How Taking an Evolutionary Perspective Can Change How We Think about Mental Illnesses: Focus on Major Depression

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Faculty Disclosure

- **Dr. Raison**: Consultant—Alkermes, Usona Institute, North American Center for Continuing Education, Emory Healthcare.

Disclosure

- The faculty have been informed of their responsibility to disclose to the audience if they will be discussing off-label or investigational use(s) of drugs, products, and/or devices (any use not approved by the US Food and Drug Administration).
  - The off-label use of psilocybin and whole body hypothermia for the treatment of depression will be discussed.

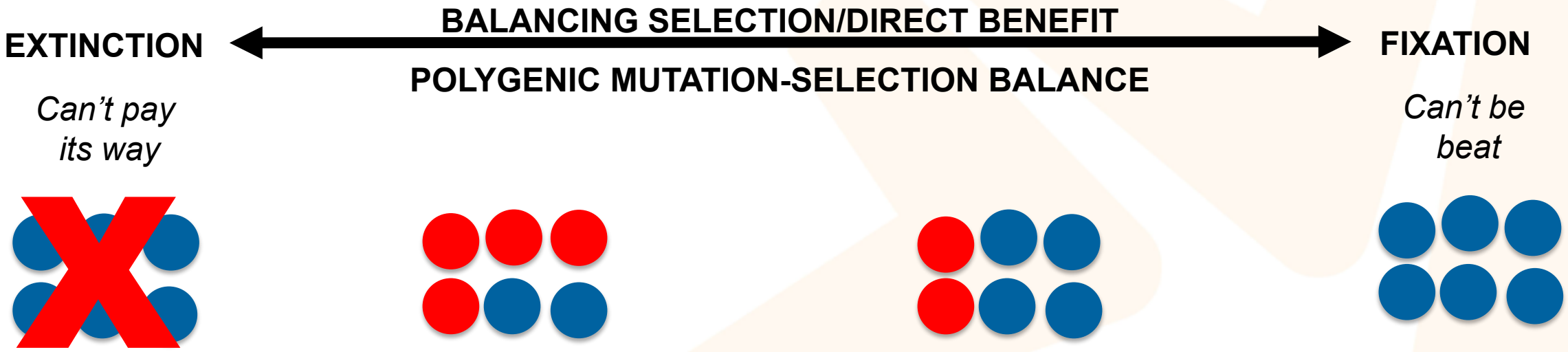
- Applicable CME staff have no relationships to disclose relating to the subject matter of this activity.

- This activity has been independently reviewed for balance.

Learning Objectives

- Describe the basic principles of survival and reproduction as these pertain to the evolution and persistence of mood disorder risk alleles in the human genome
- As an example of how evolutionary understandings can provide new scientific understandings of the disorders we treat, explain how depression may have served adaptive purposes across human evolution by signaling failure at prototypical activities that enhance human reproductive success
- Describe how an evolutionary understanding of depression helps explain why currently used pharmacologic agents do and do not work and provides a framework for implementing novel treatments in patients with depression

The Two Options Evolution Allows



NON-ADAPTIVE | **ADAPTIVE**

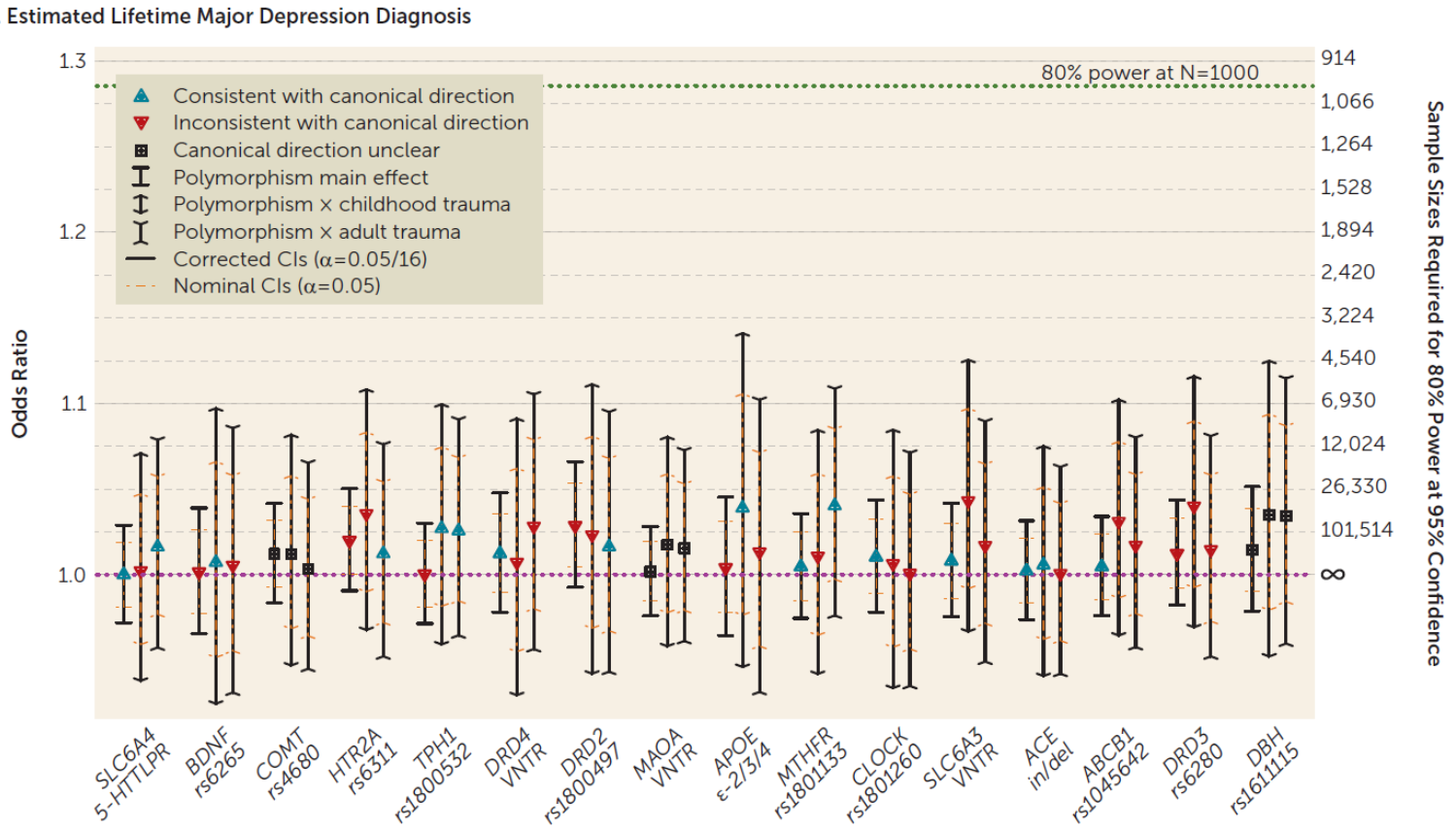
Keller MC, et al. *Behav Brain Sci*. 2006;29(4):385-404.

Challenges to Depression as an Adaptation

We Don’t Understand the Genetics of Depression

In samples ranging from 62,138 to 443,264, no clear evidence was found for any candidate gene polymorphism associations with depression phenotypes or any polymorphism-by-environment moderator effects. As a set, depression candidate genes were no more associated with depression phenotypes than non-candidate genes.

FIGURE 2. Main effects and gene-by-environment effects of 16 candidate polymorphisms on estimated lifetime depression diagnosis and current depression severity in the UK Biobank sample[a]



Border R, et al. *Am J Psychiatry*. 2019;176(5):376-387.

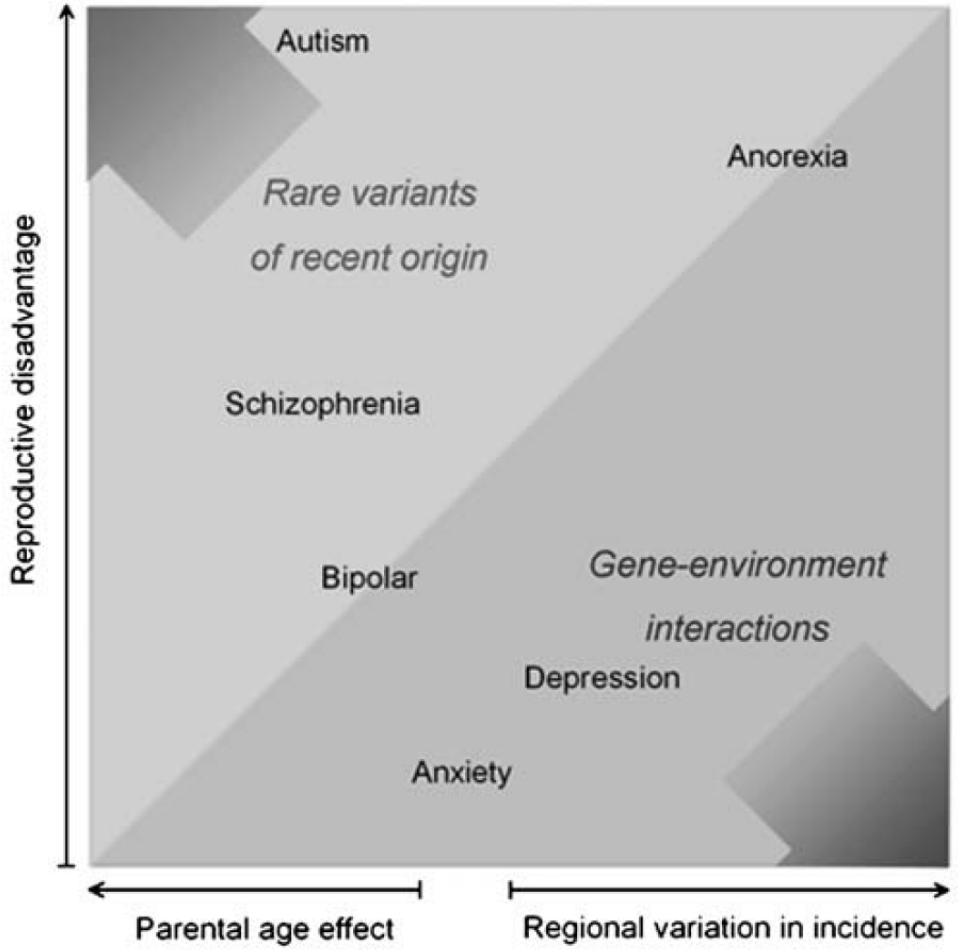
Just No Damn Good:
Polygenic Mutation-Selection Balance

Keller MC, et al. *Behav Brain Sci*. 2006;29(4):385-404.

