MEDS, MINDFULNESS, AND MORE:
THE NEUROBIOLOGICAL CASE FOR AN INTEGRATIVE APPROACH TO THE TREATMENT OF DEPRESSION

Dr. Robert Johnson
Medical Director, Sierra Tucson
Diplomate, ABPN, ABAM

PROLOGUE

The Data Supporting a More Integrative and Broad-Based Approach :

- The limited efficacy and specificity of antidepressant medication
- The neurobiological research on the powerful role that belief and expectation play
- Research around the *actual* mechanisms of action of antidepressants, anxiolytics, and analgesics
- The data around the psychobiological effects of psychotherapy
- Epigenetic findings that are helping us understand why a patient can be affected by so many different healing modalities

These are challenging some of the most fundamental assumptions of our traditional treatment model, and helping us understand how we can help patients learn to create environments and lifestyles that support their long-term healing.

Antidepressant Medications: Hope or Hype?

- In 1998 two psychologists - Irving Kirsch and Guy Sapirstein – published a controversial meta-analysis comparing the mean effect size of antidepressants vs. psychotherapy vs. placebo vs. no treatment in symptoms of depression across 3000 patients in 19 double-blind studies.

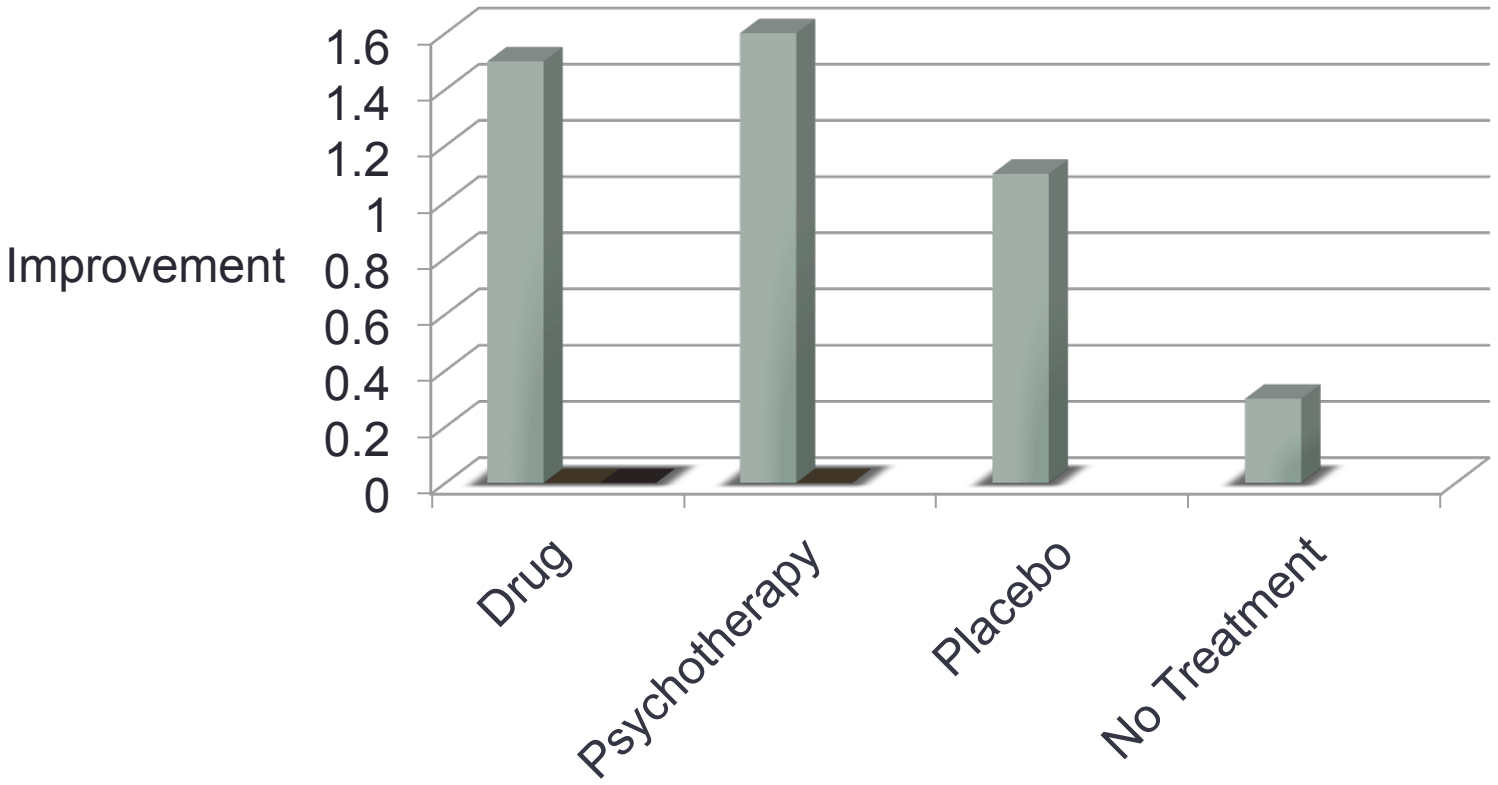
(Kirsch, I., & Sapirstein, G. (1998). Listening to Prozac but hearing placebo: A meta-analysis of antidepressant medication. *Prevention & Treatment*, *1*, art. 0002a)

Antidepressant Medications: Hope or Hype?

- **Drug Effect:** the difference between what happens if people are given the active drug and what happens when they are given a placebo
- **The Placebo Effect:** the difference between what happens if people are given placebos and what happens when they are not treated at all (spontaneous improvement)

Antidepressant Medications: Hope or Hype?

- Results: While antidepressants did in fact cause significant improvement in 75% of patients, a full **75% of the AD's effectiveness could be attributed to the placebo effect**.
- Suggested that only 25% of the benefit of antidepressants treatment was really due to the chemical effect of the drug – that the placebo effect was twice as large as the drug effect.



Kirsch, I., & Sapirstein, G. (1998). Listening to Prozac but hearing placebo: A meta-analysis of antidepressant medication. *Prevention & Treatment*, *1*, art. 0002a.

Antidepressant Medications: Hope or Hype?

"Maybe It's All in Your Head"… "Make-Believe Medicine"… "New Study of Brain Illustrates the Power of Placebo"… "Antidepressants: Hype or Help?"… "Misguided Medicine: A Stunning Finding about Antidepressants Is Being Ignored"

Antidepressant Medications: Hope or Hype?

- In 2002 Kirsch and Sapirstein used the Freedom of Information Act to acquire data from all corporate-funded AD studies (47) submitted to the FDA for approval of the six most widely prescribed antidepressants between 1987-99. The results replicated and extended their earlier results.

(Kirsch, I; Moore, Thomas J.; Scoboria, Alan; Nicholls, Sarah S.. "The emperor's new drugs: An analysis of antidepressant medication data submitted to the U.S. Food and Drug Administration". *Prevention & Treatment* (American Psychological Association) **5:** July 2002)

Antidepressant Medications: Hope or Hype?

Four interesting facts emerged:

- 40% of the studies conducted had gone *unpublished* (mostly those that failed to beat placebo)
- When all studies were included, the drugs came out *less* effective, with placebo response accounting for 82% of their effectiveness.
- The non-placebo improvement reflected less than a 2-point difference on the HAM-D, a statistically significant "but not clinically meaningful difference".
- Efficacy between antidepressants and placebo demonstrated virtually no difference at mild and moderate levels of depression, to only a relatively small difference for patients with very severe depression.

Antidepressant Medications: Hope or Hype?

In a provocative piece in the Washington Post entitled "Against Depression, a Sugar Pill Is Hard to Beat", NPR science correspondent Shankar Vedantam (2002) asserted:

> "After thousands of studies, hundreds of millions of prescriptions and tens of billions of dollars in sales, two things are certain about pills that treat depression: antidepressants like Prozac, Paxil and Zoloft work. And so do sugar pills"

Vedantam, S. (2002, May 7). Against depression, a sugar pill is hard to beat. *Washington Post*, A01. http://www.washingtonpost.com/ac2/wp-dyn/A42930-2002May6.

Antidepressant Medications: Hope or Hype?

- **Bottom Line:** contrary to some of the media "hype" on this topic, antidepressant research confirms an empirically demonstrated drug-placebo difference, it's just not nearly as large as most of us thought
- People obtain considerable benefit from many medications, but also can experience symptom improvement just by knowing they are being treated (the 'placebo effect')

Maybe the Drugs Aren't Equally Effective?

- The newer AD's (SSRIs, SNRIs, NRI's, etc) are no more effective than each other, or than the older medications (TCA's, MAOI's)
- A startling finding: the consistency of the *size* of the drug effect. Not only were the percentages close, they were virtually *identical* - they ranged from 24 to 26 percent.
- The lack of difference between one class of AD's and another is now a rather frequent finding in AD research

(Williams, J, et al, A systematic review of newer pharmacotherapies for depression in adults: evidence report summary, Annals of Internal Medicine 132(2000):743-56)

If It Doesn't Matter What Antidepressant You Use, Then What Makes Them Effective?

- Why should drugs with different mechanisms of action, and even non-AD medications, be equally effective in treating depression? What do they *all* have in common?
- "Enhanced placebos"
  - Produce easily noticeable side effects
  - Placebos can also produce side effects, but typically to a much lesser degree than active medication

    (Philipp, M, et al, Hypericum extract versus imipramine or placebo in patients with moderate depression: randomized multicenter study of treatment for eight weeks, British Medical Journal 319 (1999):1534-39)

Antidepressants as Enhanced Placebos

- 80% of patients in studies accurately identify whether they are on drug or placebo
- In 87% of the cases their doctors also guess correctly
- Odds of this occurring randomly: < 1 in 1,000,000
- **Conclusion**: Most patients and most doctors "broke blind"

Antidepressants As Enhanced Placebos

- Expectancy of improvement is a central factor in the placebo effect
- If patients realize they are in the placebo group, their expectancy of improvement declines
- Kirsch coined the term '*response expectancy*' to denote the expectations that are evoked by placebos; this has since become an accepted factor in theories of the placebo effect

(Kirsch, I, Response expectancy as a determinant of experience and behavior, American Psychologist 40 no. 11 (1985):1189-202)

What If Patients Know They Are Receiving Active Drug? "*Comparator Trials*"

- Joel Sneed et al, at Colombia University in New York, compared the response of pts in comparator trials (all patients receive an active drug, and know it) to that of pts in placebo-controlled trials
- **Result:** Pts in the comparator trials were significantly *more likely* to improve
  - 60% of pts responded to AD's in comparator trials
  - 46% of pts improved in the placebo-controlled trials

(Sneed, J, et al, Design makes a difference: a meta-analysis of antidepressant response rates in placebo-controlled versus comparator trials in late-life depression, American Journal of Geriatric Psychiatry 16, no. 1(2008):65-73)

Correlation Between Improvement and Experience of Side-Effects

- Study looked at all the published and unpublished studies that GlaxoSmithKline had conducted on their SSRI, Seroxat.
- Result: Once you adjust for drug-placebo differences in side-effects, differences in rates of improvement are no longer statistically significant.

(Barbui, C, Cipriani A, Kirsch I, Is the paroxetine-placebo efficacy separation mediated by adverse events? A systematic re-examination of randomized double-blind studies, submitted for publication 2009)

What Happens When *Active* Placebos Are Used?

