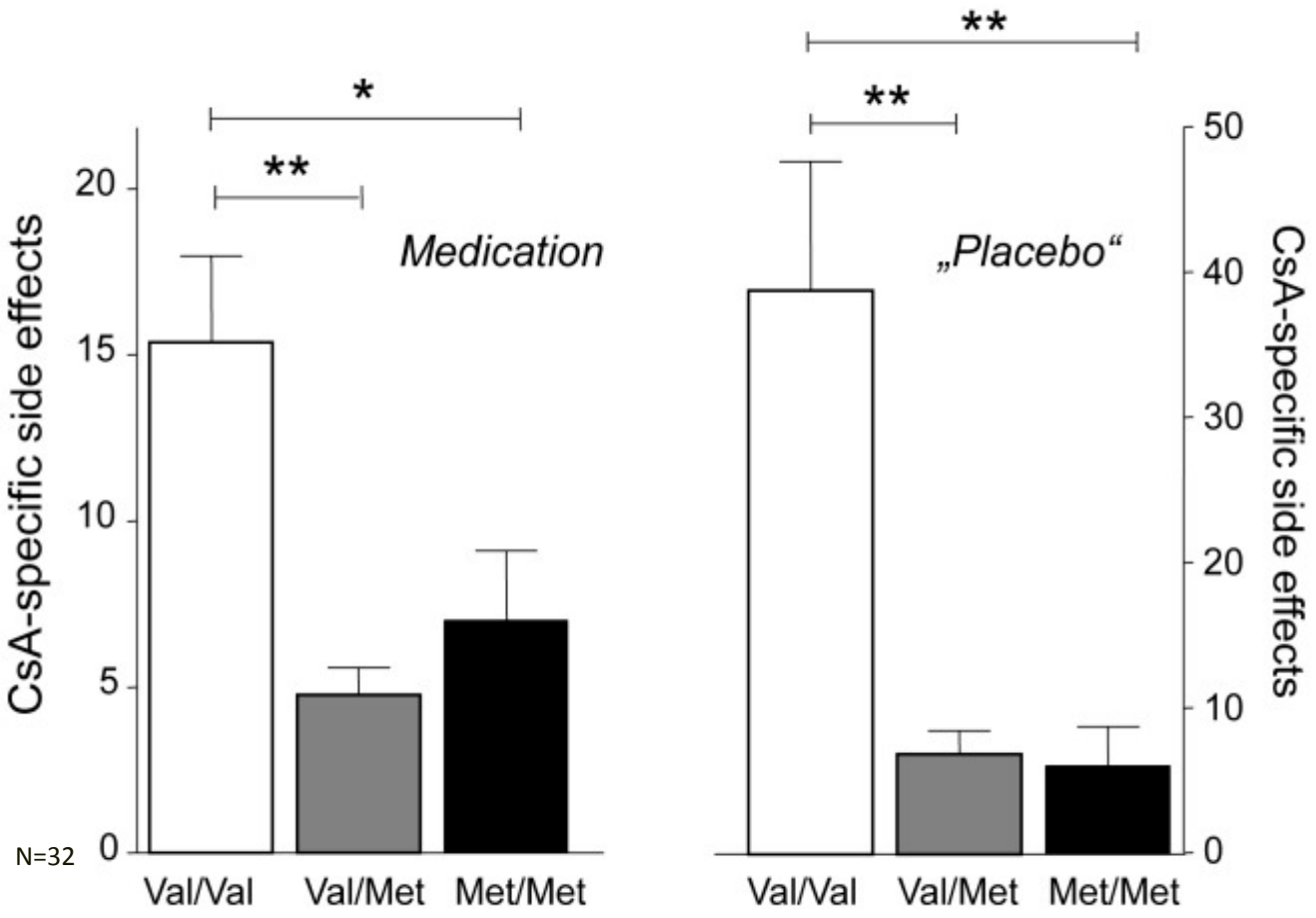
met/met in the augmented arm have largest placebo response