Just No Damn Good:
Polygenic Mutation-Selection Balance

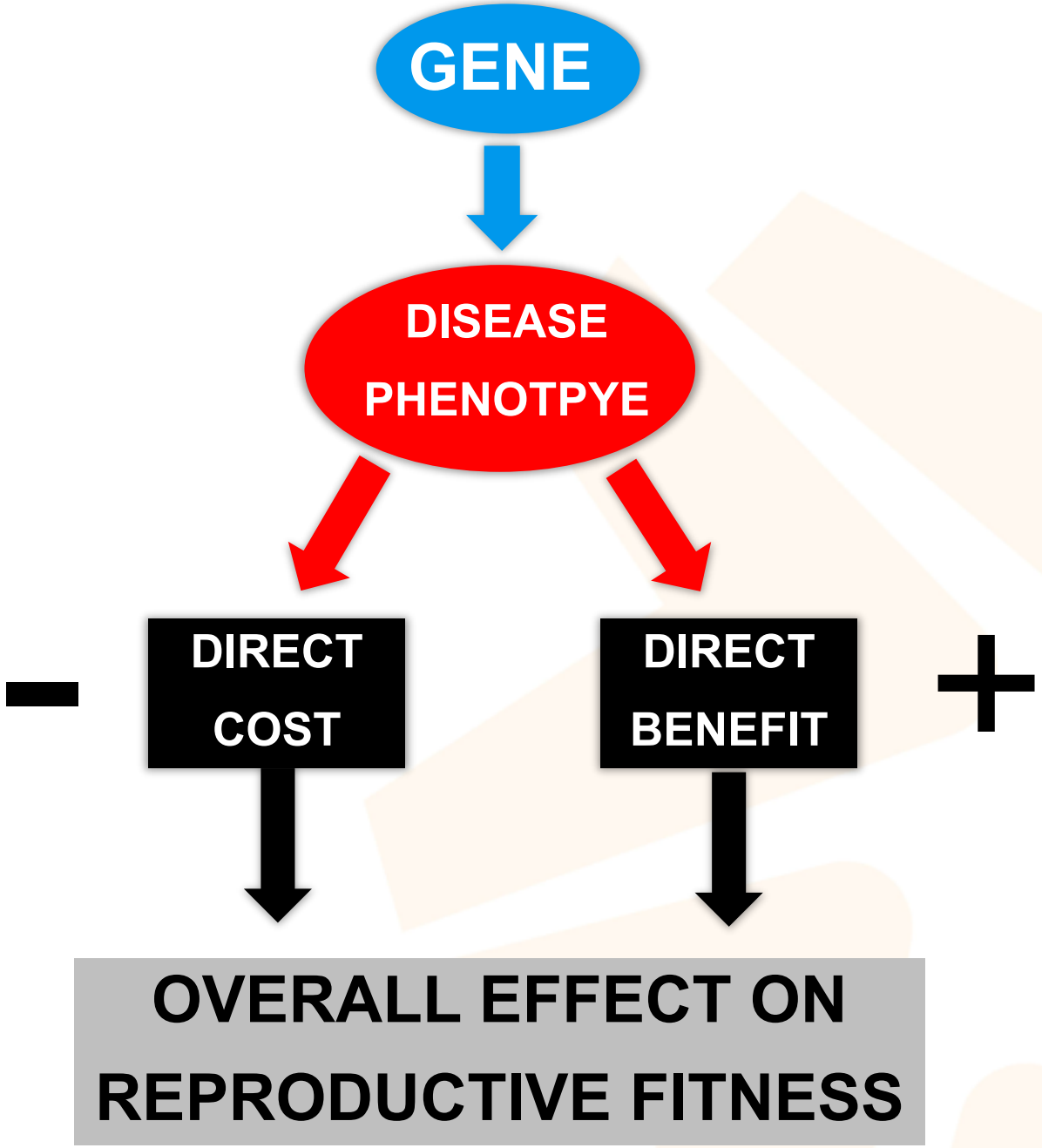
Keller MC, et al. ***Behav Brain Sci***. 2006;29(4):385-404.

Psychiatric Disorders: Adaptive and Otherwise



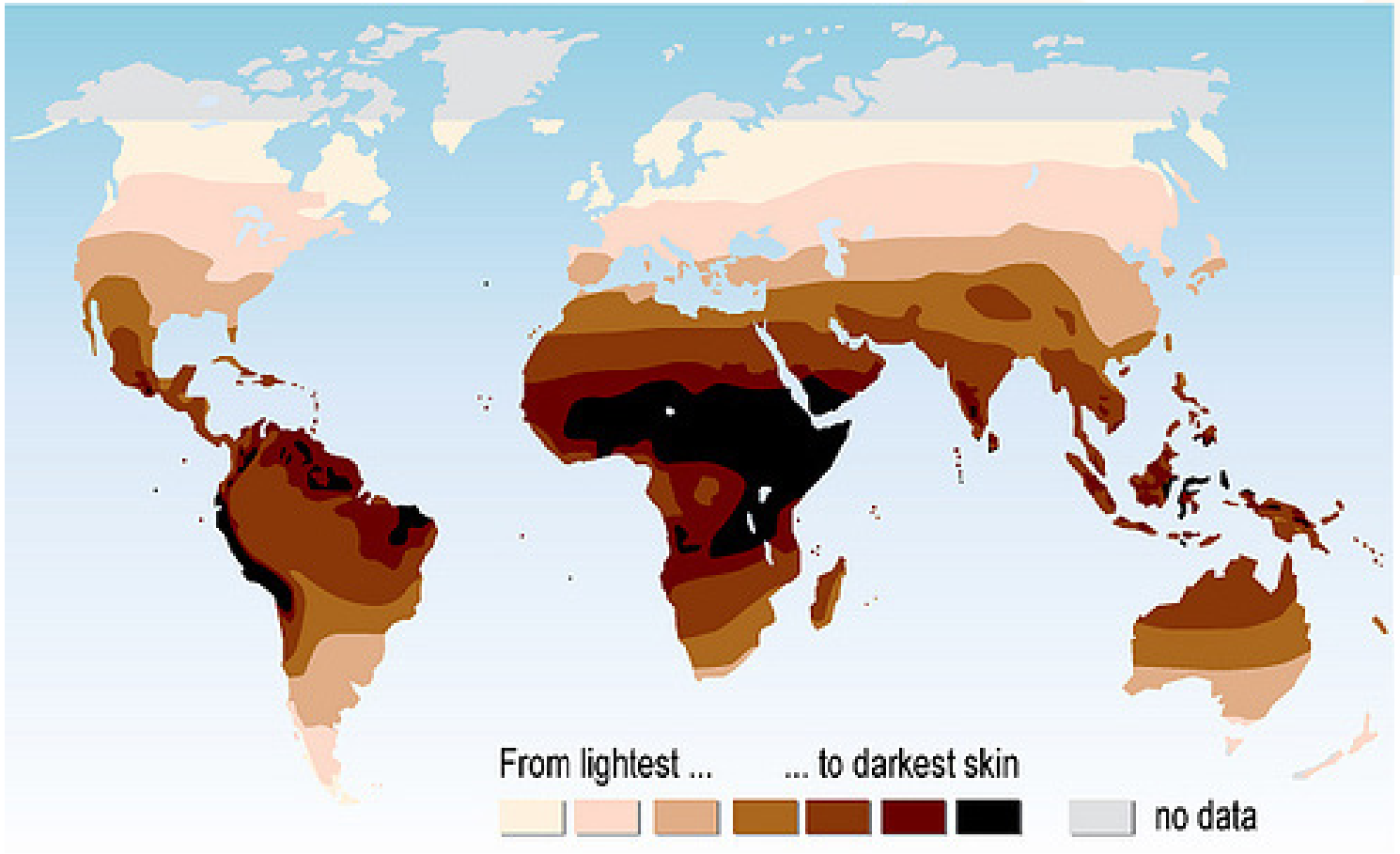
Uher R. *Mol Psychiatry*. 2009;14(12):1072-1082.

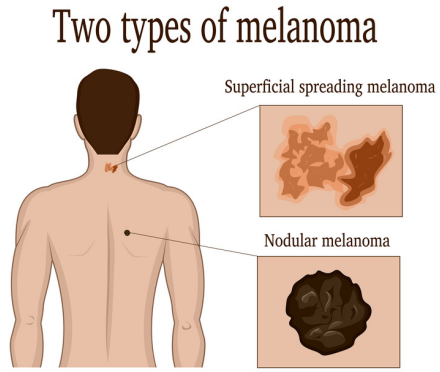
How can something Problematic be an Adaptation?


