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If low serotonin levels aren't responsible for depression, what is?

By studying the other effects that antidepressants have in the brain, we may arrive at more effective ways to treat depression

Scicurious blogs at Neurotic Physiology

Depression is not caused by low levels of serotonin, but recent discoveries may hold out hope for sufferers. Photograph: Sipa Press/Rex Features

We've all seen the commercials. There's a sad little white marshmallow, a person in a darkened room unable to attend the party, or unable to enjoy a beautiful day. And then a voice shouts out that here is hope. That depression of yours is a result of imbalances in chemicals in your brain and, if you can correct those chemicals, you will feel better. Easy!

It's not that these commercials sell you a pack of lies. Most antidepressants do increase the levels of chemical messengers in the brain called neurotransmitters. A specific type of neurotransmitter, the monoamines, appear to be the chemicals of choice for these drugs. Scientists once thought that simply increasing the amount of

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guardian.co.uk
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monoamines in the brain would treat the symptoms of depression. And that meant, of course, that depression itself must be caused by low levels of monoamines, particularly serotonin.

For years, scientists have tried to find drugs that increase these serotonin levels in the brain safely, and tried to find evidence that decreases in monoamines are responsible for depression itself.

Well, after much searching, we did find a lot of very interesting things. But some things just didn't add up.

The first problem was one of time. If low serotonin levels were really what made you feel depressed, then increasing levels of serotonin should alleviate the symptoms right away. But antidepressants don't work immediately, and in fact can take more than a month to alleviate symptoms. Strike one.

The second problem was one of whether the drugs actually worked. Serotonin-specific antidepressant drugs don't work on everyone. In fact, new estimates show that the current antidepressants on the market only work in about 60% of patients. If low serotonin levels were really responsible for depression, then increasing serotonin should have worked on more than 60% of patients. Strike two.

The final problem is one of evidence. If low serotonin levels were responsible for depressed mood, then we should be able to induce depression in people by decreasing serotonin, and we should find low levels of serotonin in patients with depression. But neither of those things exist. Decreasing serotonin in humans can lower your mood, but it doesn't always work. And studies looking for low serotonin in depressed patients have been inconclusive. It appears that even though antidepressants increase serotonin, a lack of serotonin doesn't cause depression (kind of like aspirin treats a headache, but headaches are not caused by a lack of aspirin). Strike three. Serotonin is out.

So what's in? After all, antidepressants do work in some patients. It's instructive to look at other things these drugs are doing in the brain.

Antidepressants increase levels of neurotransmitters in the brain, but they also increase neurogenesis, the birth of new cells in the brain. Throughout your life, you will grow new neurons in an area of the brain called the hippocampus. And if you take antidepressants for several weeks, you will get increased neurogenesis.

These new neurons correspond to changes in animal behaviours that are associated with long-term antidepressant treatment. The behaviours are novelty-induced hypophagia, which measures how much of a tasty food an animal will eat in a novel environment and reflects aspects of anxiety and anhedonia (the inability to experience pleasure); and the tail suspension test, which measures behavioural despair.

Animals show improvement in both of these tests (eating more, or moving more) after long-term treatment with antidepressants, and these improvements correlate with neurogenesis in the brain.

Not only that, if you make animals display signs of depression, you can reduce this neurogenesis, and you can reverse both the behaviour and the neurogenesis by treating them with antidepressants.

Antidepressants may increase serotonin in your brain, but the alleviation of depression may be due to the long-term effects of the drugs on neurogenesis.

The neurogenesis theory of depression fulfils many of the criteria that the serotonin theory did not. It takes the right amount of time to develop, the three to fours weeks that matches up with long-term treatment with antidepressants. We find reduced neurogenesis in animals and patients that display signs of depression.

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So far, we're two-thirds of the way towards an explanation. Many scientists are now examining the role of neurogenesis in depression, and looking for new targets to increase neurogenesis directly, rather than increasing neurotransmitters as the current drugs do.

The role of neurogenesis in the potential treatment of depression is an exciting idea. But it is not flawless. Many studies cannot discern whether there are real changes in neurogenesis in humans with depression. Some studies show changes, but others do not.

While traditional antidepressants do increase neurogenesis and relieve depression symptoms in some animal models, others show that neurogenesis and antidepressant behaviours are unrelated.