- Active placebos have been compared to AD's in 9 clinical trials.
- Atropine was used as the active placebo (used to treat IBS, diarrhea, peptic ulcers, motion sickness, enuresis, Parkinson's Disease, etc.)
- Side-effects: dry mouth, insomnia, HA's, drowsiness

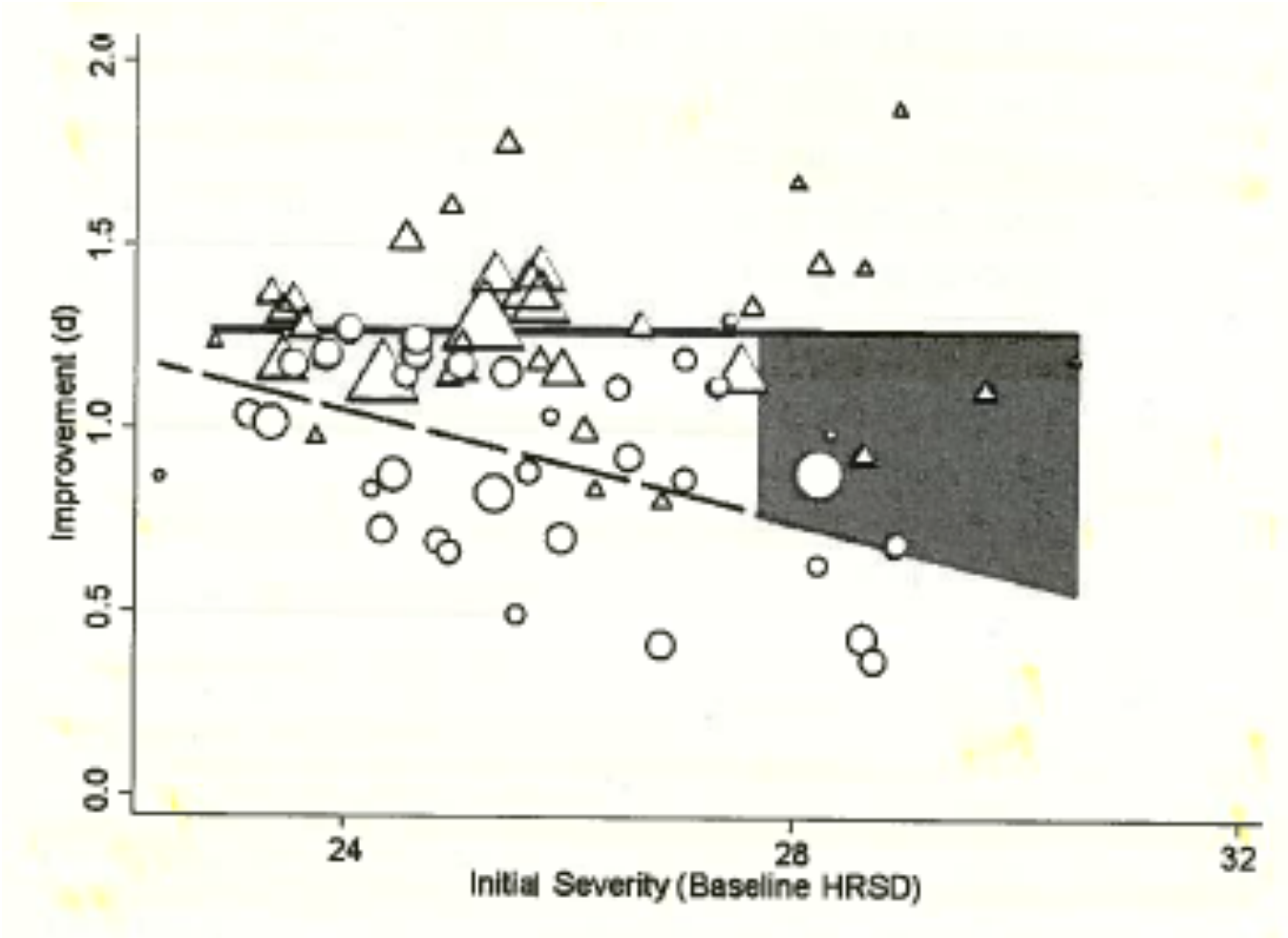
(Moncrieff, J, The creation of the concept of an antidepressant: an historical analysis, Social Science & Medicine 66, no. 11 (2008a): 2346-55)

What Happens When Active Placebos Are Used?

- When an active placebo is used, most clinical trials do not show a significant benefit for AD's
- When an AD was compared to atropine, a significant difference between drug and placebo was found in only 2 of the 9 clinical trials
- **Conclusion:** Studies that use *inactive, inert* placebos are much more likely to enhance the apparent efficacy of drugs over placebo than studies using *active* placebos.

Depression Severity and Antidepressant Efficacy

- Among the ‘very severely depressed’ pts there was a statistically significant difference between drug and placebo, but it was only 2 points on the Ham-D, well below the 3-point criterion for clinical significance.
- The drug effect was small even for severely depressed patients
- Still, there was a relationship between severity and the AD effect



_____ = Average Drug Response

---------- = Average Placebo Response

The difference between them is the drug effect

Depression Severity and Antidepressant Efficacy

Several recent studies have replicated those results, including one published in the Journal of the American Medical Association (JAMA) that culled the results from six antidepressant trials that included mild and moderate cases, totaling 718 participants,. (JAMA. 2010;303(1):47-53)

Results: The magnitude of benefit of antidepressant medication compared with placebo may be minimal or nonexistent, on average, in patients with mild or moderate symptoms. Although the benefits of medication over placebo increased slightly with severity of depression.

"The evidence we now have suggests there is very little benefit [from antidepressants] for people with less than very severe depression."

Study co-leader Robert DeRubeis, PhD, a psychologist at the University of Pennsylvania.

Maybe the AD's Were Under-Dosed?

- Perhaps the drug effect had been underestimated because pts were given too low doses of the AD?
- Comparing the effect of treatment with the lowest dose of the drug to that of treatment with the highest dose:
  - 40 statistical comparisons between specific doses of the same drug; ***there is no relationship*** between how much of an AD people take and how much they improve
  - The avg improvement on HAM-D was 9.97 on highest dose and 9.57 on the lowest dose

Antidepressant Dosing

- Why do doctors increase the dose of AD's when their patients do not improve?
- The official "Summary of Product Characteristics" for Prozac provides a clue:
  - It notes that in the fixed dose studies of pts with MDD, there is a ***flat*** **dose response curve**, indicating no advantage in efficacy when using higher than the recommended dosage.

Antidepressant Dosing

Despite the evidence that higher doses are not more effective, the very same document advises physicians as follows:

“The recommended dose is 20 mg daily. Dosage should be reviewed and adjusted as necessary, within 3-4 weeks of initiation of therapy and thereafter as judged clinically appropriate. Although there may be an increased potential for undesirable effects at higher doses, in some patients, with insufficient response to 20 mg, the dose may be increased gradually up to a maximum of 60 mg. dosage adjustments should be made carefully on an individual patient basis, to maintain the patients at the lowest effective dose.”

Antidepressant Dosing

- A study reported by Otto Benkert and colleagues at the Dept. of Psychiatry at the University of Mainz shows how this works:

  (Benkert, O, et al, Dose escalation vs continued doses of paroxetine and maprotiline: a prospective study in depressed out-patients with inadequate treatment response, Acta Psych Scand 95 (1997);288-96)

- Depressed pts who failed to respond to AD meds were given an increased dose of the drug, following which **72% improved significantly** by showing at least a 50% reduction in depression symptoms
- **The catch:** the dose had only been increased for half the subjects. Yet the response rate was the same 72% in both groups.

“The Dirty Little Secret”

“Many have long been unimpressed by the magnitude of the differences observed between treatments and controls, what some of our colleagues refer to as the ‘dirty little secret’ in the pharmaceutical literature.”

(Hollon, s, et al, The emperor’s new drugs: effect size and moderation effects, Prevention & Treatment 5, Article 27 (2002)

How Was This Secret Kept?

- How is it that even the doctors who prescribe antidepressant did not know how limited their effects were compared to dummy pills?
- Pharmaceutical companies have used a number of devices to make their products look better than they actually are. They have:
  - Withheld negative studies from publication
  - Published positive studies multiple times
  - Published only some of the results from multi-site studies
  - Published data that was different from what they submitted the FDA.
  - Employed “thought leaders”

How Companies Sell Psychiatrists on Their Drugs

Keep Running Studies Until You Get the Results You Want

- Companies are required to furnish at least 2 studies showing the drug is safe and is significantly better than a placebo pill. Companies will conduct several trials ensure they can make magic number of 2.
- Forest pharmaceuticals conducted 5 trials for Celexa to get 2 that beat placebo

  (Turner, e, Matthew AM, et al, "Selective Publication of Antidepressant Trials and its Influence on Apparent Efficacy", New England Journal of Medicine 358 (2008):252-60
- The efficacy of Prozac could not be distinguished from placebo in 6 out of 10 clinical trials

  (Moore, T. J. (1999, October 17). No prescription for happiness. *Boston*)

- Companies are allowed as many tries as they want, since the FDA doesn't count negative trials against them.

How Companies Sell Psychiatrists on Their Drugs

Publication Bias

- Hans Melander and his colleagues at the Medical Products Agency (MPA) in Sweden found that almost all the successful clinical trials had been published, whereas most of the negative trials had not been published.

(Melander, H, et al, Evidence B(I)Ased Medicine – selective reporting from studies sponsored by pharmaceutical industry: review of studies in new drug applications, British Medical Journal 326 (2003):1171-73)

How Companies Sell Psychiatrists on Their Drugs

Publication Bias

- In the 1990's GlaxoSmithKline conducted three clinical trials on the efficacy of paroxetine (Paxil in the US, Seroxat in the UK) in the treatment of major depression in children and adolescents.
  - One study showed mixed results, a second showed no significant differences between drug and placebo, and the third trial suggested that the placebo might actually be more effective than Seroxat for children aged seven to eleven
  - Only one of these trials was ever published. The other two remained hidden
  - According to internal company documents, the company's 'target' was to 'effectively manage the dissemination of these data in order to minimize any potential negative commercial impact'.

"But, But…
Antidepressants Work in Clinical Practice!"

"Antidepressants work in clinical practice – everybody knows they work. Dozens of clinical trials plus decades of clinical practice plus millions of contented patients can't be that wrong. Whatever the bias in whatever the study, common sense clearly says: the sum of the parts attesting antidepressants' efficacy blatantly outnumbers the evidence showing the opposite. The use of these antidepressants is now deeply rooted and well-established in medical society worldwide, it's safe, it works, and there's no shadow of doubt about it."

David Nutt, head of the Psychopharmacology Unit at the University of Bristol

"But, But…
Antidepressants Work in Clinical Practice!"

- The question is not *whether* antidepressant work, but *why* they work. It is because the chemical in the pill specifically targets the pathophysiology of depression, or is it because of the placebo effect?
- We as physicians do not systematically prescribe placebos to our patients. Hence we have no way of comparing the effects of the drugs we prescribe to placebos. When we prescribe a treatment and it works, our natural tendency is to attribute the cure to the treatment.
  - Powdered stone, lizard's blood, crocodile dung, frog's sperm, pig's teeth
  - "Patients have been 'purged, puked, poisoned, punctured, cut, cupped, blistered, bled, leached, heated, frozen, sweated, and shocked'

(Shapiro, AK, A contribution to a history of the placebo effect, Behavioral Science 5, no. 109-35 (1960)

Clinical Practice Versus Clinical Trials

The "Tailoring Hypothesis"

- One difference between clinical trials and clinical practice is that each of the pts in the clinical trials are given only one kind of treatment. But when a patient seen in clinical practice fails to respond to a particular antidepressant, psychiatrists often prescribe a different one.
- The assumption*: **One has to find the right drug for the right patient.***
- Sometimes the second antidepressant works. When it doesn't, a third might be prescribed and then a fourth and a fifth, until one is found that works.
- The implicit logic behind this practice is that different pts suffer from different 'chemical imbalances'.

Clinical Practice Versus Clinical Trials: The STAR*D Trial

The Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial.

(Warden, D., Rush, A., Trivedi, M., Fava, M., & Wisniewski, S. (2007). The STAR*D project results: A comprehensive review of findings *Current Psychiatry Reports, 9* (6), 449-459)

(Trivedi MH, Fava M, et al: Medication augmentatino after the failure of SSRIs for depression, N Engl J Med 354:1243-1252, 2006a)

- Designed to be more representative of what happens in 'real world' clinical practice.
  - A broader range of pts were included than in normal clinical trials
  - There was no placebo control group
  - Pts who did not get better on the first drug were given a different treatment
  - A more stringent clinical response criteria – examined the number of pts who achieved *remission*

Clinical Practice Versus Clinical Trials: The STAR*D Trial

- Using this very strict criterion of remission, the STAR*D researchers reported
  - 37 percent of the pts in the trial recovered from depression on the first medication they were given.
  - Another 19 percent of the full group of pts recovered on the second medication
  - 6 percent on the third, and 5 percent on the fourth
  - Altogether, **67 percent of the pts recovered**
  - However, the remission of symptoms turned out to be only temporary for most – 93 percent of the pts who recovered relapsed within a year.
  - Sort of a bleak picture…

Clinical Practice Versus Clinical Trials: The STAR*D Trial

- Still, the study did seem to show that switching from one antidepressant to another might make a difference.
- But does it?
- To understand the real significance of the STAR*D trial, it is helpful to consider a much older study.