GENE
DISEASE PHENOTPYE
DIRECT COST
DIRECT BENEFIT
OVERALL EFFECT ON REPRODUCTIVE FITNESS

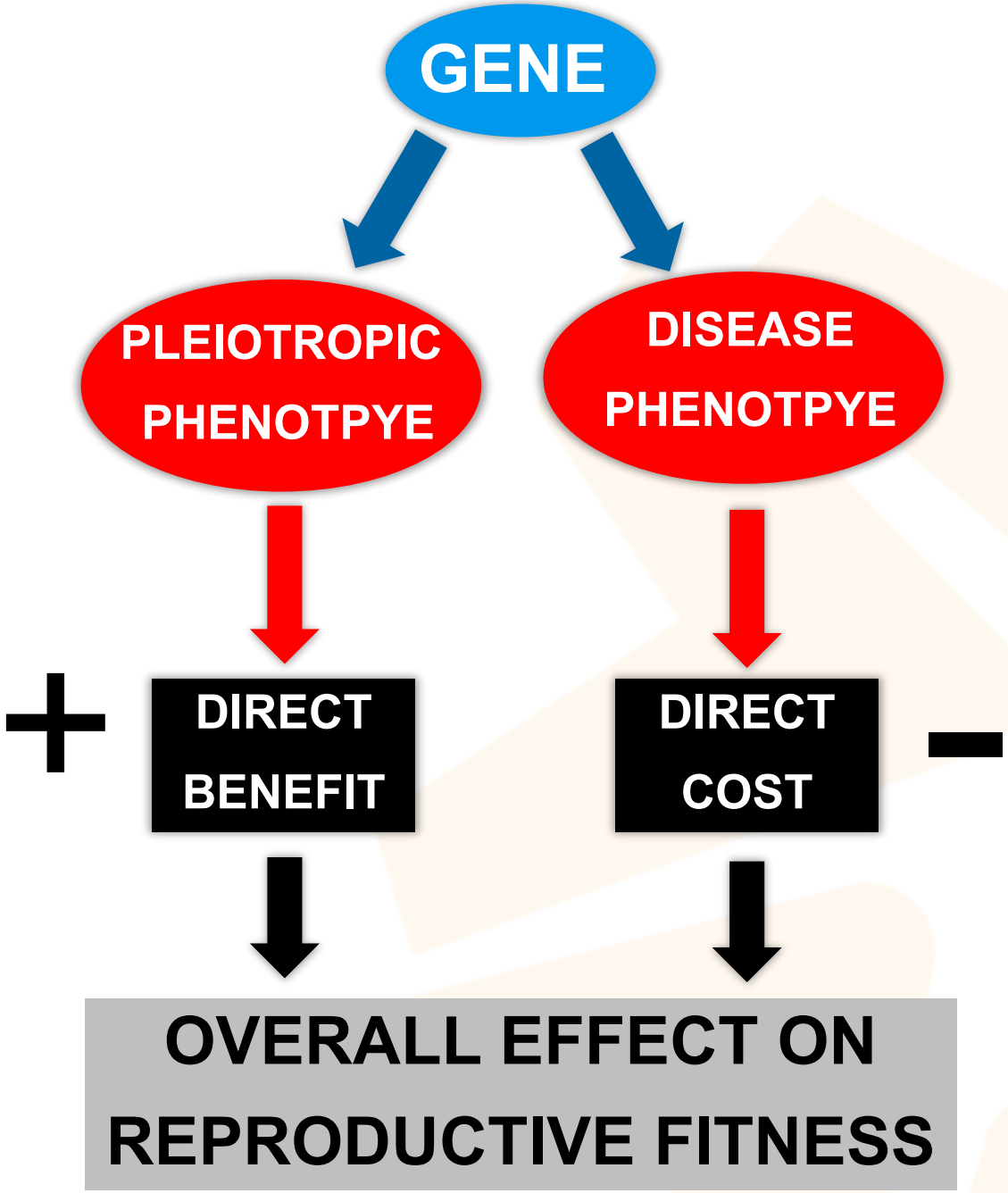
Skin Color Map for Indigenous People

Predicted from Multiple Environmental Factors



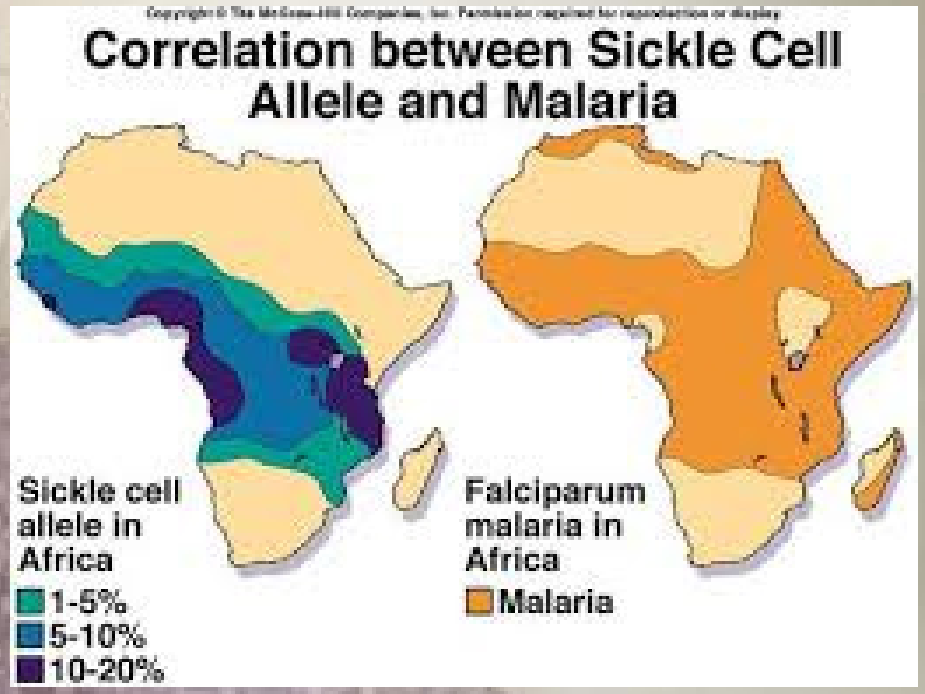


Chaplin G. *Am J Phys Anthropol*. 2004;125(3):292-302.


GENE
PLEIOTROPIC PHENOTPYE
DISEASE PHENOTPYE
+
DIRECT BENEFIT
DIRECT COST
−
OVERALL EFFECT ON REPRODUCTIVE FITNESS

Normal red blood cell

Sickle cell



Is there evidence that Depression is an Adaptation?

The Best Evidence is Right in Front of Us

Depression appears to be a maladaptive state

AND YET

- Genes contribute—at least to some degree—to depression
- Depression is highly prevalent in human populations
- Depression strikes early in life when reproductive costs likely to be highest
- Depression has common features and results from similar environmental conditions across widely divergent cultures, suggesting it is to some degree "hard wired"

THEREFORE

- Either depression itself, or the genes that promote it, must be providing some benefit that maintains these genes (and consequent behavior) in the human genome

Raison CL, et al. *Mol Psychiatry*. 2013;18(1):15-37.

Depression and Reproductive Success

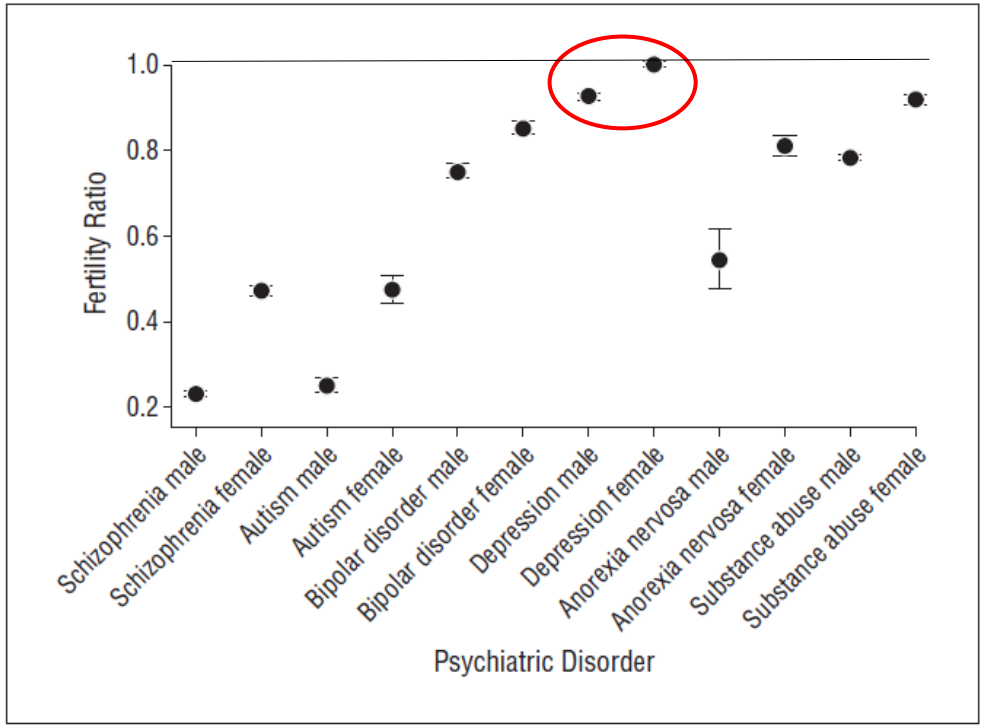


Figure 1. Fertility ratios for individuals with schizophrenia, autism, bipolar disorder, depression, anorexia nervosa, and substance abuse. A fertility ratio of 1 (highlighted) represents that of the general population.