COMT genotype (β = 0.19; p = .02)
COMT genotype x treatment arm (β = 0.17; p = .035)
(N=104)

Hall et al., *PLoS ONE.* 2012

val/val have more side-effects

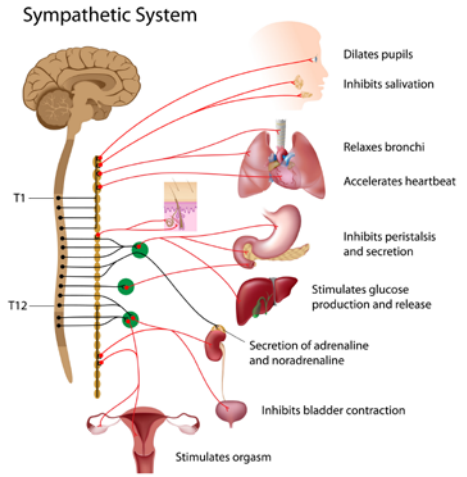


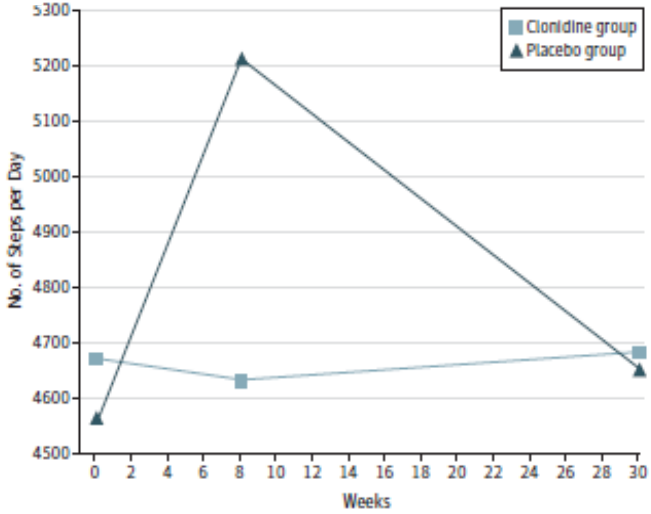
PLOS ONE

Wendt et al., *PLoS ONE.* 2014

NorCAPITAL trial showed placebo > clonidine for Chronic Fatigue Syndrome

- CFS:
  - higher catecholamine levels
  - overactive sympathetic nervous system
- Clonidine:
  - α_2-adrenergic receptor agonist
  - lowers blood pressure
  - lower norepinephrine levels
- The primary outcome:
  - Steps per day after 8-weeks of treatment