Clinical Practice Versus Clinical Trials: The STAR*D Trial

- In 1957, a team of researchers at the University of Oklahoma School of Medicine gave **ipecac** – a drug used to induce nausea and vomiting - to a group of volunteer subjects.
- After verifying that ipecac did indeed elicit nausea and vomiting in their subjects, the researchers then gave them a treatment to prevent nausea and vomiting, followed by ipecac again.
- As in the STAR*D trial, they repeated this procedure with different medications, in this case switching medications regardless of whether the previous one had worked.
- They did this **seven** times, and on each occasion they measured the success of the treatment at preventing nausea/vomiting.

(Wolf, S., Effects of suggestion and conditioning on the action of chemical agents in human subjects – the pharmacology of placebos, Journal of Clinical Investigation 29 (1950):100-09)

Clinical Practice Versus Clinical Trials: The STAR*D Trial

- The Oklahoma study in fact showed the same pattern of results as the STAR*D trial – that different people respond to different medications, so the key might be finding the right treatment for the right person.
  - More than half of the subjects responded successfully to the first treatment:
  - 17 percent additional subjects responded to the second
  - 20 percent responded to the third
  - By the time the sixth treatment was tried, 100 percent of the subjects had successfully responded to at least one of them.

Clinical Practice Versus Clinical Trials: The STAR*D Trial

- **The Catch**: none of the medication were real treatments for nausea or vomiting. They were *all* placebos.
- So the STAR*D results might have had nothing to do with switching antidepressants - instead, they might have simply been due to the placebo effect, as the Oklahoma study showed

Clinical Practice Versus Clinical Trials: The STAR*D Trial

- Switching non-responsive pts from an SSRI to an **SNRI** led 25% of them to get better.
- Change from an SSRI to **bupropion** produced virtually the same remission rate (26%).
- But what of the pts who were not switched to a different class of antidepressant, but instead were simply given another SSRI?
  - 27% of these pts also got better – a remission rate that is virtually *identical* to that produced by changing to a different type of medication.
  - In other words, **improvement did not depend on the kind of drug to which the pt had been switched**.
    - Simply changing from one SSRI to another was as effective as changing to a completely different type of antidepressant.
  - Once again we have **the strange 'coincidence' of virtually identical effects produced by chemically different drugs.**
  - This suggests that it is not the specific chemical action of the drug that alleviates the person's depression; it may simply be **the idea of changing treatment.**

The Tailoring Hypothesis

- A later meta-analysis found **no difference** between switching to a new drug and staying on the old medication; although 34% of treatment resistant patients responded when switched to the new drug, 40% responded without being switched.

[Bschor, T., & Baethge, C. (2010). No evidence for switching the antidepressant: systematic review and meta-analysis of RCTs of a common therapeutic strategy. Acta Psychiatrica Scandinavica, 121(3), 174-179.]

Combination Antidepressant Therapy

Combination Antidepressant Therapy May Not Improve Odds of Remission Among Chronically Depressed

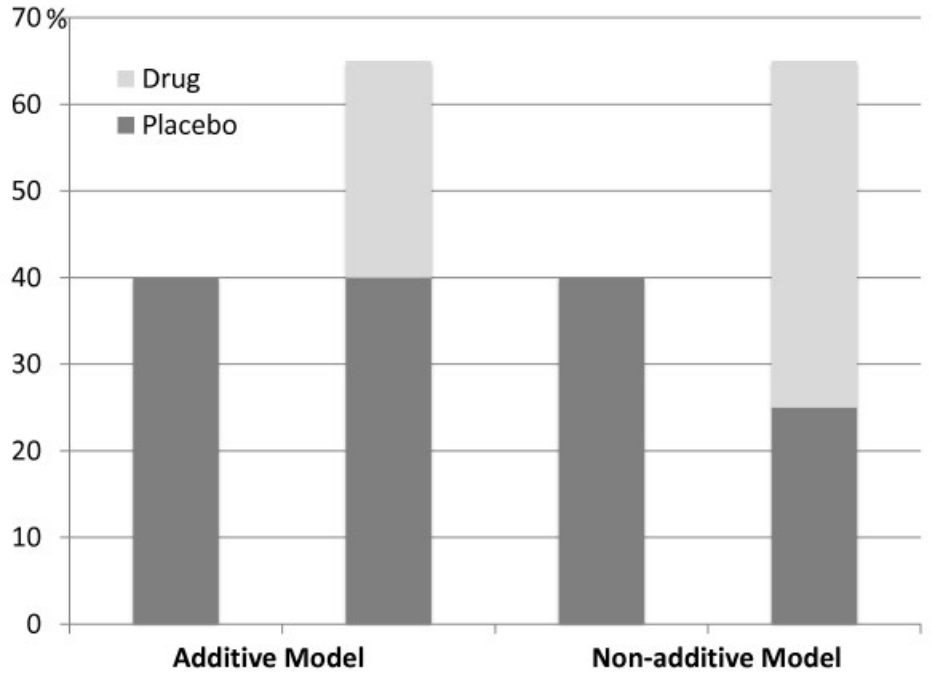
- A combination of two antidepressants may not be any more effective in treating chronic major depression than a single antidepressant, according to an NIMH-funded study published online ahead of print May 2, 2011, in the *American Journal of Psychiatry*.

Rush AJ, e al, Combining medications to enhance depression outcomes (CO-MED): Acute and long-term outcomes: a single-blind randomized study. *Journal of American Psychiatry*. online ahead of print

Drug + Placebo Effect: Additive Like Oil and Water?

- The general assumption in the design of standard placebo-controlled trials is that drug and placebo effects are **additive**, "like oil and water", so that *the total improvement* pts experience = the drug effect + the placebo effect
- However, drug effects and placebo effects may not be additive (i.e., AD's have powerful direct effects and people would get equally better when given them even if they were given the drug without knowing it).
- If they are *not* additive , then the additivity thesis is not valid and we risk false negative results with standard trial design

  - (Dobson, KS, et al, Randomized trial of behavioral activation, cognitive therapy, and antidepressant medication in the prevention of relapse and recurrence in major depression, Journal of Consulting and Clinical Psychology 76, no. 3 (2008):468-77)
  - (Waring DR (December 2008). "The antidepressant debate and the balanced placebo trial design: an ethical analysis". International Journal of Law and Psychiatry 31 (6): 453–462.)



The "additive model" and the "non-additive model" according to Kirsch (2000): All placebo-controlled drug trial are currently based on the assumption that the placebo response in the drug arm of the study is equal to the placebo response in the placebo arm; however, it may be either smaller or greater.

(Klosterhalfen, E, Zipfel, S, Novel study designs to investigate the placebo response, BMC Med Res Methodol. 2011 Jun 10;11:90)

Drug + Placebo Effect: Additive Like Oil and Water?

- Donald Klein and others have criticized the results of studies using FDA data, arguing that the methodological flaws in these studies are responsible for the poor differentiation between antidepressants and placebos.
- Klein points out that when methodologically sound antidepressant trials are analyzed, the benefit of antidepressants over placebos is often clear and substantial

  (Am J Psychiatry. **2000** Mar;157(3):327-37. Validity of clinical trials of antidepressants. **Quitkin** FM, **Rabkin** JG, **Gerald** J, **Davis** JM, **Klein** DF.)

Drug + Placebo Effect: Additive Like Oil and Water?

- A number of studies have tested whether various drug and placebo effects are additive.
- These studies use an experimental method called the '***balanced placebo design***', which makes it possible to assess whether or not drug and placebo effects are additive, or whether the placebo merely masks effects that are really being produced by the drug.

Oil and Water?

		Told They Are Getting Drug	Told They Are Getting Placebo
Actually Get:	**Drug**	**A**	**C**
	Placebo	B	D

Figure 3.1. The Balanced Placebo Experimental Design

Oil and Water?

- The results indicate that some drug effects are additive and some are not.
- The pure drug effect of antidepressants has not been assessed in a balanced placebo study; it is possible that a test of this sort would reveal a larger effect than that shown in typical clinical trials.
- You might think that drug companies would be eager to try a study of this sort. They are not.
  - Studies could show that AD's work independently of the placebo effect
  - Or could confirm that AD's are little more than active placebos

The Good News About Antidepressants

- A recent meta-analysis of 31 placebo-controlled antidepressant trials, mostly limited to studies covering a period of one year, found that 18% of patients who had responded to an antidepressant relapsed while still taking it, compared to 41% whose antidepressant was switched for a placebo.

[Geddes JR, Carney SM, Davies C (February 2003). "Relapse prevention with antidepressant drug treatment in depressive disorders: a systematic review". *Lancet* **361** (9358): 653–61]

Psychiatric vs. “Medical” Drugs

- Meta-analyses of 94 meta-analyses of 48 drugs in 20 medical diseases (e.g., CV disease, HTN, RA, chronic asthma, type 2 DM, Hep C), and 33 meta-analyses of 16 drugs in 8 psychiatric disorders (schizophrenia, bipolar disorder, MDD, OCD, ADHD, DAT)
- Large variability in effect size for medical conditions (an effect size of 0.2 is considered significant but low; 0.8 or greater is high. The median of all effect sizes was 0.40)

- High
  - 1.39 for proton pump inhibitors to treat GERD
  - 2.27 for interferon to treat Chronic Hepatitis C
- Low
  - 0.12 for aspirin for secondary prevention of CV events
  - 0.15 for statins for CV events

(Leucht, S, et al. Putting the efficacy of psychiatric and general medicine medication into perspective: review of meta-analyses. Br J Psychiatry, 2012; 200:97-106)

Psychiatric vs. "Medical" Drugs

"Psychiatric drugs were right in the middle of most of the drugs used in internal medicine."

- AD's used as maintenance treatment to prevent a relapse of MDD had effect size of 0.64
- Antipsychotics used to prevent relapse in schizophrenia had effect size of 0.92.

- Some of the most important outcomes take years to develop, and you can't measure them with double-blind studies that are often only 6-8 weeks long; have to look at other methodologies
  - "Many psychiatric drugs not only improve the acute episode but also prevent further episodes. Patients with severe, recurrent depression might have 20 episodes in their lifetime, which could be reduced by medication to 10."

(Leucht, S, et al. Putting the efficacy of psychiatric and general medicine medication into perspective: review of meta-analyses. Br J Psychiatry, 2012; 200:97-106)

Clinical Use of Antidepressants

- All AD's are effective against depression when administered at therapeutic doses
- The data that supports specific AD choice is based on several factors, including:
  - History of previous treatment response and tolerabilty
  - Family members' history of response
  - Medication side-effect profiles
  - Drug-drug interaction potentials
  - The presence of comorbid disorders that may respond to (or preclude the use of) specific AD's.

Clinical Use of Antidepressants

"We are much further away from understanding the neurobiology of emotions than most patients think. Patients often view psychiatrists as wizards of neurotransmitters, who can choose just the right medication for whatever chemical imbalance is at play. This exaggerated conception of our capabilities has been encouraged by drug companies, by psychiatrists ourselves, and by our patients' understandable hopes for cures."

Dan Carlat, MD, author of The Carlat Letter and "Unhinged"

Antidepressant Medications: Hope or Hype?

Summary

- Contrary to some of the media "hype" on this topic, even critics of antidepressants acknowledge that a genuine difference exists between AD's and placebos; the debate is focused on how large this difference is and the mechanisms responsible for it.

Antidepressant Medications: Hope or Hype?

Bottom Line

- Individuals vary widely in response to specific depression treatments, and the variability is largely unpredictable.
- Future research should focus on identifying true moderator effects – variables that will enable us to develop more personalized medication regimens.
- At this time, our inability to match patients with treatments implies that systematic follow-up assessment and adjustment of treatment are more important than initial treatment selection.
- The data suggests that regardless of initial baseline depression severity, treatment should be the simplest and most tolerable (and affordable) for the patient.

(Simon, G, et al, Personalized Medicine for Depression: Can We Match Patients With Treatments?, Am J Psychiatry 2010; 167:1445-1455)

(Friedman, ES et al., Baseline Depression Severity as a Predictor of Single and Combinatino Treatment Outcome: Results from teh CO-MED. Trial, Eur Neuropsychohparm 22 (3); 183-199, March, 2012)

The Placebo Effect and the Power of Belief

How can this be?

- How is it possible that a dummy pill with no active ingredients can produce substantial improvement in a condition as serious as clinical depression?
- Placebo effects are part of a broader phenomenon – the power of suggestion to change how people feel, how they behave, and even their physiology. If placebos can produce such powerful effects, it is important to understand them.