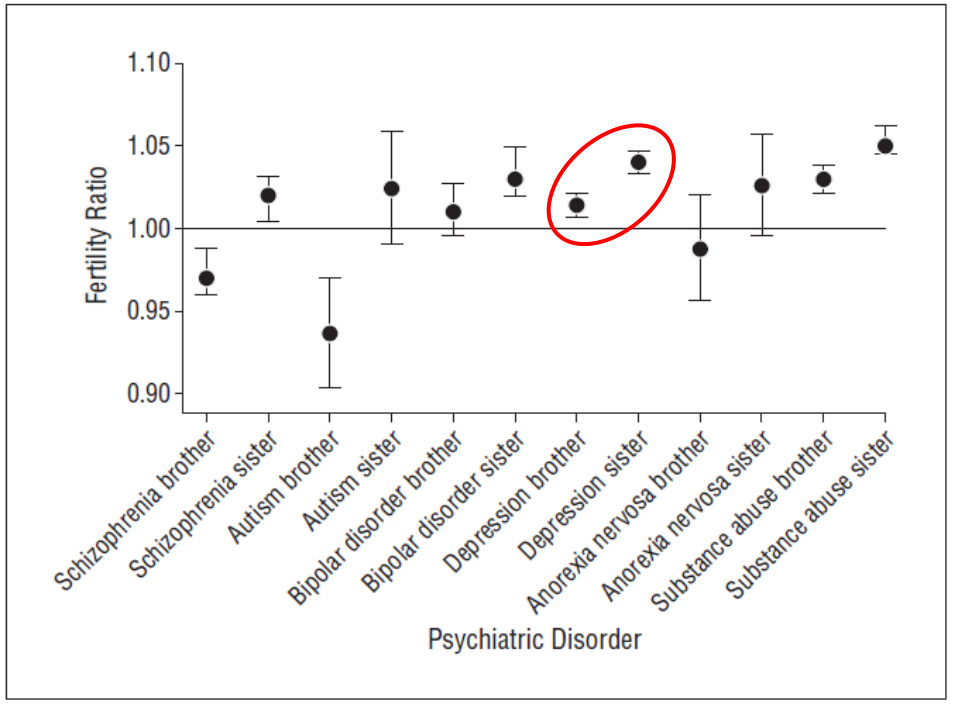
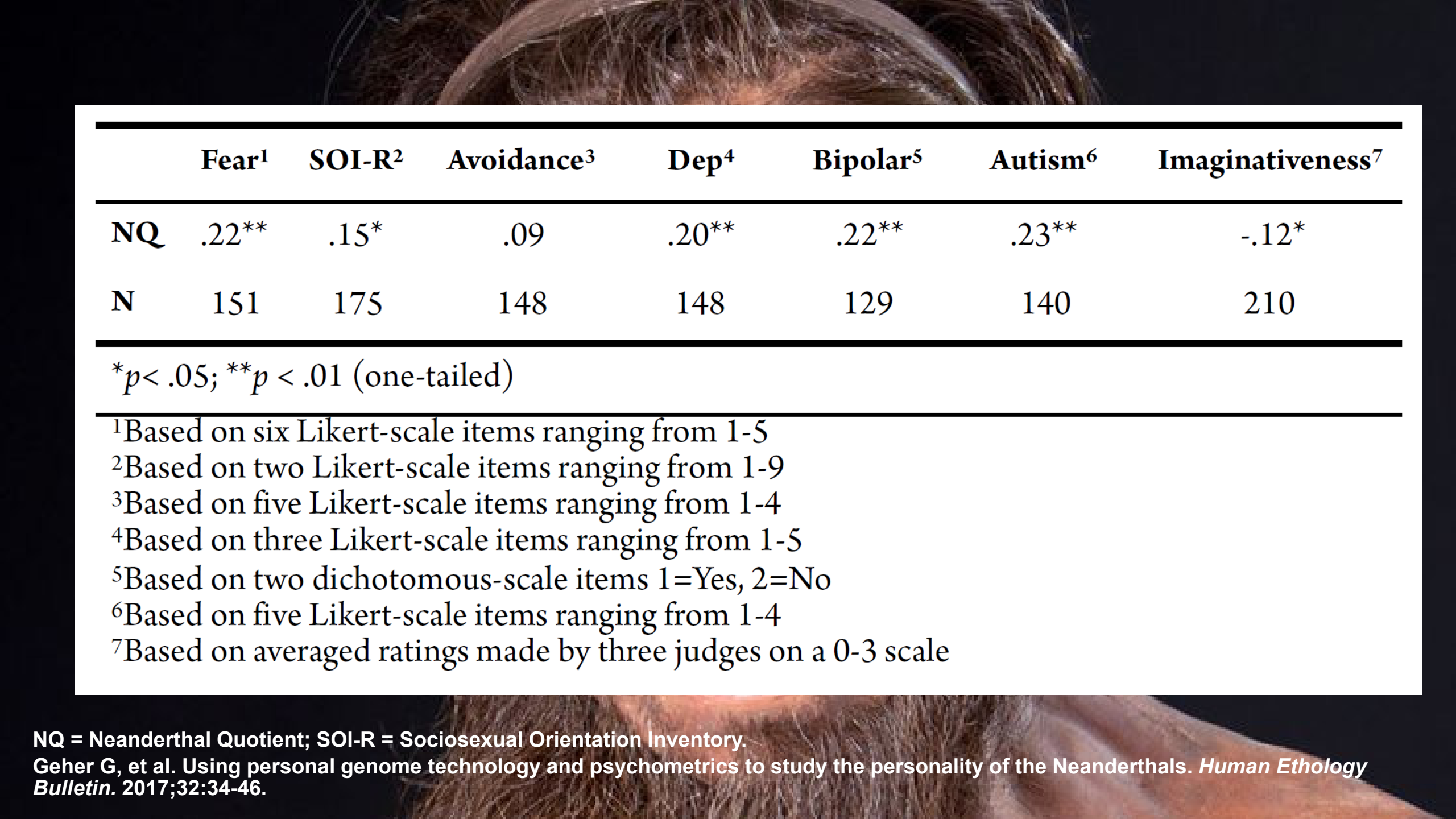


Figure 2. Fertility ratios for unaffected siblings of individuals with schizophrenia, autism, bipolar disorder, depression, anorexia nervosa, and substance abuse. A fertility ratio of 1 (highlighted) represents that of the general population.

Power RA, et al. *JAMA Psychiatry*. 2013;70(1):22-30.



	Fear[1]	SOI-R[2]	Avoidance[3]	Dep[4]	Bipolar[5]	Autism[6]	Imaginativeness[7]
NQ	.22**	.15*	.09	.20**	.22**	.23**	-.12*
N	151	175	148	148	129	140	210

*$p < .05$; **$p < .01$ (one-tailed)

[1]Based on six Likert-scale items ranging from 1-5
[2]Based on two Likert-scale items ranging from 1-9
[3]Based on five Likert-scale items ranging from 1-4
[4]Based on three Likert-scale items ranging from 1-5
[5]Based on two dichotomous-scale items 1=Yes, 2=No
[6]Based on five Likert-scale items ranging from 1-4
[7]Based on averaged ratings made by three judges on a 0-3 scale

NQ = Neanderthal Quotient; SOI-R = Sociosexual Orientation Inventory.

Geher G, et al. Using personal genome technology and psychometrics to study the personality of the Neanderthals. *Human Ethology Bulletin.* 2017;32:34-46.

Neanderthals and Pathogen Host Defense

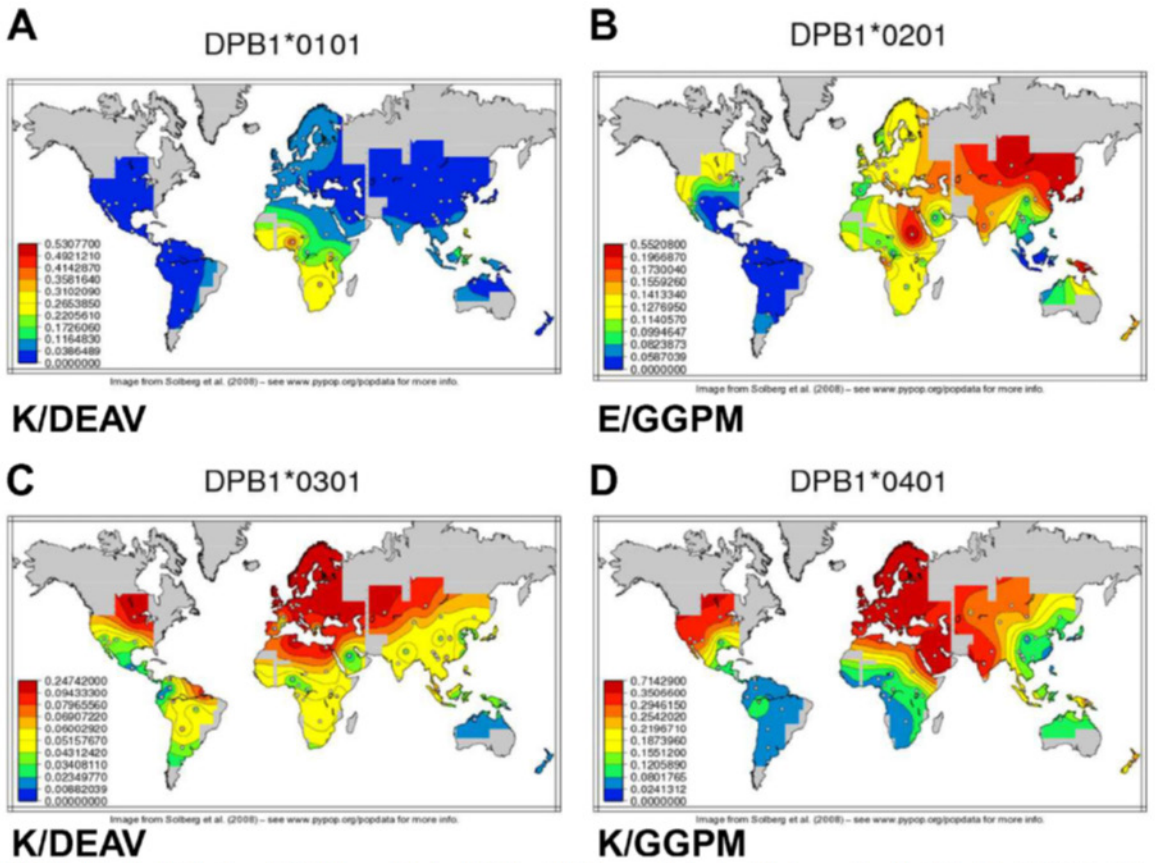


FIGURE 8. **World-wide distribution of DPB alleles and the Lys/GGPM motifs.** The maps display the allele frequencies of the DPB alleles 0101, 0201, 0301, and 0401 on the basis of non-migratory populations. Higher frequencies are displayed in *red*, and lower frequencies are *blue*. The frequency scaling between the maps is not identical and is displayed as *inset*. The DPB1*0401 allele (*panel D*) is relatively rare in sub-Saharan Africa but progressively more frequent in northern European populations (*red*). Neanderthals carry both Lys-69 and GGPM-(84–87) and differ from DPB1 from modern human by a single residue over the available sequence. Note though that Lys-69 and GGPM-(84–87) occur independently in other alleles, which makes interpretation of the origin of their arrangement difficult to determine.

Temme S, et al. *J Biol Chem*. 2014;289(2):639-653.