Sulheim et al., JAMA Pediatrics 2014

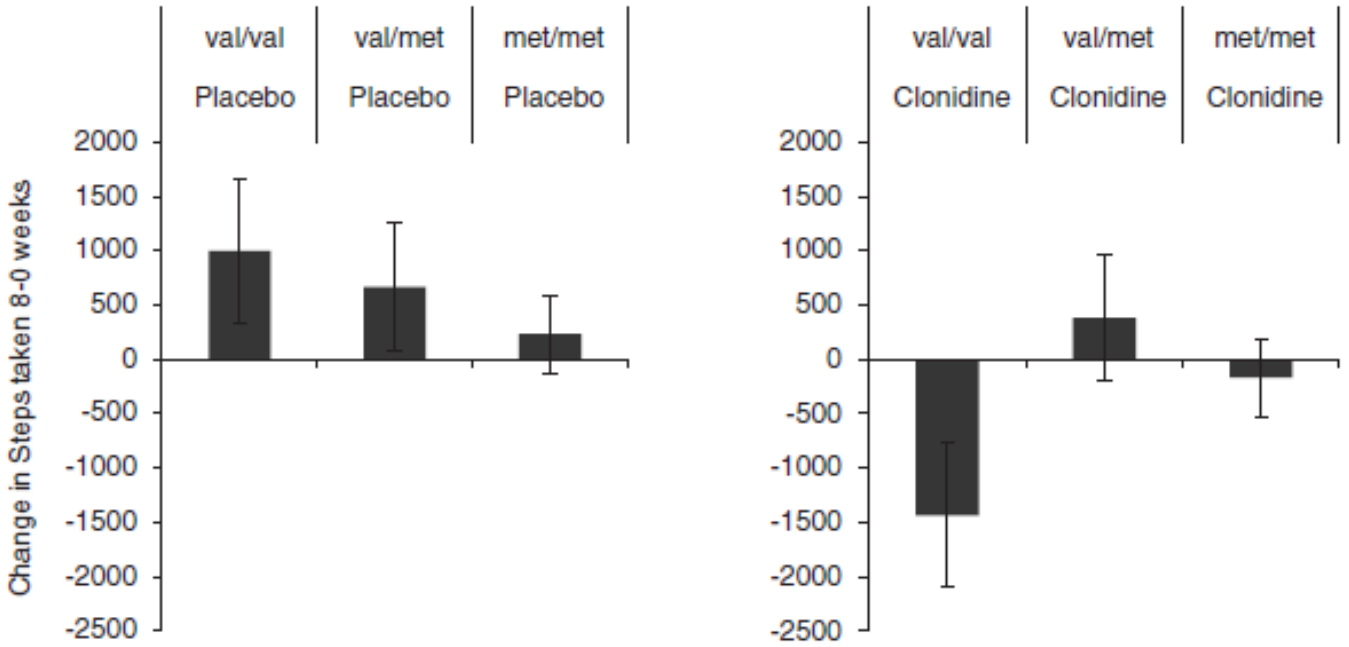
ORIGINAL ARTICLE

Genetic variation in catechol-*O*-methyltransferase modifies effects of clonidine treatment in chronic fatigue syndrome

KT Hall[1,2,14], J Kossowsky[2,3,4,14], TF Oberlander[5], TJ Kaptchuk[2,6,7], JP Saul[8], VB Wyller[9], E Fagermoen[10], D Sulheim[11], J Gjerstad[12], A Winger[13] and KJ Mukamal[2,6]

val/val patients took 2400 fewer steps on clonidine than placebo

($P_{interaction}$ = 0.04)