The Placebo Effect and the Power of Belief

- In 1955 Henry Beecher published an article entitled "The Powerful Placebo", which may be the single most influential paper on the placebo effect ever written

  (Beecher, HK, The powerful placebo, Journal of the American Medical Association 159, no. 17 (1955): 1602-06)

- Beecher claimed that, averaged across 15 studies involving a variety of conditions – including severe post-operative pain, headache, anxiety, seasickness, coughs and colds – about **one out of three patients** given a placebo showed significant improvement, a figure that has come to be enshrined as gospel.

The Placebo Effect and the Power of Belief

- And yet it is a myth.
  - The percentage of pts who respond to a placebo can vary from none at all to almost everyone.
- Placebos are not panaceas. They may be very powerful for some conditions, less effective for others, and have no effect at all on some ailments.
  - E.g.: They have a huge effect on depression, a substantial effect on pain, but have little effect on infertility.

The Placebo Effect and the Power of Belief

- There is not just *one* placebo effect; the placebo effect depends on a host of factors:
  - the condition being treated
  - the way in which the placebo is administered
  - the color of the placebo
  - its price
  - whether it has a recognized brand name
  - the dose that is prescribed
- E.g.: Taking placebo pills four times per day is more effective than taking them only twice per day; placebo injections are more effective than placebo pills; and more expensive placebos are better than cheaper ones.

  (de Craen, et al, Placebo effect in the treatment of duodenal ulcer, British Journal of Clinical Pharmacology 48 (1999): 853-60)

The Power of Belief: Placebo Surgery

- Dr. Bruce Moseley, surgeon at the VA medical Center in Houston, Texas, and physician for the Houston Rockets basketball team
- Routinely performed arthroscopic surgery for osteoarthritis of the knee.
- Two procedures were in use at the time, and there was a debate as to which was better.
  - One procedure involved making small incisions in the knee and rinsing the joint.
  - In the second procedure, the joint was scraped as well as rinsed.
  - Some doctors thought that scraping rough surfaces of the joints made the operation more effective, whereas others suspected that it might cause some damage.

The Power of Belief: Placebo Surgery

- Wray and Moseley designed a clinical trial aimed at comparing real arthroscopic surgery to placebo surgery.
  - They recruited 180 pts for the study
  - One-third of them were given the full rinsing and scraping procedure.
  - For another third of the pts the joint was rinsed but not scraped.
  - The rest were given placebo surgery.
    - Three incisions were made with a scalpel so that there would be scars afterwards. Then the surgeon asked for all instruments an manipulated the knee as if arthroscopy were being performed. Saline was splashed to simulate the sounds of lavage.

(Wray, NP, Moseley, B, O'Malley, K, Arthroscopic surgery for osteoarthritis of the knee (Letter), New England Journal of Medicine 234 (2002): 1718-19)

The Power of Belief: Placebo Surgery

- The placebo operation was significantly ***more effective than the actual surgery***
  - **Two weeks** after their operation, pts in the placebo group reported significantly less pain than those in either of the surgery groups, and they also showed more improvement on an objective test of walking and climbing stairs.
  - **One year** after the operation, pts in the placebo group still walked and climbed stair *significantly better* than those whose knee joints had been both rinsed and scraped
  - **Two years** after the surgery there were *no significant differences* between the groups.
  - **In the long run**, rinsing the knee joint did no good at all – and – as Moseley had expected – scraping it actually caused damage lasting at least a year.

The Power of Belief: Placebo Surgery

- **Parallels** between Mosely and Wray's study of arthroscopic surgery and the meta-analyses that Kirsch and his colleagues reported for antidepressants:
  - The failure to find substantial differences between real and placebo treatment was not because of a lack of response to the treatment.
    - Patients given real surgery in Moseley and Wray's study reported having much less pain than they had before treatment, just as pts given antidepressants report being less depressed.
  - But in both cases, patients also showed substantial improvement after placebo treatment.

Mind and Brain

- Placebo effects are not ‘all in the mind’.
- Placebos affect *physiology* as well as psychology.

How Placebos Work: The Psychobiological Mechanisms

1. **The involvement of endogenous opioids in placebo analgesia**
   - The expectation of pain relief activates *μ*-opioid receptor signaling in the human brain

     (Zubieta J. K., Bueller J. A., Jackson L. R., Scott D. J., Xu Y., Koeppe R. A., Nichols T. E., Stohler C. S. 2005 Placebo effects mediated by endogenous opioid activity on mu-opioid receptors. *J. Neurosci.* **25**, 7754–7762)
   - The placebo response in patients with post-operative pain can be blocked with the opiate antagonist naloxone

     (Levine J. D., Gordon N. C., Fields H. L. 1978 The mechanism of placebo analgesia. *Lancet* **2**, 654–657.)

How Placebos Work: The Psychobiological Mechanisms

2. Expectation and Classical Conditioning

- There is compelling evidence for the validity of classical conditioning theory for explaining placebo effects, because drug-like effects also occur when active treatments administered repetitively are replaced with pharmacological inert interventions such as saline solutions or sugar pills

[Vits S., Cesko E., Enck P., Hillen U., Schadendorf D., Schedlowski M. 2011 Behavioral conditioning as the mediator of placebo responses in the immune system. *Phil. Trans. R. Soc. B* **366**, 1799–1807)

(Colloca L., Miller F. G. 2011 How placebo responses are formed: a learning perspective. *Phil. Trans. R. Soc. B* **366**, 1859–1869)

(Colloca L., Miller F. G. 2011 Harnessing the placebo effect: the need for translational research. *Phil. Trans. R. Soc. B* **366**, 1922–1930)

How Placebos Work: The Psychobiological Mechanisms

3. Additional factors:

- Motivation
- Emotions
- Characteristics of the healing ritual itself
- Personality factors (novelty seeking and reward responsiveness, altruism, optimism, empathy, and spirituality all positively modulate placebo response)
- There is also some experimental evidence of different genetic variants in placebo responsiveness

There is not one common mechanism that subserves all types of placebo responses

How Placebos Work: The Psychobiological Mechanisms

- A team led by Helen Mayberg, a neurologist at Emory University ad the University of Toronto, have used PET scanning to study changes in brain activity associated with the experience of depression
- **Study 1:** the researchers identified the areas of the bran that are associated with *normal sadness*.
  - They asked volunteer subjects to think about some very sad personal experiences – and about some emotionally neutral experiences – while their brains were being imaged in a PET scanner.
- When thinking about the sad experiences, the volunteers demonstrated **increased blood flow in the limbic system, and decreased blood flow in parts of the brain that are involved in the control of attention.**

(Mayberg, H, et al, Regional metabolic effects of fluoxetine in major depression: serial changes and relationship to clinical response, Biological Psychiatry 48 (2000): 830-43)

How Placebos Work: The Psychobiological Mechanisms

Study 2: Mayberg and group scanned the brains of depressed patients involved in a clinical trial of Prozac. The patients were scanned twice, once before the treatment had begun and once again after six weeks of treatment.

- About half of the patients responded positively to the treatment by showing at least a 50 percent reduction in their symptoms; the other half did not improve as much and were classified as non-responders.
- Successful treatment *decreased* brain activity in areas where sadness produces increased activity, and it increased brain activity in areas where sadness decreases it.
- **Just as expected** – Prozac reversed the metabolic changes observed in brain regions associated with clinical depression.

How Placebos Work: The Psychobiological Mechanisms

- This appeared to be evidence for a specific neurophysiological effect of Prozac on depression.
- **The catch:** *only half of the successfully treated patients had been given Prozac*.
- The rest had recovered on a placebo, and the changes in brain activity that the researchers had found were 'independent of whether the substance administered was active fluoxetine or placebo.'
- In other words: **when placebos were successful in lowering depression, they produced changes in brain activity that mirrored the changes produced by real drugs.**

How Placebos Work: The Psychobiological Mechanisms

- The physiological changes are exactly what would be expected of *any* effective treatment for depression, no matter how the treatment works. They are changes in patterns of brain activity that correspond to sadness and depression.
- When depression is overcome, these changes in brain activation are reversed, no matter how the improvement in depression is brought about, whether by drugs, placebos or some other form of treatment - like psychotherapy, which is a learning experience, and learning changes the brain.

(Blakemore, SJ, Frith, U, The learning brain: lessons for education, Malden, MA: Blackwell Publishing, 2005)

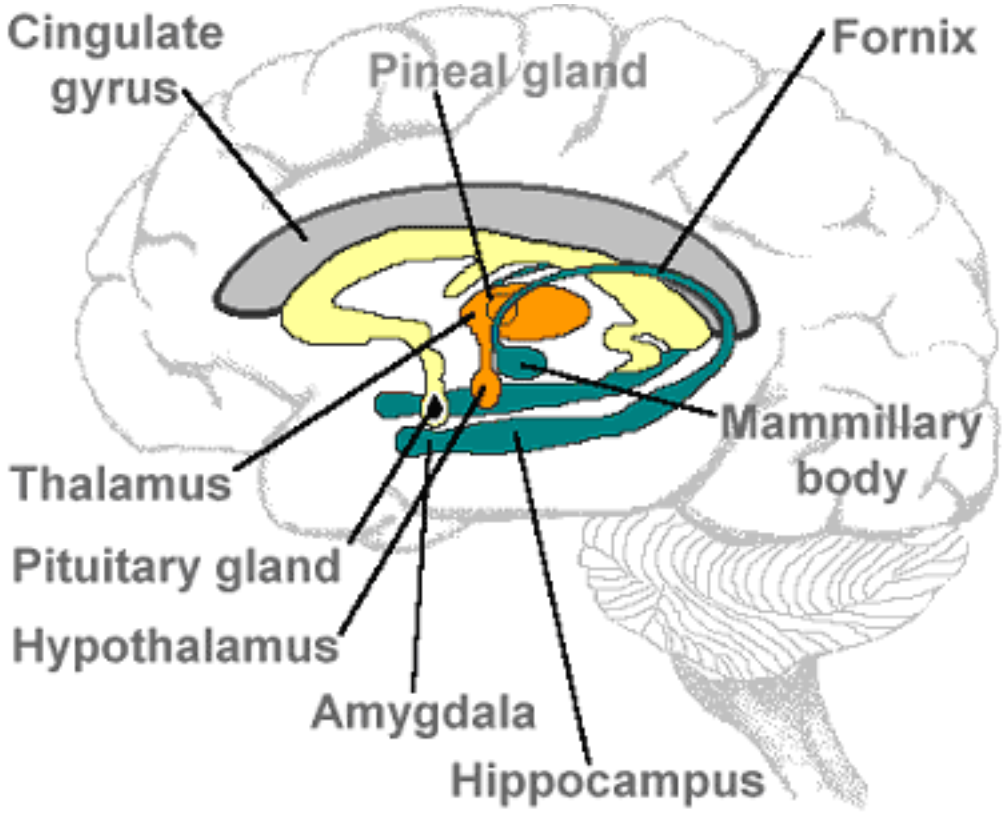
How Placebos Work: Pain vs. Misery

The experience of pain can be divided into sensory and affective aspects, corresponding to the (physical) *sensory* intensity and the (emotional) *unpleasantness* of pain.