Sickness and Depression

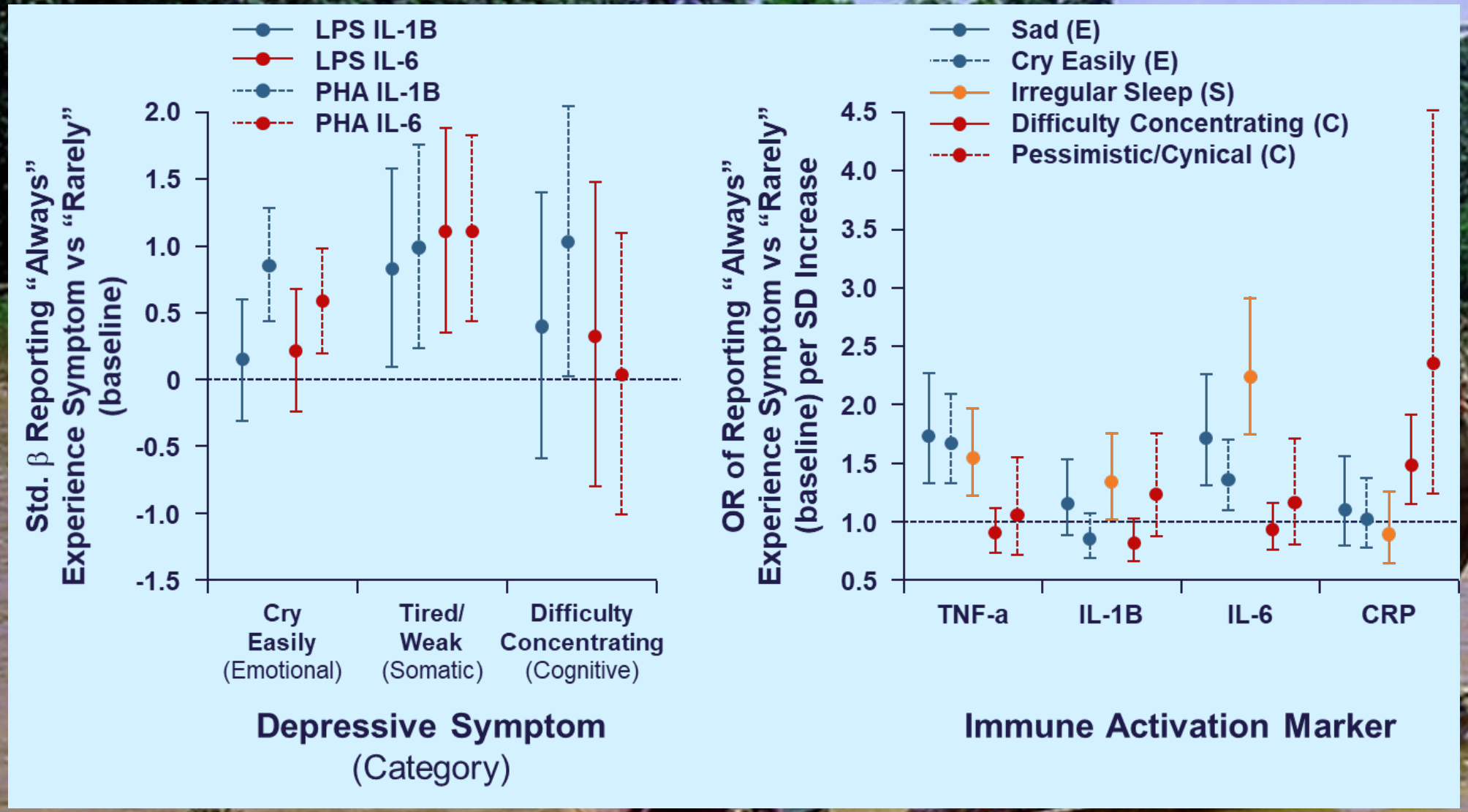
SICKNESS

- Loss of pleasure*
- Loss of appetite*
- Weight loss*
- Cognitive disturbance*
- Decreased sexual energy*
- Fatigue*
- Physical slowness*
- Sleep disturbance*
- Social isolation*
- Increased pain*
- Fever *
- Sad mood†
- Suicidal ideation†
- Worthlessness/guilt†

DEPRESSION

- Loss of pleasure*
- Loss of appetite*
- Weight loss*
- Cognitive disturbance*
- Decreased sexual energy*
- Fatigue*
- Physical slowness*
- Sleep disturbance*
- Social isolation*
- Increased pain complaints*
- Increased body temperature *
- Sad mood†
- Suicidal ideation†
- Worthlessness/guilt†

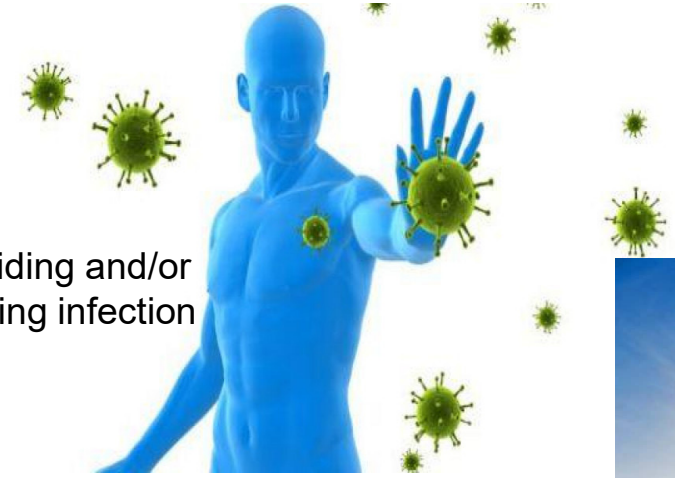
Raison CL, et al. *Semin Clin Neuropsychiatry*. 2001;6(4):277-294.



CRP = C-reactive protein; IL = interleukin; LPS = lipopolysaccharide; PHA = phytohaemagglutinin; TNF-α = tumor necrosis factor alpha.

Stieglitz J, et al. *Brain Behav Immun*. 2015;49:130-139.

In what ways might Depression itself be an Adaptation?



Avoiding and/or fighting infection

To be human is to struggle with managing our relationships with microbes, parasites, and other humans

In each of these instances, depression is about managing these relationships

Raison CL, et al. *Neuropsychopharmacology*. 2017;42(1):5-27. Keller MC, et al. *J Affect Disord*. 2005;86(1):27-35. Buist-Bouwman MA, et al. *J Affect Disord*. 2004;82(3):363-371.


CHANGE
For The Better

Sometimes Depression May Still Do What It Evolved to Do…

Mean score of SF-36 scales on different waves in a cohort with MDE between T_0 and T_2, but not in the years preceding T_0 and T_2 and a control group without depression during that period and comparison between mean SF-36 scores on different waves within the cohort

	T_0				T_1				T_2				Comparison within cohort		
	Cohort (n=165)		Control (n=4178)		Cohort (n=165)		Control (n=4178)		Cohort (n=165)		Control (n=4178)		T_0-T_1	T_1-T_2	T_0-T_2
	Mean	S.D.	Mean	S.D.	Mean	S.D.	Mean	S.D.	Mean	S.D.	Mean	S.D.	p	p	p
Physical functioning	88.0	17.0	92.5	15.1	87.7	18.5	92.2	15.5	85.7	20.2	91.1	16.2	0.76	0.14	0.09
Physical role functioning	78.2	35.2	87.2	28.5	72.0	39.5	87.8	28.4	80.8	33.9	87.1	28.7	0.08	0.01	0.48
Vitality	63.3	18.1	73.4	17.0	54.9	20.1	71.1	15.6	65.4	16.2	71.6	15.6	0.00	0.00	0.17
Pain	80.1	23.5	86.1	20.6	80.1	24.1	86.3	20.4	80.2	23.4	85.9	20.5	0.98	0.92	0.95
Psychological health	73.9	16.5	83.9	12.7	64.7	18.7	81.4	12.1	76.5	13.6	82.3	11.8	0.00	0.00	0.03
Psychological role functioning	85.7	30.4	94.9	18.7	73.3	37.0	95.2	18.2	93.3	21.2	95.9	16.9	0.00	0.00	0.01
Social functioning	82.8	19.7	91.3	16.2	76.2	23.0	91.2	15.2	86.4	17.5	91.1	15.4	0.00	0.00	0.05
General health	68.3	18.9	75.5	16.8	66.1	17.1	73.8	16.3	70.1	18.4	73.6	16.5	0.09	0.00	0.15

165 adults aged 18–65 years with MDE with no depression in year prior to first assessment or in 12 months prior to third assessment followed for 2 years (so looking at impact of 1 new MDE during this period).

MDE = major depressive episode; SF-36 = Short-Form-36 Health Survey.

Buist-Bouwman MA, et al. *J Affect Disord*. 2004;82(3):363-371.

The Evolution of Jack: A Case History

HPI

35-year-old medically-healthy white male presents with 2 months of worsening anxious depression: diurnal mood variation (worse in AM) middle/terminal insomnia, 10 pounds weight loss, reduced concentration “always distracted”, markedly reduced functioning in career as corporate lawyer, “feels powerless and paralyzed, “nervous wreck”

PMH

One prior 3-month episode of anxious MDD age 22 after failing to pass the bar exam on first attempt; episode resolved completely with fluoxetine which Jack tolerated without significant side effects, which was discontinued after 6 months once bar passed; no history of mania, hypomania, OCD, PTSD, or substance use disorder

Family Hx

Significant MDD maternal grandmother

MDD = major depressive disorder; OCD = obsessive-compulsive disorder; PTSD = posttraumatic stress disorder.

The Evolution of Jack: A Case History

Social History

Successful corporate lawyer, partner × 2 years in large firm; married × 8 years to Lucile; when asked about marriage, Jack responds, “You’d have to ask the boss” and laughs somewhat ruefully

Most Appropriate Next Treatment Step from Evolutionary Perspective

1. Restart fluoxetine based on prior good response and minimal side effects
2. Send patient to psychologist in the office for psychotherapy
3. Start fluoxetine and make psychotherapy referral
4. None of the above

The Evolution of Jack: A Case History

Treatment Plan

Restart fluoxetine at 10 mg po qD for 4 days then increase to 20 mg po qD; return for follow-up in 4 weeks

4-week Follow-up

Patient's symptoms remarkably improved, anxiety and depression resolved, sleep normalized, appetite normal, work productivity markedly increased. Patient states, "This medicine is a miracle! It gives me the feeling that everything is going to be OK after all."

Assessment of Care

Successful intervention, treatment goals met, Jack stayed on fluoxetine × 18 months and did well; discontinued treatment thereafter

Jack's Assessment 7 Years Later

"The antidepressant was the worst thing that ever happened to me."

What Happened?

Additional History at Time of First Visit

- Despite leadership success at work, Jack had a passive personality style in romantic relationships and had become increasingly "beaten down" over the 8 years of marriage to Lucile as she became increasingly angry, critical, and demanding
- Despite the relationship becoming increasingly distant and hostile, Lucile desperately wanted a child
- Being unable to conceive, she and Mark had agreed to do IVF despite Jack's growing unspoken fears that the marriage was not stable enough to support a child
- Sensing his hesitation, Lucile became increasingly angry and threatened to end the relationship if he didn't go through with the IVF
- As his depression/anxiety increased, Lucile suggested he go back on fluoxetine because "it helped you get over your fears in the past"

IVF = *in vitro* fertilization.

What Happened?