Much of this debate comes down to the fact that we don't yet have a real understanding of neurogenesis, how it works, and how it is controlled both in normal brains and in the presence of antidepressants. Until we know, finding a truly effective antidepressant may remain out of reach. So while the monoamine/serotonin hypothesis for depression may be out, neurogenesis needs to step it up a little to make it in.

Scicurious *blogs at Neurotic Physiology*

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dirkbruere
28 September 2010 12:59PM

Recommend (37)
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By "depression" I assume that it refers to being depressed for no major reason? If you have just lost your spouse, job and home being depressed is not a surprise, and the cure is not drugs.

daviddobbs
28 September 2010 01:01PM

Recommend (4)
Responses (0)
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This is a nice write-up, Scicurious -- though two-thirds of the way to an answer may be optimistic.

How so? As I noted in a recent blog post at Neuron Culture, the link between low serotonin levels and depression appears to break down in cultures that have a) less individualistic cultures and b) higher prevalence of the 'risk' gene for depression (and thus more people with lower serotonin levels). If this is so, we're missing some major variables by focusing on serotonin levels and gene variations only as they cross with overly limited definitons of 'environment' or experience.

eduardo22
28 September 2010 01:44PM

Recommend (5)
Responses (0)
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Serotonin enhancers can and do have a positive effect; a Cambridge U study just released today, for example, demonstrates how users of SSRIs "have an increased aversion to harming others, viewing such actions as morally forbidden": http://www.physorg.com/news204872017.html

fd203
28 September 2010 01:44PM

Recommend (12)
Responses (0)
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What you're failing to put across is your article is that depression is not a homogeneous condition, and that lesions to different parts of the brain can cause depression. This article from Science explains it rather more clearly than I can.

Sure, there are cases in which monoamine levels probably aren't the main causative factor, and may be an effect of other processes occuring in the brain. But what you can't ignore is that depleting monoamines can induce depression in at least some people (cf. reserpine, even though I'll admit the evidence is now seen to be a little shaky), which tells us that they must play at least *some* role in *some* patients with depression.

To say that the monoamine hypothesis is "out" is a little bit like saying "antibiotics don't treat all throat infections, therefore no throat infection can be bacterial".

andrewnholding
28 September 2010 02:14PM

Recommend (0)
Responses (0)
Report
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Really interesting, I knew the serotonin hypothesis didn't add up from Ben Goldacre. Glad to hear what people ideas are to more on from it.

offworldguy
28 September 2010 02:35PM

Recommend (19)
Responses (0)
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Well here it is from the horses mouth.

I suffered moderate to severe depression for over 20 years since my time as an undergraduate, complete with suicidal thoughts, before I managed to get myself to my GP to talk about it. There and then he put me on 20mg Citalopram, which inhibits the re-absorption of what little serotonin my brain was making. Within a week, after feeling "fuzzy" for several days I was no longer depressed.

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GrrlScientist

scicurious
28 September 2010 02:50PM

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Hi Everyone!

David (and fd203), great comments, and the serotonin thing does break down in some cultures. What I'm trying to get across is that in many people, SSRIs DO help depression because the increases in serotonin INCREASE neurogenesis (we think). In others, they may not, and this may be why treatment fails. So monoamine increases may increase neurogenesis, but this does not work in all people, and the increases in neurogenesis may be more responsible for the treatment of depression than the increases in monoamines by themselves. This may mean that by targeting neurogenesis with specific drugs (rather than increasing monoamines) we may get better clinical effects. That is my view on the literature right now and where the field is heading.

HumbleLife
28 September 2010 03:48PM

Recommend (53)
Responses (0)
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After being treated by a Psychiatrist during crisis, who simply poo-pooed all my experiences, said I was just emotional and implied I was just crap I decided to investigate this doctors history. He was 45 minutes late and left within 10. His colleagues were no better.

When I researched his history after recovery, I discovered he had lost a surgeons license as he had operated drunk several times and had killed 5 patients and permanently damaged 7. He was amazingly allowed to retrain as a Psychiatrist in Reading, where he drove a client to suicide, leading to a letter to being written to the home office. He has not been stopped. I find this depressing...

HumbleLife
28 September 2010 03:50PM

Recommend (13)
Responses (0)
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apologies for the crap grammer,. i'm wound up over all of this crap.

the UK mental health system fails because it's full of pseudo intellectualism from old colonial mindsets who have no intention of accepting failure. So it's a surprise that drugs companies get the feedback they actually need at all.... That's the point...