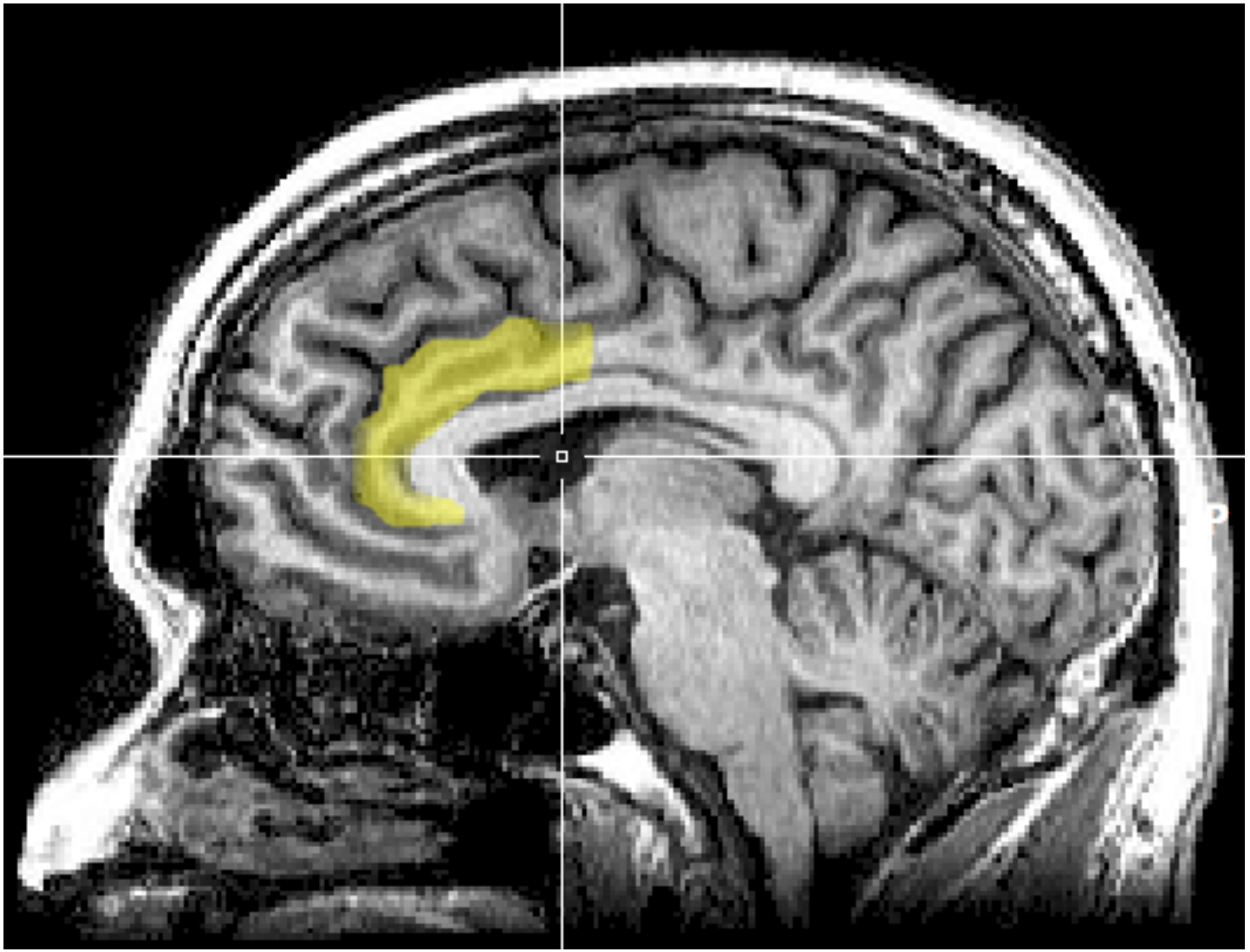
(Melzack and Casey, 1968; Price, 2000).

Neuroimaging work has recently suggested that these two aspects of pain are neurally dissociable as well. Whereas the sensory aspects of pain, including its intensity and location, are represented primarily in somatosensory cortex and the insula, the 'misery' of pain is represented in the amygdala and ACG.

(Peyron et al, 1999; Coghill et al, 1999), pain unpleasantness is represented in the dorsal anterior cingulate (dACC) (Peyron et al, 2000; Rainville et al, 1997; Tolle et al, 1999).



The **anterior cingulate cortex** (ACC) is the frontal part of the cingulate gyrus. It appears to play a role in regulating BP and HR, as well as rational cognitive functions such as reward anticipation, pleasure/pain, decision-making, empathy, and emotion.



How Placebos Work: Pain vs. Misery

Patients who have had their anterior cingulate surgically removed report that they are still able to feel the intensity of pain, *but are no longer bothered by it*.

(Foltz and Lowell, 1962).

In contrast, a patient who had his somatosensory cortex removed could still report pain distress despite difficulties in reporting on *sensory aspects of the pain*.

(Ploner et al, 1999).

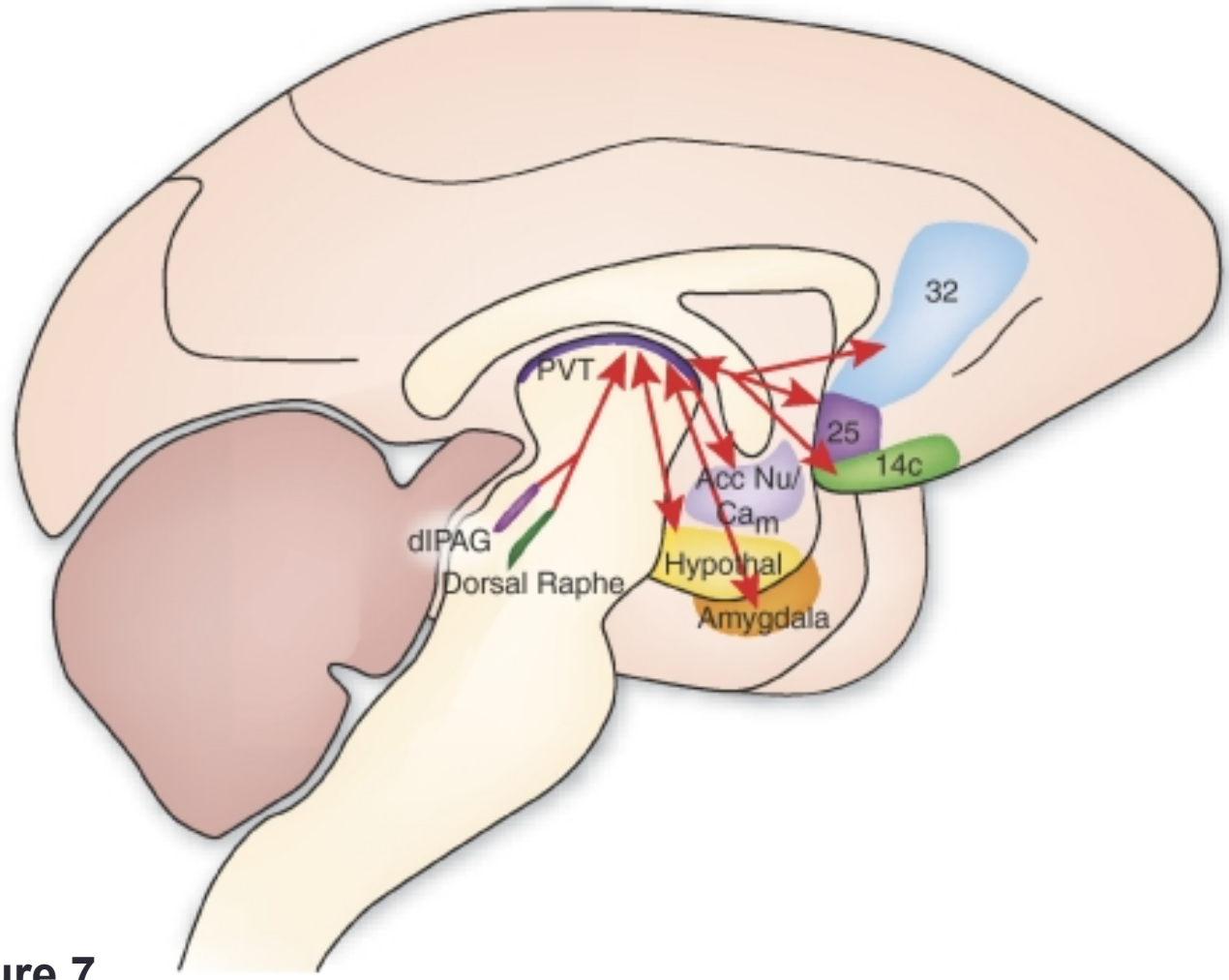


Figure 7

Neuropsychopharmacology. 2010 January; 35(1): 192–216.

Diagram of connections between the dorsal midline paraventricular nucleus of the thalamus (PVT) with areas of the frontal cortex, striatum, hypothalamus, amygdala, and dorsal midbrain.

How Placebos Work: Pain vs. Misery

Hypothesis: That changes in the Dorsal Anterior Cingulate Cortex (dACC) represent one possible end result of a placebo's (neuro-cognitive) effects on pain analgesia.

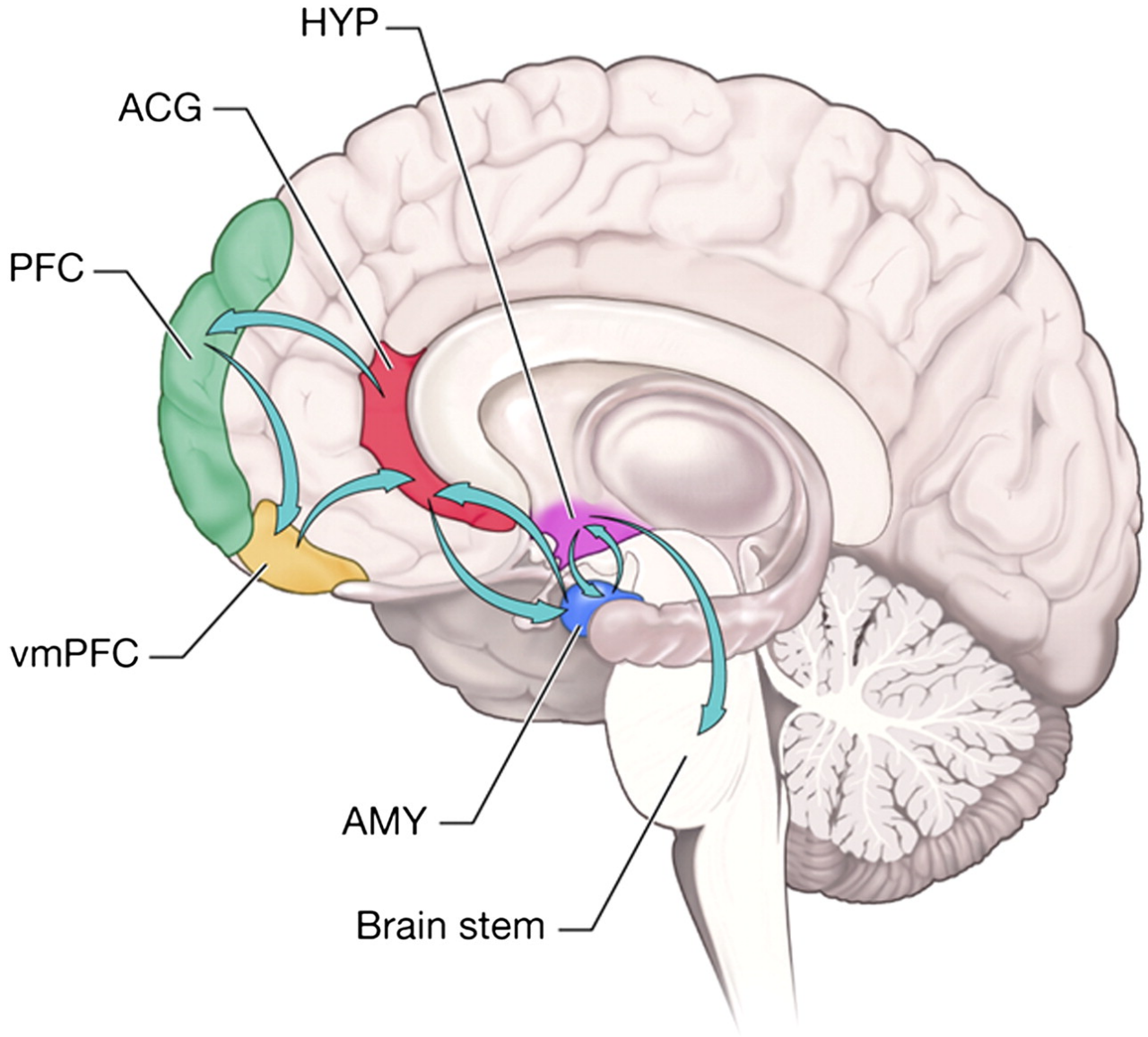
Study: Petrovic et al compared placebo-induced analgesia to opioid-induced analgesia, and found that whereas **both** placebos and opioids led to similar changes in the anterior cingulate gyrus and brainstem, **only the placebo led to increased activity in right pre-frontal cortex (PFC).**

(Petrovic et al, 2002. Pain-related cerebral activation is altered by a distracting cognitive task. Pain 85, 19-30)

How Placebos Work: Pain vs. Misery

These results are consistent with "**Disruption Theory**", which proposes that activation of PFC regions associated with thinking about negative affect can dampen dACC and amygdala reactivity and reduce pain perception.