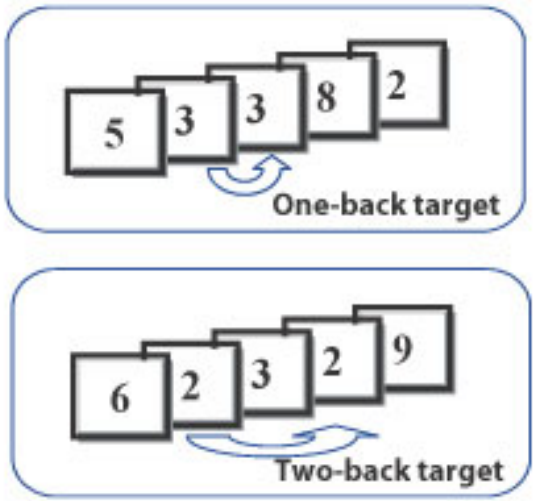


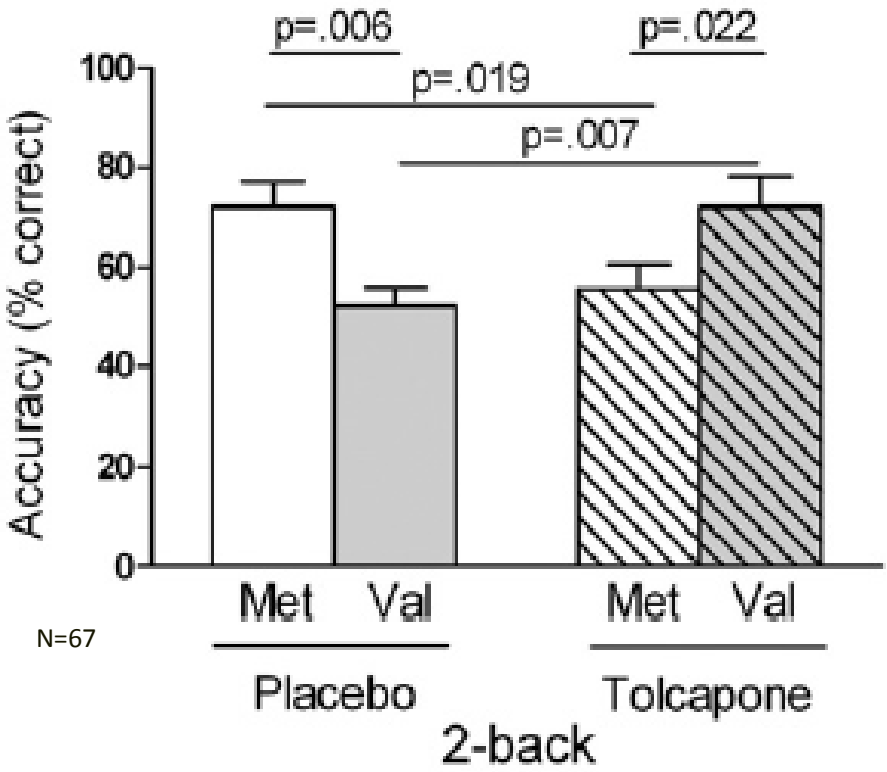
The Pharmacogenomics Journal (2016) 00, 1–7

www.nature.com/tpj

Is there evidence of gene-drug/placebo interactions?

Tolcapone a COMT inhibitor appears to modify placebo response?





Farrell et al., *Biological Psychiatry* 2012

Aspirin and placebo response?

Journal of Abnormal Psychology
1970, Vol. 75, No. 3, 308–314

MODIFICATION OF PLACEBO EFFECTS BY MEANS OF DRUGS:

EFFECTS OF ASPIRIN AND PLACEBOS ON SELF-RATED MOODS [1]

ALBERT J. DINNERSTEIN [2] AND JEROME HALM
New York Medical College

How do drugs and placebos interact? As a model experiment, changes in self-rated mood were measured in four treatment groups. The *Ss* in each group received either aspirin or lactose, plus a placebo liquid described to *Ss* as being either a "tranquilizer" or an "energizer." Aspirin had no significant main effect on mood, but did cause significant changes in the placebo effects, adding dimensions of friendly intoxication to the tranquilizer effect and of asocial sobriety to the energizer effect. These results, plus analogous results in other studies, argue that *Ss*' expectancies concerning treatment effects should be manipulated in any study of potentially psychoactive drugs.

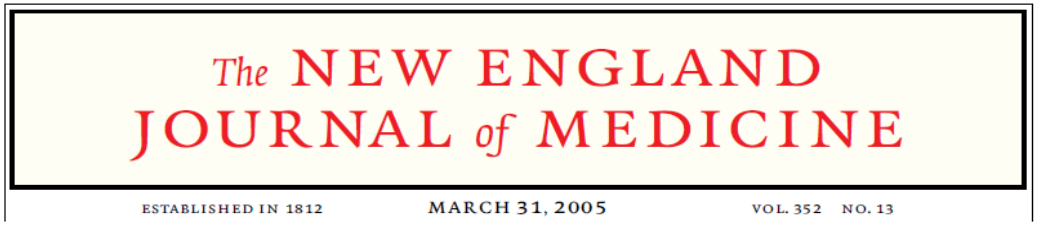
"Energizer" Placebo	"Energizer" Aspirin
"Tranquilizer" Placebo	"Tranquilizer" Aspirin

CHANGES IN CLYDE MOOD SCALE MEANS (POSTMEASURE–PREMEASURE)