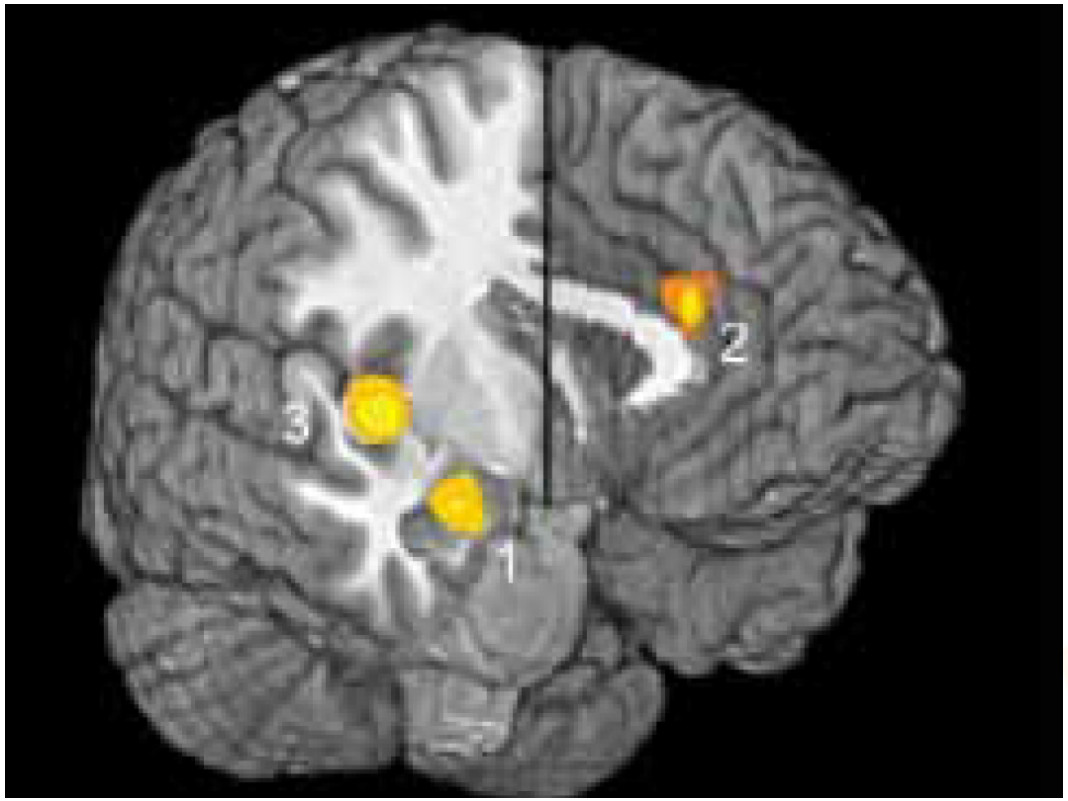
Additional History Following Treatment

- Prior to starting fluoxetine, Jack described himself as “paralyzed”; he “knew in his heart that getting pregnant was a bad idea” and yet he felt he was “too far in to back out”
- On fluoxetine, Jack’s anxiety subsided; as he became more hopeful, he decided to go forward with IVF, believing in his new positive mood that somehow things would work out. He found renewed interest in work and refocused on this as a source of pleasure
- Jack and Lucile had a girl. The stress of raising a child caused a further deterioration in their relationship. 2 years later they moved into separate rooms
- 6 months later, a financially ruinous, protracted, and painful divorce ensued that ended with Lucile moving out of state with a new partner, leaving Jack alone and separated from his young daughter, with whom he had developed a close relationship

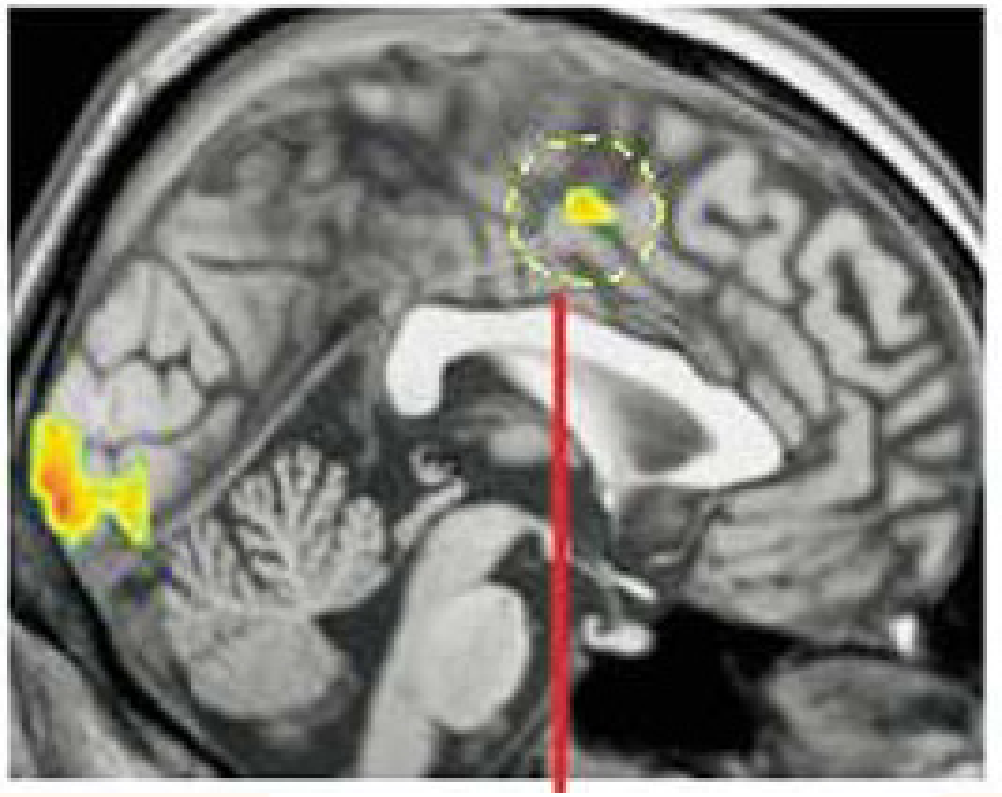
How It All Ended

- Jack's depression returned with increased severity
- **His conclusion**: "I should have listened to my feelings in the first place"
- **His decision**: Commenced psychotherapy to better understand why he tends to cede so much emotional power to romantic partners and to help him cope with grief of separation from his daughter

An Immunological Correlate to Jack's Story



MAJOR DEPRESSION



BRAIN EFFECTS OF INFLAMMATION

Hamilton JP, et al. *Am J Psychiatry*. 2012;169(7):693-703. Capuron L, et al. *Biol Psychiatry*. 2005;58(3):190-196.

But Adaptations Can Go Wrong

INSUFFICIENT

Too little activation in an appropriate situation

Failure to activate in an appropriate context

The SSRI did this to Jack

EXCESSIVE

Too much activation in an appropriate situation

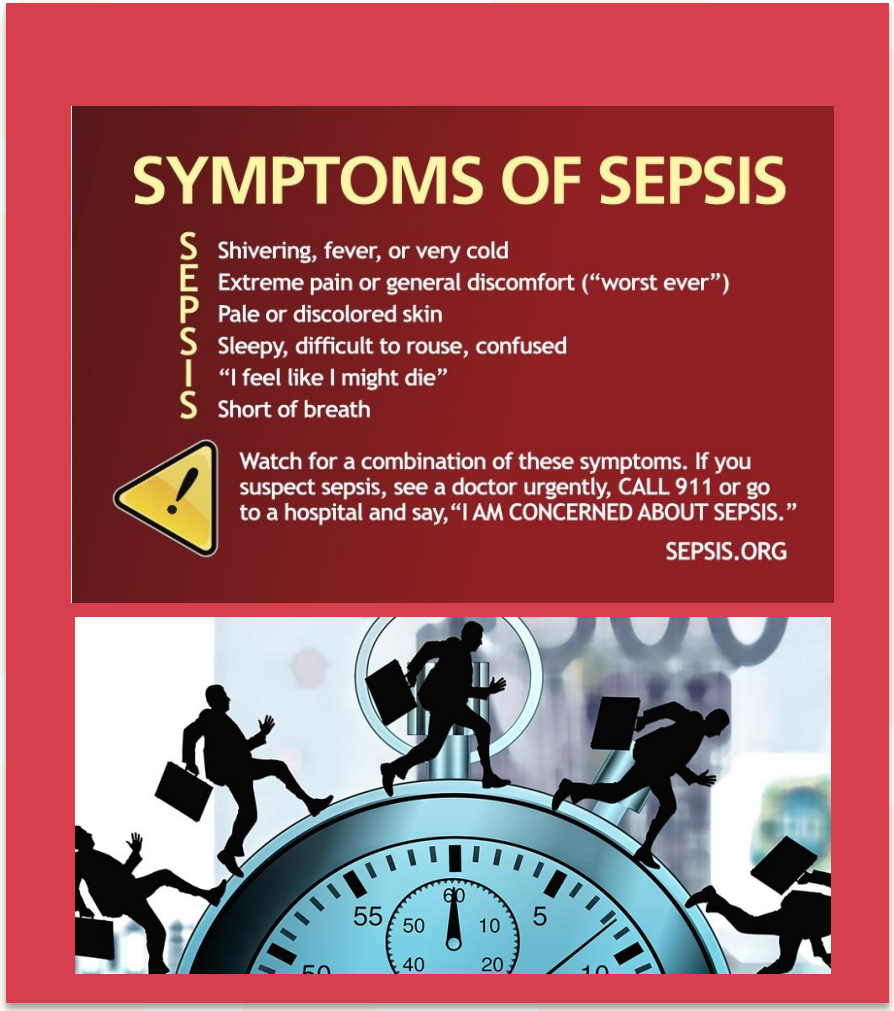
Activation in an inappropriate context

This is Often MDD in the Modern World

SSRI = selective serotonin reuptake inhibitor.