(Lieberman, MD., 2003. Reflective and reflexive judgment processes: a social cognitive neuroscience approach. In: Forgas, JP, Williams, KR, et al, Social Judgments: Explicit and Implicit Processes. Cambridge Univ. Press, New York pp. 44-67)


HYP
ACG
PFC
vmPFC
AMY
Brain stem

How Placebos Work: Pain vs. Misery

- **Conclusion:** Placebos may operate, in part, by converting placebo-related thoughts, beliefs, and expectations - such as thoughts about the expected reduction in pain unpleasantness - into increased activation in the right ventrolateral pre-frontal cortex (RVLPFC), which in turn reduces activation in the amygdala and anterior cingulate, where the pain is 'felt'.
- This may be the mechanism by which placebo-related beliefs and expectations produce the neural, behavioral, and experiential effects that have fascinated humans throughout time.
- Such a process would be consistent with the role of 'response expectancy' in placebo effects

How Placebos Work: Pain vs. Misery

A study using PET imaging to assess the brain response of patients with IBS to induced intestinal discomfort (using rectal balloon inflations), both before and after a 3-week placebo regimen. Increases in right ventrolateral prefrontal cortex (RVLPFC) activity from pre- to post-placebo predicted symptom improvement, and this relationship was mediated by changes in dorsal anterior cingulate (dACC), typically associated with pain unpleasantness.

This is one of the first studies to identify a neural pathway from a region of the brain associated with placebos and affective thought to a region closely linked to the placebo-related outcome of diminished pain unpleasantness.

(Lieberman, M et al, The neural correlates of placebo effects: a disruption account; NeuroImage 22 (2004);447-455)

How Placebos Work: Pain vs. Misery

The Role of the Frontal Lobe in Placebo Response

- Benedetti *et al* (2006b) studied the placebo response to pain in Alzheimer patients at the initial stage of the disease and after 1 year to see whether the placebo component of the therapy was affected by the disease.
- In this study, the placebo component of the analgesic therapy was correlated with both cognitive status, as assessed using Frontal Assessment Battery (FAB) test, and functional connectivity among different brain regions, as assessed using EEG data.
- **Result:** Alzheimer's patients with reduced FAB scores showed a reduced placebo response.

(Benedetti F, Arduino C, Costa S, Vighetti S, Tarenzi L, Rainero I *et al* (2006b). Loss of expectation-related mechanisms in Alzheimer's disease makes analgesic therapiesless effective. *Pain* **121**: 133–144)

How Placebos Work: Anxiety

Study: On the first day of the experiment, subjects were treated with either the benzodiazepine Versed (midazolam), or the benzodiazepine receptor antagonist, flumazenil, before the presentation of pictures that induced unpleasantness.

- As expected, whereas midazolam reduced the unpleasantness, flumazenil reversed this effect. Therefore, on the first day strong expectations of the treatment effect were induced.
- On the second day, the subjects were told that they would be treated either with the same antianxiety drug or the anxiolytic blocker as the previous day. However, instead of receiving the real medication, they received a placebo.

How Placebos Work: Anxiety

- A robust placebo response (reduced unpleasantness) was found when the subjects *thought* that they had been treated with the anxiolytic drug, whereas no response occurred if they thought they had received the benzodiazepine receptor blocker flumazenil.
- In these placebo responders fMRI showed that regional blood flow changed in both the anterior cingulate cortex and lateral orbitofrontal cortex, which are the very same areas also involved in placebo analgesia.

(Petrovic *et al*, 2002; Wager *et al*, 2004). This suggests that similar mechanisms might be at work in the placebo response of emotional stimuli and in placebo analgesia)

Petrovic P, Dietrich T, Fransson P, Andersson J, Carlsson K (2005). Placebo in emotional processing–induced expectations of anxiety relief activate a generalized modulatory network. *Neuron* **46**: 957–969.

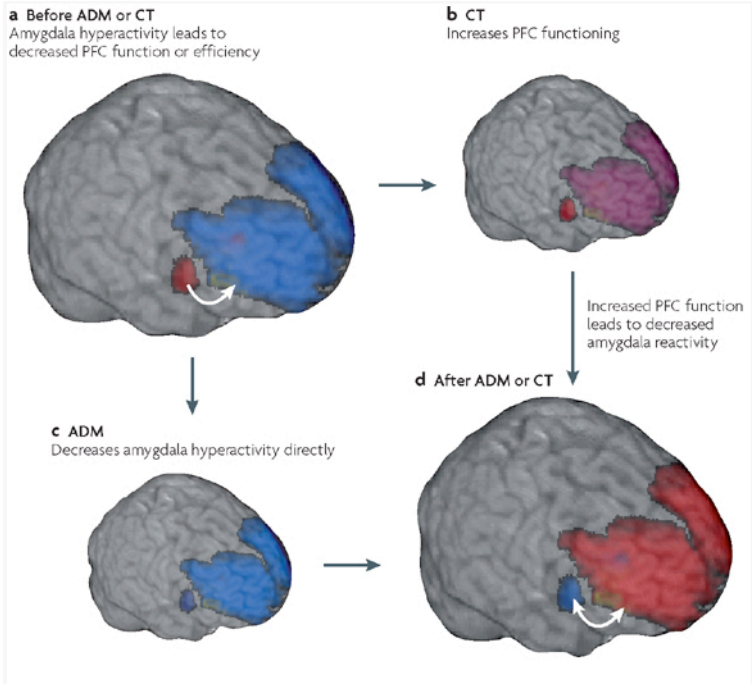
Med/Placebo Therapeutic Effects

- It has been suggested that successful treatment of depression is related to bottom-up actions of antidepressants and top-down activity of the placebo

(Mayberg, HS, et al, Regional metabolic effects of fluoxetine in major depression: serial changes and relationship to clinical response. Biol Psychiatry, 2000. 48(8):830-43)

Meds/Placebo Therapeutic Effects

- In clinical treatment, *top-down treatments* such as CBT and DBT, in conjunction with antidepressant treatments, may act to shorten the lag time for drug effect by initiating the top-down cortical control of maladaptive self-defeating cognitive and affective styles inherent to MDD.



a | During acute depression, amygdala activity is increased (red) and prefrontal activity is decreased (blue) relative to activity in these regions in healthy individuals. b | Cognitive therapy (CT) effectively exercises the prefrontal cortex (PFC), yielding increased inhibitory function of this region. c | Antidepressant medication (ADM) targets amygdala function more directly, decreasing its activity. d | After ADM or CT, amygdala function is decreased and prefrontal function is increased. The double-headed arrow between the amygdala and the PFC represents the bidirectional homeostatic influences that are believed to operate in healthy individuals.

(*DeRubeis, R, et al,* Cognitive therapy versus medication for depression: treatment outcomes and neural mechanisms, *Nature Reviews Neuroscience* 9, 788-796, October 2008)

Med/Placebo Therapeutic Effects

- By employing neuroimaging techniques, it may be possible to better evaluate the pharmacological and therapeutic potential of lead compounds by removal of subjects with this functional profile of the placebo effect.
- E.g., responders to 6-week fluoxetine or placebo both demonstrated metabolic increases in several cortical regions (e.g., PFC and parietal cortex) with concomitant decreases in the subcortical regions (e.g. parahippocampus and thalamus).
- In addition, the fluoxetine-treated groups had metabolic alternations in multiple subcortical regions (e.g. brainstem, striatum, hippocampus).

(Lidstone SC and Stoessl, AJ, Understanding the placebo effect: contributions from neuroimaging. Molec Imaging Biol, 2007. 9(4):176-85)

(Maybert, HS, et al, The functional neuroanatomy of the placebo effect. Am J Psychiatry, 2002. 159(5):728-37)

Beyond Antidepressants:

- There are alternatives to the prescription of either antidepressant drugs or placebos.
- These alternative treatments mobilize the placebo effect, and some of them may do much more than this, but they carry neither the side-effect risks of active drugs nor the ethical risks of deception.

Psychotherapy

- The results of clinical trials, meta-analyses, and reviews point to one inescapable conclusion: Psychotherapy works for the treatment of depression, and the benefits are substantial.
- In head-to-head comparisons, in which the short-term effects of psychotherapy and antidepressants are pitted against each other, psychotherapy works as well as medication.
  - This is true regardless of how depressed the person is to begin with.
- It works for people who are moderately depressed, those who are severely depressed, and even for patients who are very severely depressed.

Psychotherapy

- Psychotherapy looks even better when its long-term effectiveness is assessed.
  - Formerly depressed patients are far more likely to relapse and become depressed again after treatment with antidepressants than they are after psychotherapy.
- The more time that has passed since the end of treatment, the larger the difference between drugs and psychotherapy.
- This long-term advantage of psychotherapy over medication is independent of the severity of the depression – it outperforms antidepressants for severely depressed patients as much as it does for those who are mildly or moderately depressed

(Imel, Zac, et al, "A meta-analysis of psychotherapy and medication in unipolar depression and dysthymia, Journal of Affective Disorders 110 (2008):197-206)

Psychotherapy

- For the most part, the differences in effectiveness of the different types of psychotherapies are not very large
- People who are depressed might well make a choice about which to seek on the basis of *how much sense the treatment makes to them.*
- A third advantage is that pharmacotherapy is associated with people are less likely to drop out of psychotherapy prematurely than they are to stop taking antidepressants.

Psychotherapy

- The most impressive demonstration of the long-term benefits of psychotherapy comes from a study conducted by a group of Italian researchers led by Giovanni Fava at the University of Bologna.
- Over a six-year period, they followed patients who had been successfully treated with antidepressants and then gradually taken off them.
- Half of the patients were given ten half-hour sessions of CBT. The others were also seen by the psychiatrist for ten half-hour sessions, but they were not given the actual therapy during these session. Instead, they received 'clinical management'.

(Fava, G, et al, "Six-year outcome of cognitive behavioral therapy for prevention of recurrent depression', American Journal of Psychiatry 161 (2004): 1872-76)

Psychotherapy

- The results were dramatic: six years after the ten-session treatment, 60 percent of the patients who had been given CBT were symptom-free, compared to only 10 percent of those who had only received clinical management.
- If both drugs and psychotherapy alleviate depression, maybe the combination of the two would work even better?
  - There does, in fact, seem to be an advantage in combining antidepressants with psychotherapy, even in the short-run, but the extra benefit of combining both treatments seems to be relatively small, and there is a catch:
  - Combining psychotherapy and medication is better than just taking antidepressants, but it may not be better than psychotherapy without drugs

(Friedman et al, "Combined psychotherapy and pharmacotherapy for the treatment of major depressive disorder, Clinical Psychology: Science and Practice 11, no. 1 (2004): 47-68)

Psychotherapy

- Combined treatment was no more successful than psychotherapy alone, but did offer a modest advantage over pharmacotherapy alone. Pharmacotherapy was associated with significantly more treatment failures and higher dropout rates than psychotherapy alone or combined therapy.
- On the basis of cost-effectiveness and side-effect considerations, the authors conclude that psychotherapy alone should usually be the initial treatment.

(Wexler BE, Chicchetti DV: The outpatient treatment of depression: implications of outcome research for clinical practice. Journal of Nervous and Mental Disease 1992; 180(5):277–286)

Psychotherapy

- Pharmacotherapy and psychotherapy are generally effective treatments for major depressive disorder (MDD); however, research suggests that patient preferences may influence outcomes. We examined the effects of treatment preference on attrition, therapeutic alliance, and change in depressive severity in a longitudinal randomized clinical trial comparing pharmacotherapy and psychotherapy.
- Prior to randomization, 106 individuals with MDD reported whether they preferred psychotherapy, antidepressant medication, or had no preference. A mismatch between preferred and actual treatment was associated with greater likelihood of attrition, fewer expected visits attended, and a less positive working alliance at session
- 2. There was a significant indirect effect of preference match on depression outcomes, primarily via effects of attendance.
- These findings highlight the importance of addressing patient preferences, particularly in regard to patient engagement, in the treatment of MDD.

(Kwan, B et al, Treatment Preference, Engagement, and Clinical Improvement in Pharmacotherapy versus Psychotherapy for Depression, Behav Res Ther. 2010, August; 48(8):799-804)

Psychotherapy

- There has also been a great deal of study about whether antidepressants ‘fix’ the underlying causes of depression.
- A 2002 review concluded that there was no evidence that antidepressants reduce the risk of recurrence of depression when their use is terminated.
- The authors of this review advocated that antidepressants be combined with therapy, and pointed to Interpersonal Psychotherapy (IPT) and Cognitive Behavioral Therapy (CBT).

(Hollon SD, Thase ME, Markowitz JC. “Treatment and prevention of depression”, Psychological Science in the Public Interest, 2002; 3:1-39)

NIMH Treatment of Depression Collaborative Research Program

- During the 1980's the National Institute for Mental Health (NIMH) in the US sponsored a massive, multi-centered research program to evaluate the effectiveness of antidepressants and psychotherapy in the treatment of depression.
- Before beginning treatment, each patient was asked the following question: "What is likely to happen as a result of your treatment?"
- Patients' answers to this question predicted their therapeutic outcome.
  - Furthermore, the effect of expectancy on treatment outcome was independent of which treatment they had been given.
  - Regardless of whether they had been treated with antidepressant medication, psychotherapy, or a placebo, patients who *expected* to get better showed the most improvement.