Mood factors	Placebo "energizer"			Placebo "tranquilizer"		
	Aspirin	Lactose	Aspirin minus lactose	Aspirin	Lactose	Aspirin minus lactose
Friendly[a**, b*]	−2.15	.65	−2.80	−2.50	−6.20	3.70
Aggressive[a**]	−1.85	2.10	−3.95	−4.35	−3.85	− .50
Clear Thinking[b*]	.70	−2.90	3.60	−5.05	−1.80	−3.25
Sleepy[a***]	−2.00	−5.05	3.05	6.80	8.40	−1.60
Unhappy[b*]	− .85	−2.30	1.45	−2.55	.60	−3.15
Dizzy	.45	− .15	.60	− .65	−1.30	.65

[a] Effects of placebo instructions on this mood were significant.
[b] Effects of Drug × Placebo interactions on this mood were significant.
* $p < .05$.
** $p < .025$.
*** $p < .001$.

In WHS no difference between aspirin and placebo



A Randomized Trial of Low-Dose Aspirin in the Primary Prevention of Cardiovascular Disease in Women

Paul M Ridker, M.D., Nancy R. Cook, Sc.D., I-Min Lee, M.B., B.S., David Gordon, M.A., J. Michael Gaziano, M.D., JoAnn E. Manson, M.D., Charles H. Hennekens, M.D., and Julie E. Buring, Sc.D.

Major CVD events

Placebo group – 522

Aspirin group – 477

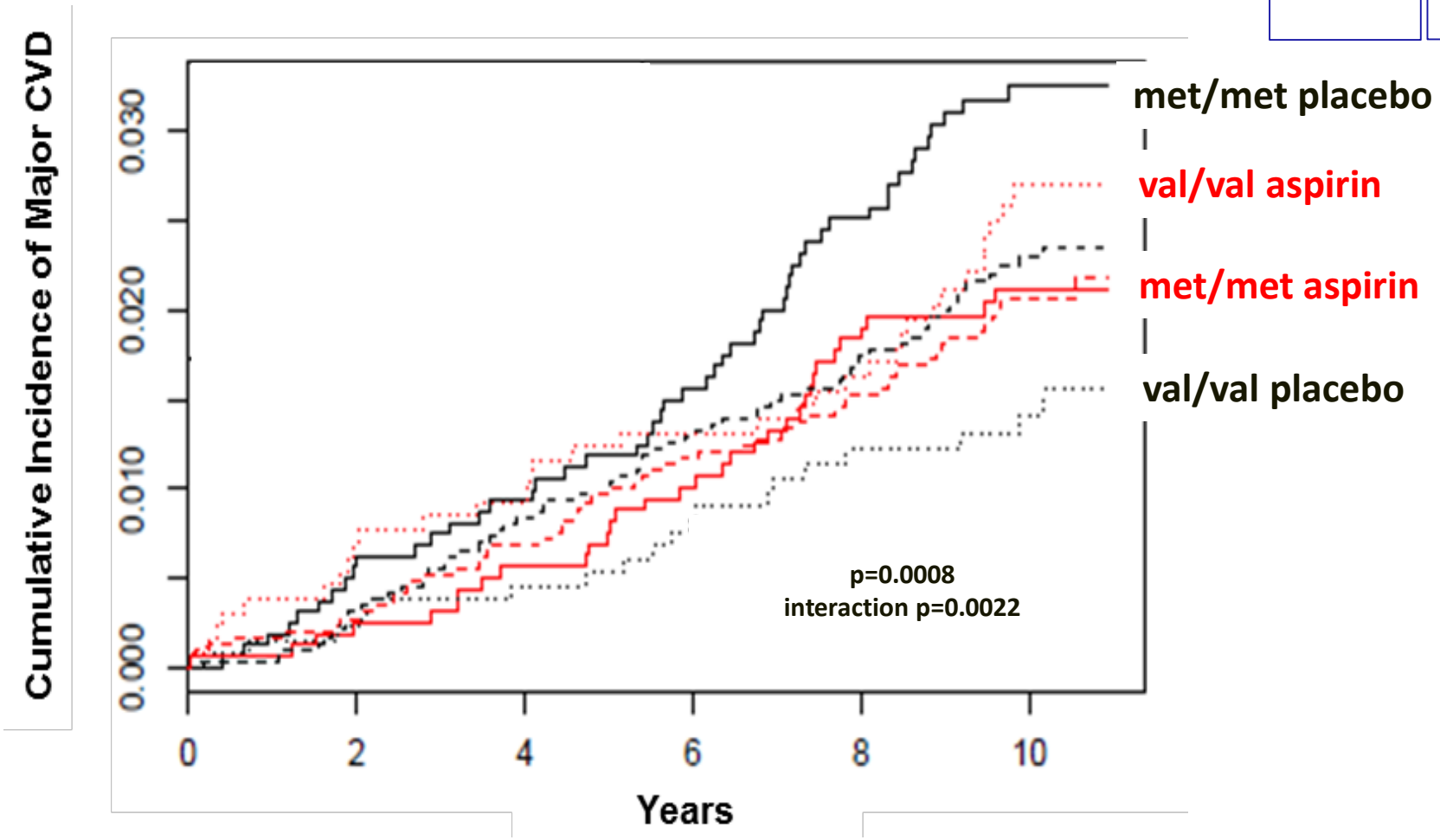
Non-significant 9% reduction in risk of major CVD with aspirin