TheBonsaiKid
28 September 2010 03:56PM

Recommend (9)
Responses (0)
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The role of hippocampal neurogenesis in the pathology and the treatment of depression certainly deserves attention. However, just has the infuriatingly high-profile, grossly oversimplified idea that serotonin levels share some equivalence with mood, this article is dangerously close to starting the new campaign by saying that levels of neurogenesis determine happiness.

Also, strike two is a little hard to follow when it is the same drugs that are ineffective in 40% of people that also increase neurogenesis.

And an argument analogous to strike three can be used against the neurogenesis hypothesis - in rodent studies where it is possible to decrease, or in fact completely ablate, neurogenesis this does not result in a "depressed" states.

I don't want to sound down on this theory as a whole, it IS the exciting development out there, but as is said in other places, this stuff is complicated...

TobySaunders
28 September 2010 05:05PM

Recommend (24)
Responses (0)
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Depression is a lack of dopamine (duh)... it doesn't seem to be a disease though, in most cases at least, it's behaviorally induced. Serotonin produces a poetic, surreal/dreamy feeling, that's all.
I used to be depressed because I believed in God & Satan PLUS I believed I had the

depression disease; I got over that via education about ethics & science... positive behavioral changes wer enough.
These synthetic drugs aren't worth it... I done lots of them, they are bogus... they damage the body too much without enough positive results.
Cannabis is the best medicine for sadness but good education is the best tool.

imipak
28 September 2010 06:26PM

Recommend (8)
Responses (0)
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Depression likely has many causes. In fact, as virtually all psychiatric terms describe symptoms and not causes, virtually all such terms will describe unrelated conditions that merely exhibit some set of symptoms that fit neatly together on a simple checklist.

In this day and age, with the kinds of diagnostic equipment we have, using the symptoms for diagnosis and as evidence of the effects of treatment is not much better than asking a witch-doctor for help. It should be a last-resort when identifying and treating the underlying causes isn't an option for whatever reason.

I find it interesting that neurogenesis is a factor. Not "the cause", but a factor. The points in a person's life when their mood is expected to change are also the points in time when brain growth and die-back rates change. Certainly, there does appear to be a correlation. But a correlation doesn't tell you which (if either) is the cause. They could both be otherwise-unrelated effects of a common cause.

This would seem to be the most likely. Think about it. The most intelligent people have the greatest rates of brain-cell growth and brain-interconnect growth. They are also amongst the least happy. It may well be that if they were happier, their brains would grow and develop even faster, but the absolute rate is clearly not sufficient. There is more to this story.

Equally, the brain is well-known to suffer substantial die-back in the mid-to-late 20s. It's why there are many more discoveries by young minds than old minds. But although this is certainly a time when moods change (so there's definitely a correlation), the 30s tends to be associated more with calm and getting things done than with the depression you'd expect.

It's the "more to the story" that interests me.

snowcat3
28 September 2010 07:09PM

Recommend (36)
Responses (0)
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fd203 is quite right : depression is not a homogeneous condition, though it is being referred to as such. The whole focus on depression being caused by brain chemistry is, may I suggest, plain wrong.

Lots of depression is caused by things such as : poor parenting early on, poor parenting later on, feeling powerless (for whatever reason or reasons), any kind of abuse, grief that hasn't been "resolved" (for whatever reason), unemployment, over-employment, poverty and all the stress that goes with poverty, etc, etc. Most depressed people will be experiencing a combination of some of these things. An imbalance in brain chemistry MIGHT be present (and it might be partly genetic in origin, though not necessarily).

As someone who has experienced clinical depression at various times in my life and to various degrees I would say, my brain chemistry has been at those times almost certainly disordered. But I doubt very much that my disordered brain chemistry was the CAUSE of me being depressed. It was a symptom (which anti-depressants sometimes, not always, alleviated.)

I am very tired of doctors (a lot of doctors) blithely accepting the brain chemistry theory.

imipak
28 September 2010 11:28PM

Recommend (7)
Responses (0)
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snowcat3: Yes and no. Yes, it is self-evidently not a homogeneous condition and yes brain chemistry is not the whole story. No, in that all experiences alter the structure, electrical properties and chemistry of the brain. Well, there really isn't anything else in the brain besides those, so even if you're looking at something as trivial as the memory of something, then you are limited to those three things. Therefore

something like poor parenting will alter (amongst other things) the chemistry of the brain, which may indeed then make you depressed.