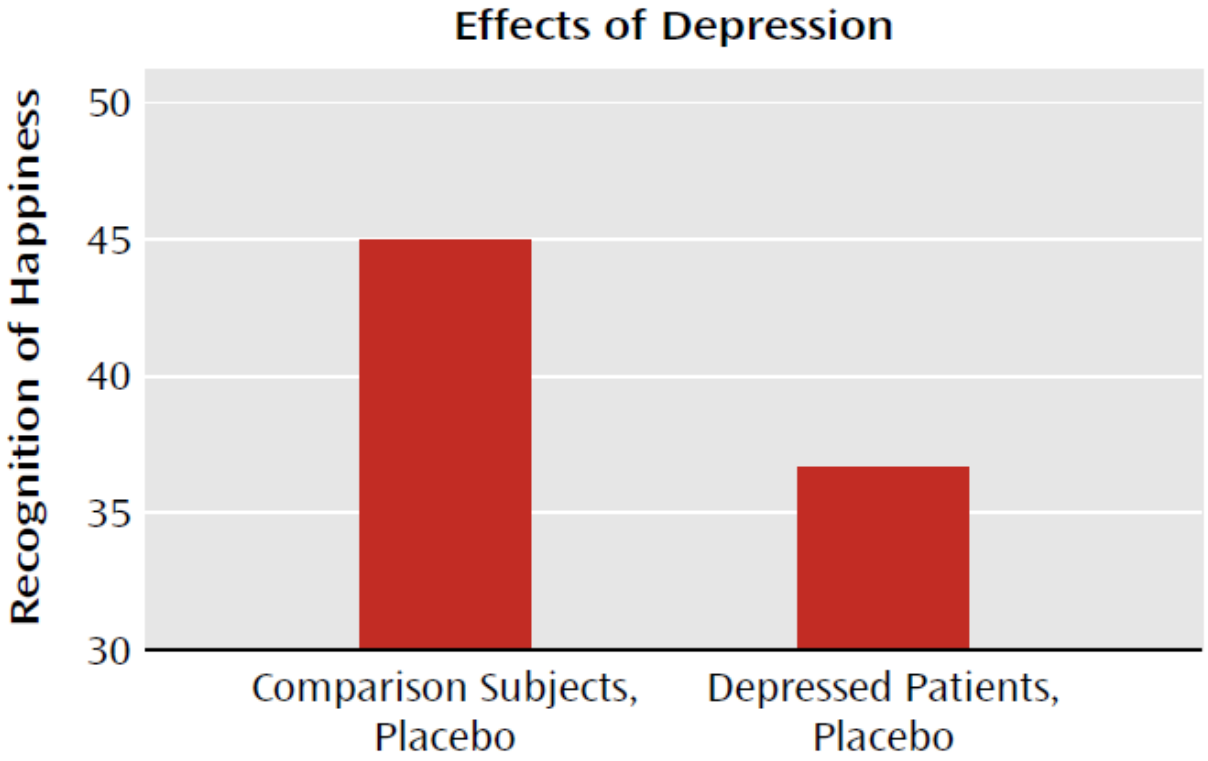
Consider Sepsis as an Example: Part I

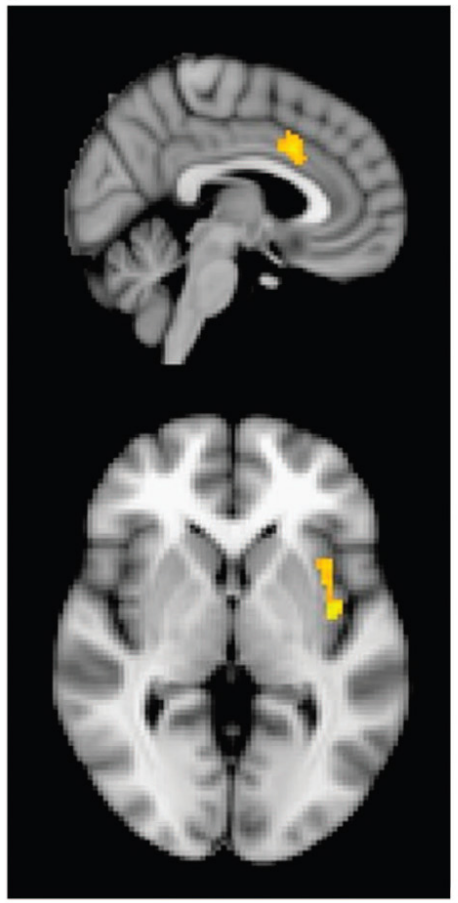
- The inflammatory response is very ancient because it is the best strategy nature has devised to provide rapid protection against infection
- Absence of an inflammatory response is incompatible with survival
- Inflammation is an adaptation
- Sepsis is an example of an adaptation gone wrong through being excessive
- A goal of sepsis treatment is to mitigate this excessive adaptive response—recent treatments do this by extracorporeal cytokine adsorption delivered early in sepsis to mitigate cytokine storm

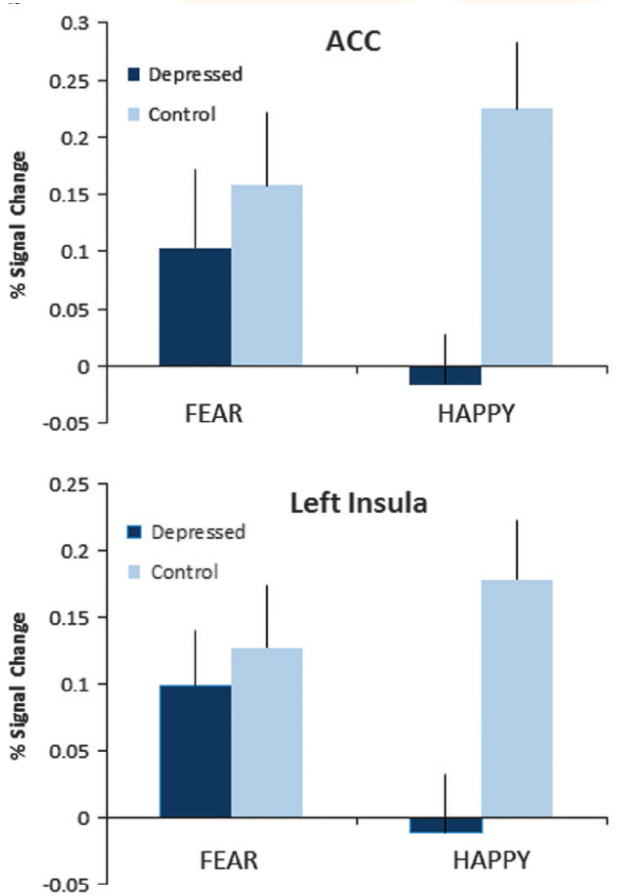


Miller AH, et al. *Biol Psychiatry*. 2009;65(9):732-741. Ankawi G, et al. *Blood Purif*. 2019: [Epub ahead of print].

Major Depressive Disorder is Associated with a Negativity Bias That Inhibits Perception of the Positive



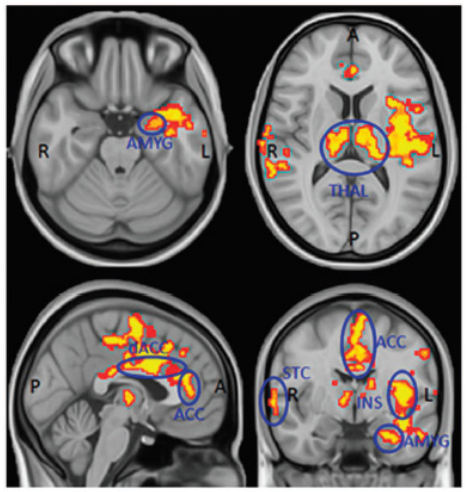


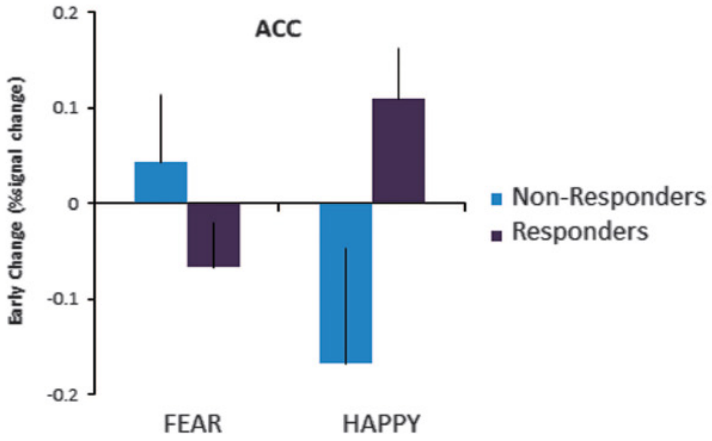


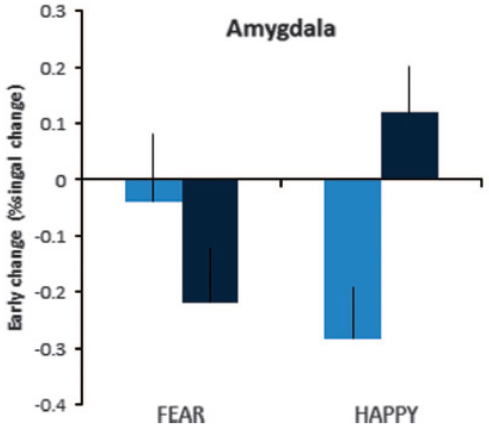
ACC = anterior cingulate cortex.

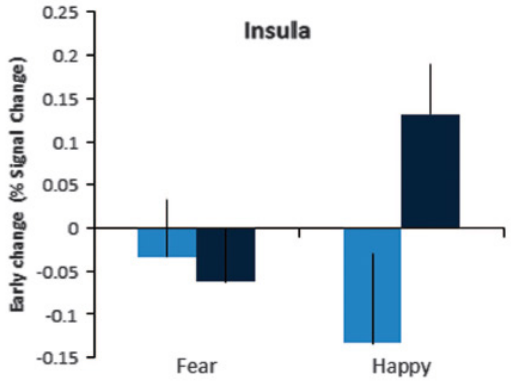
Harmer CJ, et al. *Am J Psychiatry*. 2009;166(10):1178-1184. Godlewska BR, et al. *Transl Psychiatry*. 2016;6(11):e957.

Antidepressants' Rapid Reduction in Fear Circuitry Predicts Later Clinical Response







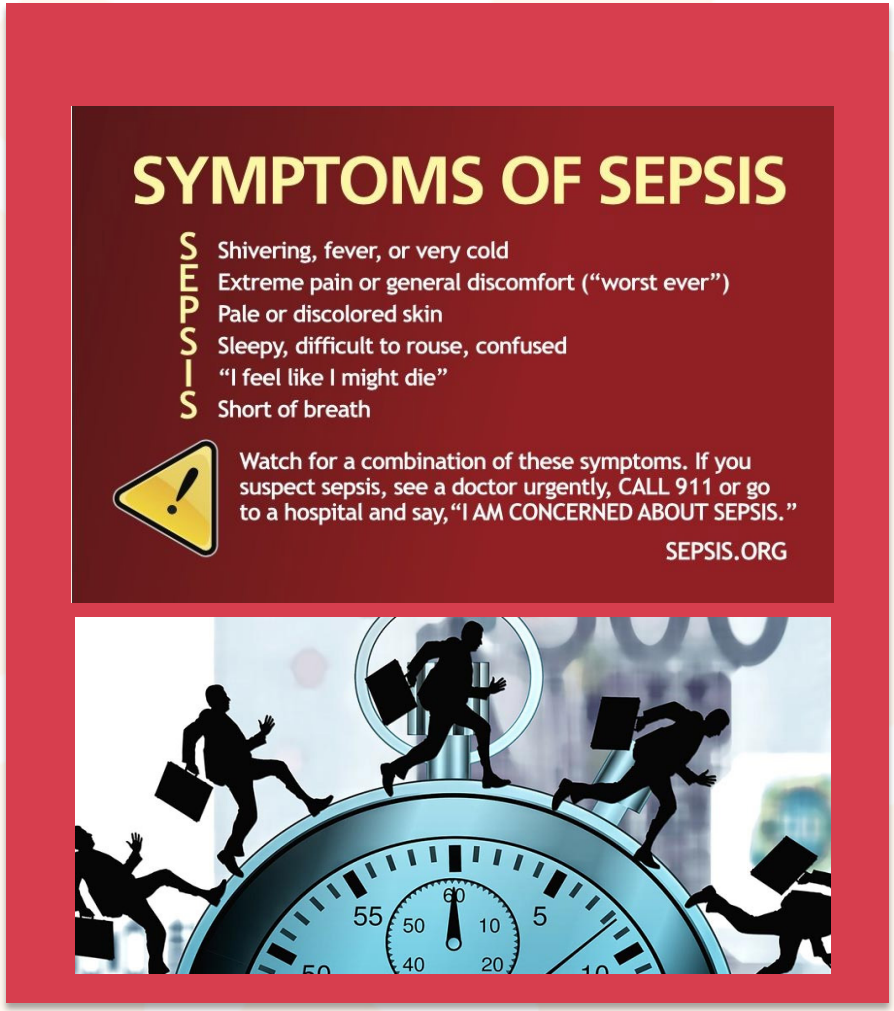


In 35 unmedicated patients with MDD treated with 10 mg escitalopram for 6 weeks, patients who responded at week 6 showed significant reduction in baseline fear circuitry response 1 week after starting treatment. This early neurobiological change predicted depressive symptom improvement after 6 weeks of treatment, even when adjusting for improvement at week 1.