RR 0.91, CI [0.80-1.03], P=0.13

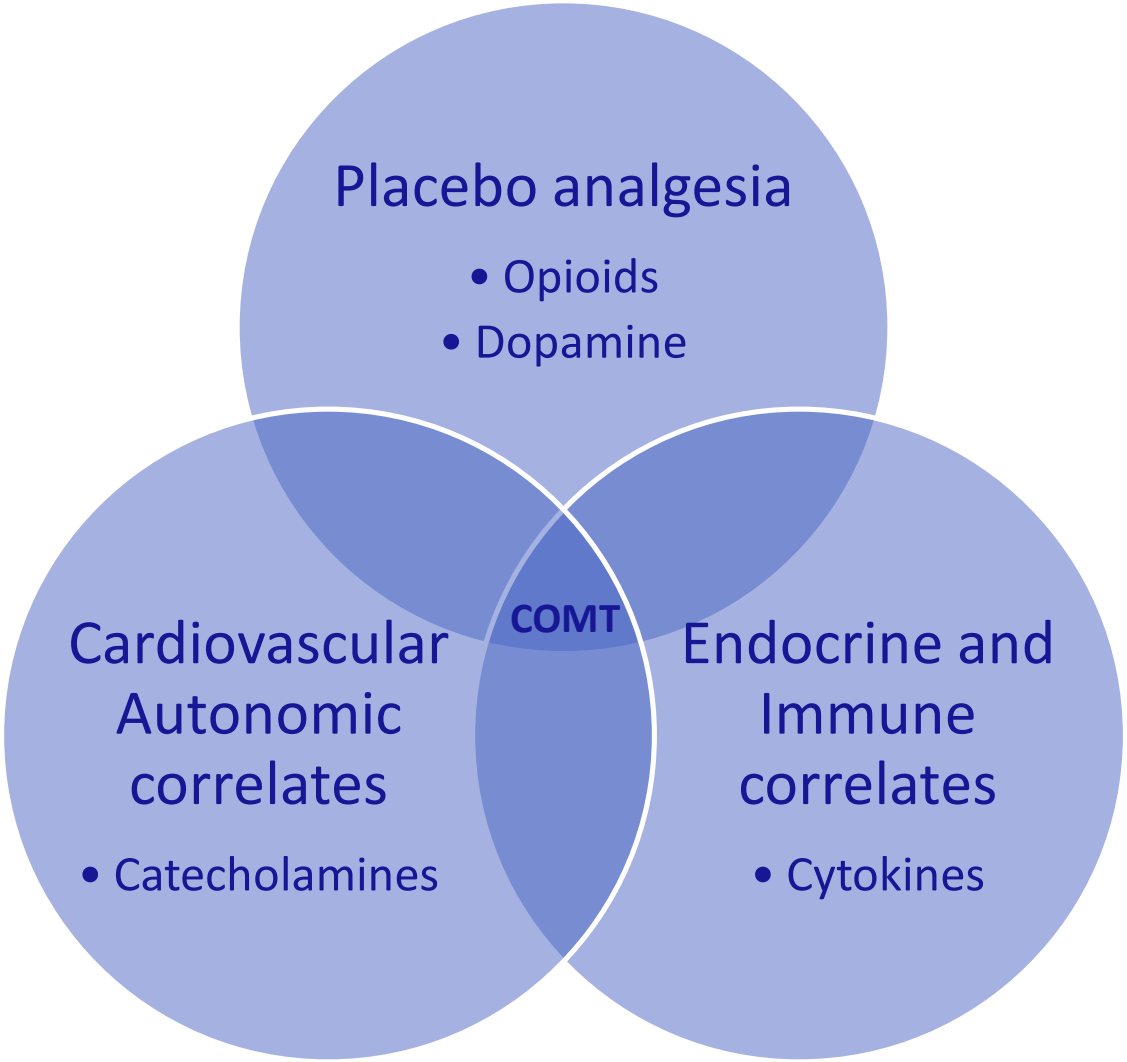
Ridker et al., *NEJM.* 2005

Wherease met/met women benefited from aspirin, val/val women had increased rates of major CVD

Placebo n=5,814	Aspirin n=5,815
Vitamin E n=5,863	Aspirin + Vitamin E n=5,802



Overlapping placebo pathways



The Placebome raises a series of important questions

- Is placebo response a trait or state?
  - How stable is the placebo response