NIMH Treatment of Depression Collaborative Research Program

To maximize therapeutic outcome, it is best to:

- Convince depressed patients that the treatment they are being offered – whatever it is – is effective and that it offers them hope for what they may until then have considered a hopeless situation.
- Change negative expectations at the outset, or treatment is not likely to be very effective.

NIMH Treatment of Depression Collaborative Research Program

To maximize therapeutic outcome, it is best to:

- Be confident in the effectiveness of treatment
- To expect substantial change
- Expect that change to occur gradually. The changes are likely to be subtle at first, and to increase over time.
- Understand that change is not automatic; one has to *work* to bring it about.
- Monitor and nurture the therapeutic relationship. A caring therapeutic relationship enhances the patient's confidence, and in so doing fosters positive expectations.

Harnessing the Placebo Effect in Clinical Practice

To maximize therapeutic outcome, it is best to:

- Aim for remission and recovery as the goal, not just improvement
- Educate patients about the benefits of ongoing, long-term treatment rather than episodic or incomplete interventions. These are chronic/ recurrent illnesses.
- Utilize a bio-psychotherapy-social treatment model that incorporates cognitive-behavioral or interpersonal therapy along with pharmacological interventions that serve to address both the initiation and maintenance factors, and can reduce risk of relapse.
- Once remission is attained, *maintenance of gains* may become the more appropriate term, rather than relapse prevention, to emphasize the necessity for an *ongoing collaboration* between patient and clinician in order to maintain neurobiological homeostasis.

Mindfulness Practices

- Mindfulness is a process whereby one is aware and receptive to present moment experiences.
- Mindfulness-enhancing interventions reduce negative affect, stress, mood disturbances, and disease-specific healthy symptoms across many patient populations.

(Baer RA. Mindfulness training as a clinical intervention: a conceptual and empirical review. Clin Psychol Sci Prac 2003; 10:125-43)

Mindfulness Practices

- "The skillful use of labeling during satipatthana (mindful) contemplation can help strengthen clear recognition and understanding. At the same time, labeling introduces a healthy degree of inner detachment, since the act of apostrophizing one's moods and emotions diminishes one's identification with them."
- "Labeling one's emotions through words promotes more effective recognition of, detachment from, and regulation of affective experiences."

(Alalayo, Bhikkhy, from Satipatthana: The Direct Path to Realization. Birmingham, UK: Windhorse Publications, 2003)

Mindfulness Practices

- **Study:** The labeling subscale in one self-report mindfulness measure was associated with higher life satisfaction *and improved emotional regulation* (Sample item: "I'm good at finding the words to describe my feelings.")

(Baer RA, Smith GT, Allen KB. Assessment of mindfulness by self-report: the Kentucky inventory of mindfulness skills. Assessment 2004; 11:191-206)

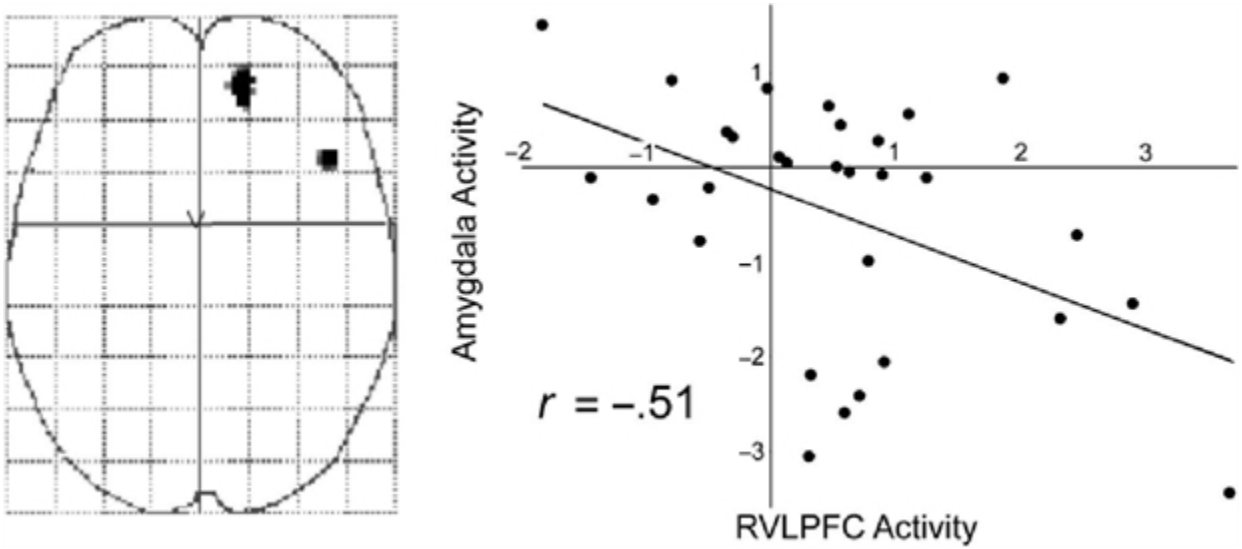
Mindfulness Practices

- *Putting feelings into words* (affect labeling) has long been thought to help manage negative emotional experiences; however, the mechanisms by which affect labeling produces this benefit remain largely unknown.
- Recent neuroimaging studies suggest a possible neurocognitive pathway for this process

Mindfulness Practices

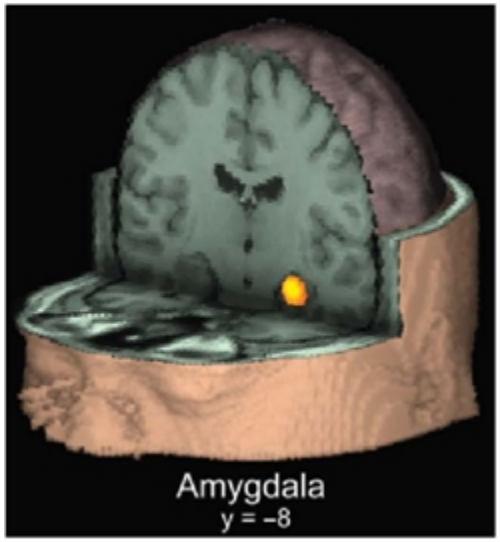
- **Study:** Participants with trait levels of mindfulness completed an affect labeling task while undergoing fMRI.
- **Result:** Dispositional mindfulness was associated with greater widespread PFC activation, and reduced bilateral amygdala activity during affect labeling, compared with the gender labeling control task. Further, strong negative associations were found between areas of PFC and right amygdala responses in participants high in mindfulness but not in participants low in mindfulness.

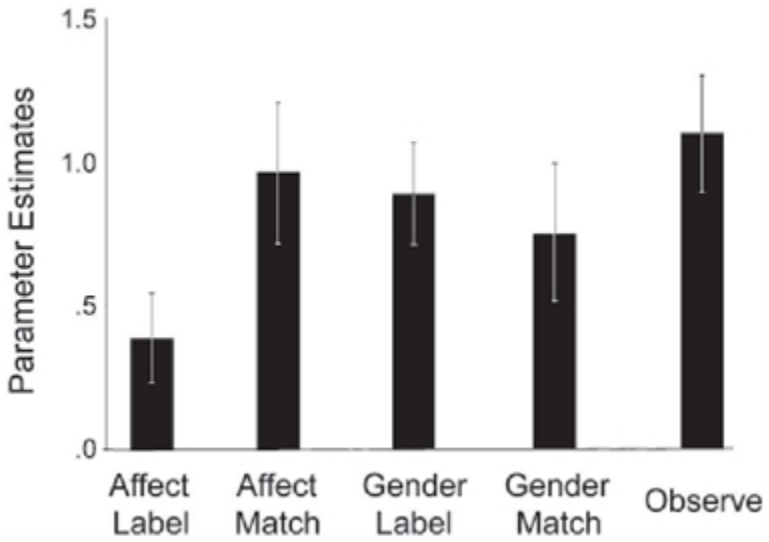
(Putting Feelings Into Words: Affect Labeling Disrupts Amygdala Activity in Response to Affective Stimuli. (Psychological Science (Wiley-Blackwell), May2007, Vol. 18 Issue 5, p421-428)



Putting Feelings Into Words: Affect Labeling Disrupts Amygdala Activity in Response to Affective Stimuli.

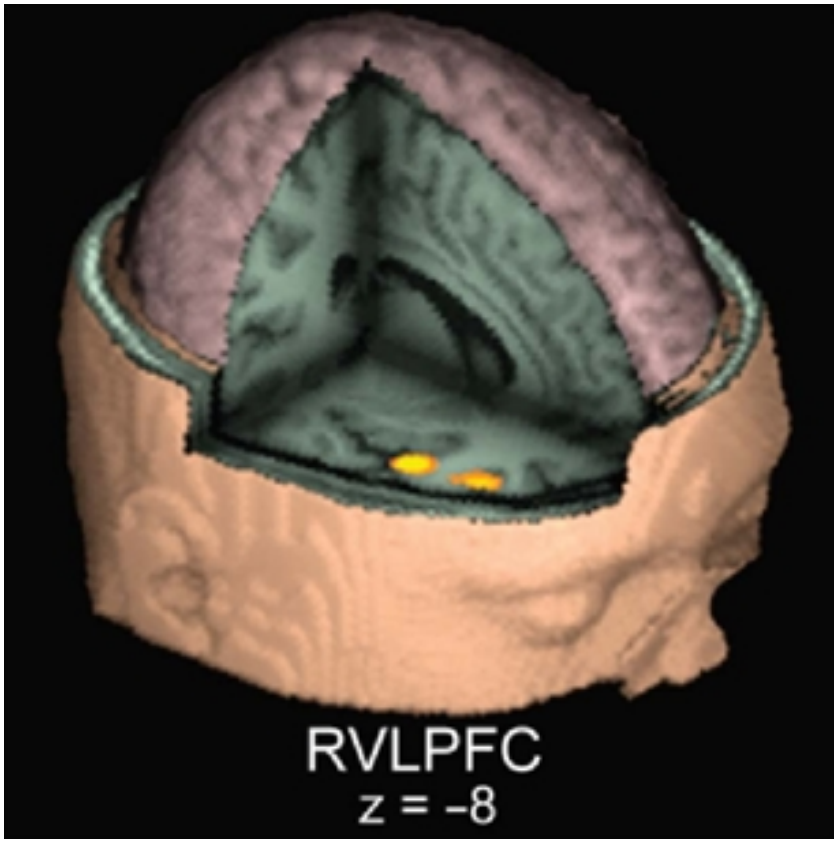
Psychological Science (Wiley-Blackwell), May2007, Vol. 18 Issue 5, p421-428, 8p, 1 Color Photograph, 1 Diagram, 1 Chart, 2 Graphs; Graph found on p. 426





Labeling one's feelings (putting feelings into words) diminishes the response of the amygdala and other limbic regions to negative emotional images, thus diminishing emotional reactivity.

(Putting Feelings Into Words: Affect Labeling Disrupts Amygdala Activity in Response to Affective Stimuli. (Psychological Science (Wiley-Blackwell), May2007, Vol. 18 Issue 5, p421-428, 8p, 1 Color Photograph, 1 Diagram, 1 Chart, 2 Graphs, Graph; found on p. 426)



It appears to do so by increasing activity in a single brain region, the right ventrolateral prefrontal cortex (RVLPFC). Illustration is of a brain showing two clusters in right ventrolateral prefrontal cortex where activity was greater during affect labeling than during gender labeling.

(Putting Feelings Into Words: Affect Labeling Disrupts Amygdala Activity in Response to Affective Stimuli. Psychological Science (Wiley-Blackwell), May2007, Vol. 18 Issue 5, p421-428, 8p, 1 Color Photograph, 1 Diagram, 1 Chart, 2 Graphs, Graph found on p426)

Mindfulness Practices

- **Conclusions:** One potential mechanism for how mindfulness meditation interventions reduce negative affect and improve health outcomes: the process of verbally labeling emotions activates right ventrolateral PFC, attenuating 'automatic' responses in the amygdala, and thus reducing the intensity and duration of reactive emotional responses.
- Labeling one's feelings reduces negative emotions and promotes improved physical and mental health.

(Creswell, JD, Way, BM, et al, "Neural Correlates of Dispositional Mindfulness During Affect Labeling", Psychosomatic Medicine 69:560-565 (2007)

Mindfulness Practices

- Specific reductions in MDD symptoms as a result of mindfulness practices have been associated with regional improvements in brain metabolic activity.