Godlewska BR, et al. *Transl Psychiatry*. 2016;6(11):e957.

Consider Sepsis as an Example: Part II

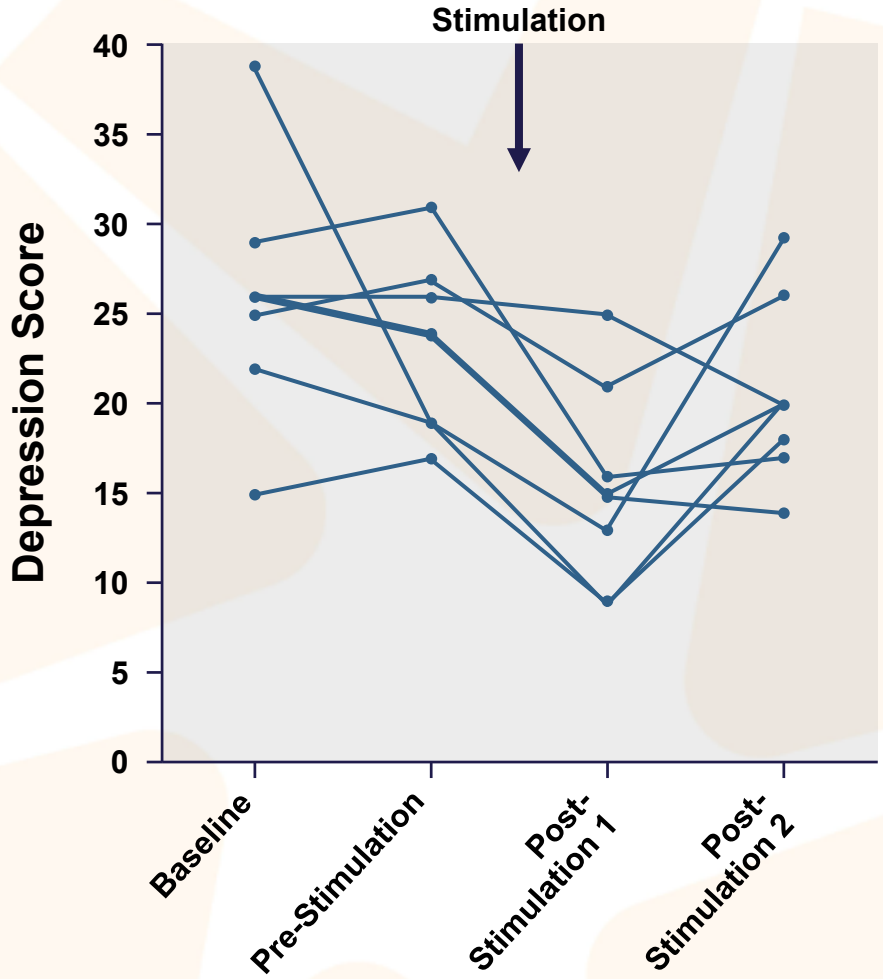
- The very intensity of the inflammatory response sets in motion a compensatory anti-inflammatory response which in modern ICU settings is often the cause of septic mortality due to infection
- Recent studies suggest that stimulating the immune system (ie, checkpoint inhibitors, IL-7) increases long-term survival from sepsis
- *Might something similar sometimes pertain in depression? Might acutely augmenting the depressive cause help resolve the syndrome?*



Miller AH, et al. *Biol Psychiatry*. 2009;65(9):732-741. Ankawi G, et al. *Blood Purif*. 2019: [Epub ahead of print].

Inflammation as a Treatment for Depression

In a small study of 7 severely depressed inpatients, the administration of LPS at 5 PM produced a significant reduction in depressive symptoms the next day (*P*=.018). The improvement was maintained in 2 of the 7 participants, whereas the other 5 relapsed following a night of recovery sleep. LPS increased IL-6 and TNF-α and suppressed REM sleep. Reductions in depressive symptoms were highly correlated with increased IL-6 after LPS administration (rs=.95, *P*<.001).



REM = rapid eye movement sleep.

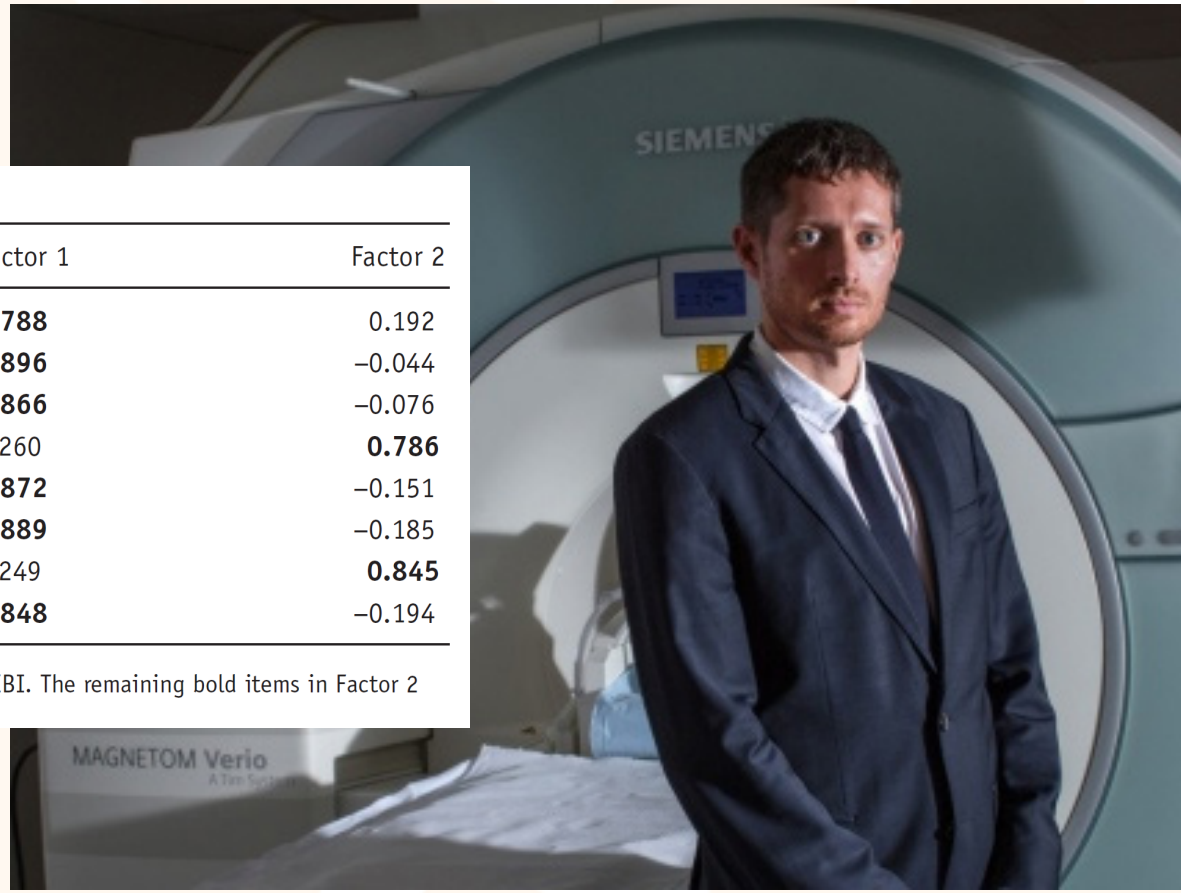
Bauer J, et al. *Biol Psychiatry*. 1995;38(9):611-621.

“Emotional Breakthrough” and Well-Being: Psychedelic Therapy

Table 1. Factor loadings from factor analysis of eight Emotional Breakthrough Inventory (EBI) items.

Item	Factor 1	Factor 2
I faced emotionally difficult feelings that I usually push aside.	**0.788**	0.192
I experienced a resolution of a personal conflict/trauma.	**0.896**	–0.044
I felt able to explore challenging emotions and memories.	**0.866**	–0.076
I was resisting and avoiding challenging feelings throughout, without breakthrough.	0.260	**0.786**
I had an emotional breakthrough.	**0.872**	–0.151
I was able to get a sense of closure on an emotional problem.	**0.889**	–0.185
I felt emotionally stuck throughout, without breakthrough.	0.249	**0.845**
I achieved an emotional release followed by a sense of relief.	**0.848**	–0.194

The extraction method was principal component analysis (PCA). The six bold Items in Factor 1 reflect the final version of the EBI. The remaining bold items in Factor 2 where not used in the final version of EBI. Factor loadings >0.5 are in bold (n=379).



Roseman L, et al. *J Psychopharmacol*. 2019 Jul 11: [Epub ahead of print].

Summary
Clinical Implications of an Evolutionary Perspective

IF DEPRESSION IS AN ADAPTATION

- **When do you suppress the adaptation?**
  - *Excessive to the situation, inappropriate to the situation, appropriate but futile (hence likely to become chronic)?*
- **When do you let it play out?**
  - *Episodic, caused by appropriate problem/life challenge, past failure of "ignoring the problem" to resolve or protect against depression?*
- **When do you augment it to resolve it?**
  - *When mitigating strategies (ie, antidepressants) have failed, early in disease course when cognitive flexibility still preserved, in people who want to (and seem cable of) "dealing with their problems, when the same issue/challenge has produced repeated depressive episodes?*