  - How can we modify the placebo response
- How can we use the placebome in clinical trials and medicine?
  - Retrospective: analysis of trials
  - Prospective: trial design
- Are there other genes in the placebome?
  - GWAS of placebo response
  - Across diseases

Placebo Acknowledgements

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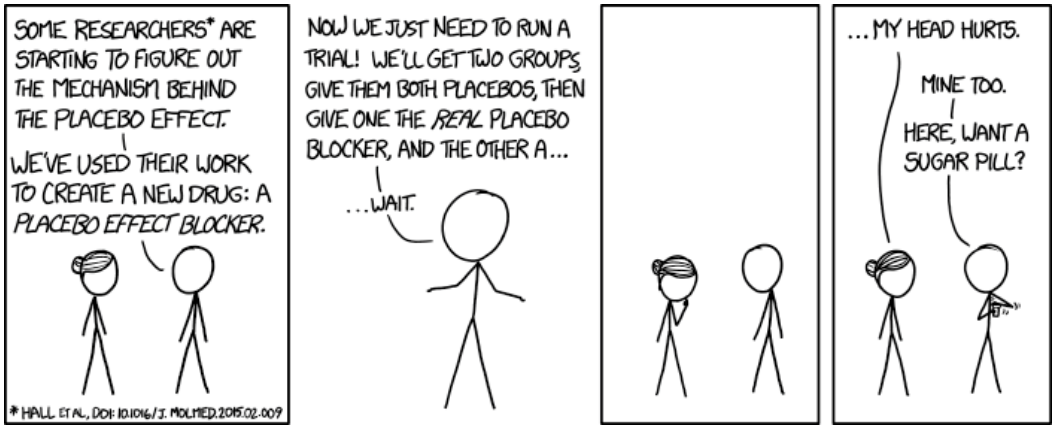
Vegard Wyller

Tim Oberlander



http://xkcd.com/1526/