- **Study:** In 39 outpatients with MDD, improvement in cognitive symptoms was correlated with increases in DLPFC, and improvements in fatigue/psychomotor retardation was associated with decreases in VMPFC activity.
- Interestingly, these changes were seen in responders regardless of whether treatment was pharmacological or psychological.
- These results suggest that affect labeling may diminish emotional reactivity along a pathway from RVLPFC to MPFC to the amygdala.

(Brody AL, et al. Brain metabolic changes associated with symptom factor improvement in major depressive disorder. *Biol Psychiatry.* 2001;50:171–8)

Mindfulness Practices

- **In Other Words**: Reflective, conscious processes marked by *intentionality, effort, and awareness* can turn off or mute negative affect states, using the same neurobiological pathways that beliefs/assumptions trigger via the placebo response, and which make medication, CBT, and DBT effective.

“Integrative” Mental Health Care

“A dramatic social shift in the US: the adoption by a large proportion of the population of so-called complementary, alternative, and integrative methods of health care. These changes have little to do with high-tech advances that make headlines, such as decoding of the human genome, DNA manipulation, new drugs, stem cells, etc., but instead with a fundamentally different approach to human health…
(and) some of these therapies may actually *work*.”

James Lake, MD

“Integrative” Mental Health Care

“Conventional medical treatment takes place in a directive relationship in which the patient follows medical advice. The collaborative relationship in which healing takes place emerges in the context of the intentions and attitudes of the patient and the skill, intuition, and compassion of the medical practitioner.”

“Ideally, in integrative health care, *an optimal healing environment* is created within which the patient’s psychological, biological, mind-body, and spiritual issues are effectively addressed in the context of an open and supportive relationship.”

(Jonas, W.B. & Chez, R.A., 2004. Toward Optimal Healing Environments in Health Care. The Journal of Alternative and Complementary Medicine, 10 (1), pp.S-1–S-6)

"Integrative" Therapies: Physical Exercise

- Exercise reduces depressive symptoms among patients with a chronic illness.
- Patients with depressive symptoms indicative of mild-to-moderate depression and for whom exercise training improves function-related outcomes achieve the largest antidepressant effects.

(Effect of Exercise Training on Depressive Symptoms Among Patients With a Chronic Illness: A Systematic Review and Meta-analysis of Randomized Controlled Trials; *Arch Intern Med.* 2012;172(2):101-111)

Meditation

- Meditation has been shown to enhance immune system functioning and have benefits similar to antidepressant medications.

(Davidson, R, Kabat-Zinn, J. (2003). Alternations in immune function produced by mindfulness meditation. Psychosomatic Medicine, 65, p. 564)

- Numerous other studies document the health benefits of meditation for HTN, strokes, cancer, chronic pain, anxiety, depression, immune functioning, etc.

(For a database of meditation studies, se the Institute of Noetic Scinces web site, http://www.noetic.org/research/medbiblio/index.htm.)

Acupuncture

- Hundreds of clinical studies have shown acupuncture to be effective for a wide variety of ailments, from reducing chest pain in cardiac patients who have been unresponsive to drugs, to depression and anxiety, to the restoration of fertility in men, to the control of chronic tension headaches.

  - (Ballegaard, S, et al (2008). Acupuncture in severe stable angina pectoris – a randomized trial. Acta Medica Scandinavia, 220 (4): 307)
  - Shealy, CN, et al (1990). Treatment of male infertility with acupuncture. The Journal of Neurological and Orthopedic Medicine and Surgery, December, 11(4): 285)
  - (Hanson, PE, Hansen, JH (1985, September). Acupuncture treatment of chronic tension headache – a controlled cross-over trial. Cephalgia, 5 (3): 137)

Acupuncture

- A recent study using fMRI, PET, SPECT, and EEG scans show brain centers such as the amygdala and hippocampus being stimulated by acupuncture, while sham acupuncture does not.
- Acupuncture appears to affect a wide network of brain regions, including those involved with the processing of emotions and thoughts, involuntary action, and pain.

(Dhond, RP, et al. (2007). Neuroimaging acupuncture effects in the human brain. Journal of Alternative and Complementary Medicine, 13:6: 603-616)

T’ai Chi

- A 2004 review of scientific studies on T’ai Chi in the Archives of Internal Medicine showed that it enhances immune system functioning, and these results were replicated in a 2007 study on subjects with herpes zoster.

(Wang, C, et al. (2004, March 8). The effect of Tai Chi on health outcomes in patients with chronic conditions: a systematic review. Archives of Internal Medicine, 164 (5): 493)

(Irwin, MR, et al. (2007). Augmenting immune responses to varicella zoster virus in older adults: A randomized, controlled trial of Tai Chi. Journal of the American Geriatrics Society, 55 (4):511-517)

Qigong

Sustainable exercise – exercise done with somatic awareness – may be the most powerful discipline for long-term health

"States of consciousness are expressed in postures, and just as an actor practices 'stances' to enhance the expression of feeling, so does a Qigong practitioner practice his or her stance to maximize power, healing, and the expression of intention"

Michael Mayer, PhD, a Western Qigong master

Therapeutic Massage

- A 2004 meta-analysis of 37 studies of massage therapy published in the Psychological Bulletin showed their effectiveness for the relief of anxiety and depression, with "benefits similar in magnitude to those of psychotherapy" alone.

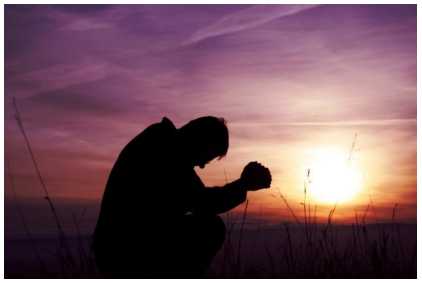
(Moyer, CA, et al. (2004). A meta-analysis of massage therapy research. Psychological Bulletin, 130 (1), p.3)

Therapeutic Massage

- Study: Massaged muscle cells had higher activation of gene pathways that spurred the growth of mitochondria, the powerhouses of cells. And massaged muscles showed fewer signs of painful inflammation.

(Crane, J, et al, Massage Therapy Attenuates Inflammatory Signaling After Exercise-Induced Muscle Damage, Sci Transl Med 1 February 2012: Vol. 4, Issue 119, p. 119)

Spirituality



- In the last few years, research investigating the relationship between spirituality, health and coping with illness and distress has blossomed.
- This research has provided neurobiological insights similar to those obtained in placebo research.
- For example, there is clear evidence that spirituality is able to alter pain perception

[Wachholtz A. B., Pargament K. I. 2005 Is spirituality a critical ingredient of meditation? Comparing the effects of spiritual meditation, secular meditation, and relaxation on spiritual, psychological, cardiac, and pain outcomes. *J. Behav. Med.* **28**, 369–384.]
[Giordano J., Kohls N. 2008 Spirituality, suffering, and the self. *Mind Matter* **6**, 179–191}.
(Kohls N., Sauer S., Offenbächer M., Giordano J. 2011 Spirituality: an overlooked predictor of placebo effects? *Phil. Trans. R. Soc. B* **366**, 1838–1848)

Therapeutic Rituals

- In a study by Bittman et al, 111 healthy volunteers participated in an hour-long drumming and story-telling ritual.
- Group drumming resulted in *multiple, positive immune responses* (increased DHEA-to-cortisol ratios, increased natural killer cell activity, and increased lymphokine-activated killer cell activity without alteration in plasma interleukin 2 or interferon-gamma), *and in mood*.

(Bittman MD, Berk LS, et al. Composite effects of group drumming music therapy on modulation of neuroendocrine-immune parameters in normal subjects (2001), Alternative Ther Health Med 2001: 7:38-47)

The Emerging Science of Epigenetics

- **Epigenetics** is "the study of heritable changes in gene function that occur without a change in the DNA sequence."

(Science (2001, August 10). Epigenetics special issue, 293, p. 5532)

- Epigenetics examines the sources that control gene expression from outside the DNA. It's a study of the *signals* that turn genes on and off.
- Some of those signals are chemical, others are electromagnetic, some come from the environment inside the body, whereas others are our body's response to signals from the environment that surround our body.

The Emerging Science of Epigenetics

"How our subjective states of mind, our consciously motivated behavior, and our perception of free will can modulate gene expression and optimize health."

Psychologist Ernest Rossi
In The Psychobiology of Gene Expression

The Emerging Science of Epigenetics

The Dogma of Genetic Determinism

- Los Angeles Times, August 11, 2007: “Researchers have identified two mutant forms of a single gene that are responsible for 99% of all cases of a common form of glaucoma.”
- National Public Radio, October 28, 2005: “Scientists today announced they have found a gene for dyslexia. It's a gene on chromosome 6 called DCDC2.” The New York Times ran a similar story the following day, you headline, “finding support that dyslexia disorder is genetic.”
- The problem with the legend: it's not true.

Epigenetics

"Life spans are nothing like a trait like height, which is strongly inherited… That's what the evidence shows. Even twins, identical twins, die at different times. On average, more than 10 years apart".

James W.Vaupel, Director of the Laboratory of Survival and Longevity at Max Planck Institute for Demographic Research, Rostock, Germany

Same genes, different outcomes. This report illustrates the dramatic difference that epigenetic factors make in health and aging.

Epigenetics

Manuel Esteller, Director of the Cancer Epigenetics Laboratory at the Spanish National Cancer Center in Madrid, and his colleagues evaluated 40 pairs of identical twins, ranging in age from 3 to 74, and found a striking trend, described in the 26 July 2005 issue of *Proceedings of the National Academy of Sciences*:

- Younger twin pairs and those who shared similar lifestyles and spent more years together had very similar DNA methylation and histone acetylation patterns.
- But older twins, especially those who had different lifestyles and had spent fewer years of their lives together, had much different patterns in many different tissues, such as lymphocytes, epithelial mouth cells, intra-abdominal fat, and selected muscles.

The Emerging Science of Epigenetics

- That much of our genetic activity is affected by factors *outside* the cell is a radical reversal of the dogma of genetic determinism, which held for half a century of who we are and what we do govern by our genes. Research is illuminating the new biology which consciousness is a primary role.

The Emerging Science of Epigenetics

- "Our genes dance with our awareness. Thoughts and feelings turn sets of genes on and off in complex relationships. While we may have a fixed set of genes in our chromosomes, which of those genes is active has a great deal to do with our subjective experiences, and how we process them"

  (Church, D, The genie in your genes, Energy Psychology Press, 2008)

- In the succinct words of neuroscientist Dr. Bruce Lipton, "beliefs become biology"– in our hormonal, neural, genetic, electromagnetic systems, plus all the complex interactions between them.

Case Study

Katherine H: 45 y/o physician, married to physician

- **Somatic Experiencing**: “It’s helped me reconnect with my own body, with my own physiology, and it’s teaching me how to self-regulate even when I’m experiencing fear or anxiety”
- **EMDR**: “I’m sleeping through the night for the first time in years!”
- **Biofeedback:** “We’ve identified the breathing pattern that increases my HRV and in turn reduces my autonomic nervous system activation… I can now practice it on my own throughout the day.”

Case Study

Katherine H: 45 y/o physician

- **Aquatics and Movement Therapy**: “Very powerful… it enables me to feel a ‘good sore’, and differentiate between injury and the healthy pain of recovery. It’s teaching me that I can expand my activity rather than ‘splinting’ and constricting my circle of activity.”
- **Rituals**: “I was given ‘Craig’s ring’… and then the Burning Ceremony made me weep, recognizing that I’m part of a larger network, an eco-system of encouragement and healing. These therapeutic threads are coming together in a whole cloth…”

Medication, Mindfulness, and More: **Summary**

- How placebos work may well mimic how mindfulness practices, and antidepressants, and CBT, and DBT, and EMDR work…
- There is a growing line of evidence that ***the therapies that work*** – whether beliefs or chemicals or somatic treatments or experiential therapies – may share common psychobiological mechanisms.
- We're beginning to gain greater understanding at a neurobiological level of the nature of the mind/body relationship.
- Given what we know about the potential toxicities and limitations of AD medications, there is a strong, emerging scientific argument to be made about the value of a more integrative and broad-based approach to the treatment of depression.

MEDS, MINDFULNESS AND MORE:
THE NEUROBIOLOGICAL CASE FOR AN INTEGRATIVE APPROACH TO THE TREATMENT OF DEPRESSION

Dr. Robert Johnson
Medical Director, Sierra Tucson
Diplomate, ABPN, ABAM