But if you look at it like that, then one specific chemical in the brain is likely immaterial. There are too many brain chemicals that could potentially affect what happens and too many non-chemical factors that could play a part. And, yes, genetics may well be a part too, although as genes don't do anything directly themselves, they presumably would be playing a part via the chemistry of the brain (and the chemistry of individual cells).

To be fair to doctors, I have never heard of any drug company stumping up the cash to use radioisotopes to track the pharmaceuticals through the brain, see what affects what, and actually study in-depth what a given medication does. There are something like 33 different ways to examine the structure and activity of the brain - I wonder how many get used when diagnosing depression or determining which treatment will work. My guess is not a single one of them.

Colin211159
29 September 2010 07:15AM

Recommend (5)
Responses (0)
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I have lived with someone for over 20 years who has suffered extreme - and drug-resistant - clinical depression, and I am glad to see the serotonin theory being challenged. The blog is excellent in that sense, in that it brings into the open some of the new theories; however, I would challenge the statement that just because drugs only work in 60% of people, serotonin can;t be the answer. In fact, for a drug to work in 60% of a population is actually quite good - the individual differences between us all in terms of how we metabolise drugs meas that it is very unlikely that a given drug will work for everyone, and I think the public would be surprised to learn the extent to which different drugs are need for different people. This is the basis for personalised - or stratified - medicine, and will be the next 'big thing' in drug treatment in the coming years.

McNultyReloaded
29 September 2010 08:38AM

Recommend (6)
Responses (0)
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"The story of depression cannot be dissociated from the story of its supposed remedies.

"Where depression had been rated at 50 per million in the early 60s, by the 90s this had jumped to 100,000. These remarkable changes coincided with the crisis in the market for minor tranquilisers such as Librium and Valium, prescribed for anxiety. As these widely used drugs were found to be highly addictive, it looked as if a substantial market was about to collapse. Hundreds of thousands of people took these drugs and the economic gains were enormous. Anxiety had to be remarketed and new agents found to respond to it. And this is where depression started to really take off as a diagnosis. First of all, however, it had to be constructed as a discrete, well-defined clinical entity.

Why couldn't the drugs companies have simply offered their products as tonics or general mood enhancers? After the thalidomide scandal in the early 60s, tough new standards were set in place and drugs had to specify their active ingredients, the outcomes sought and the delivery period for attaining them. This meant a new kind of surface precision. Drugs would have to pass expensive trials proving they were more effective than placebo and do better than other drugs used for this same group of target patients. These new standards brought with them a new technology to evaluate. Randomised controlled trials became the norm, together with a silver bullet model of illness according to which each specific disorder would have a specific cause and a specific treatment.

These changes in the landscape of prescription medicines framed the market for the antidepressants. Since the new diagnosis needed to be publicised, drug companies paid for adverts in medical journals, glossy pullout supplements, conferences and clinical studies to show the prevalence of depression. When Frank Ayd wrote his book Recognising the Depressed Patient, the pharmaceuticals giant Merck bought 50,000 copies and distributed them to GPs. The book argued that depression was going undetected and untreated in the community. This dissemination of knowledge coincided nicely with their marketing of a new treatment for depression in the form of amitriptyline.

The later generation of SSRI drugs had an even more exponential success: by the late 90s Prozac was a household word, with millions of prescriptions and a whole cult of novels, films and memoirs based around it. In 2005, traces of Prozac were even found to be present in British tap water.

This process of marketing depression helped create the clinical category itself. If the new drugs affected mood, appetite and sleep patterns, then depression consisted of a problem with mood, appetite and sleep patterns. A subtle shift in the defining symptoms of depression took place over the years, so that the category itself became taken for granted. Lost here was the simple idea that there is a difference between surface symptoms (insomnia, loss of appetite, feeling low) and underlying causes, which may be different from case to case. The creation of the antidepressant market effectively disallowed this once crucial distinction.

The creation of the Prozac myth, The Guardian, 27 Feb 2008

Gabbyco
29 September 2010 09:44AM

Recommend (14)
Responses (0)
Report
Clip | Link

It depends what you call Depression,

There are two types:

Internalised and organic or Endogeneous which Anti Depressants are meant to treat.

Alternatively, Reactive Depression due to life events and circumstances, loss of job, loss of home, bereavement, and what most transexuals continue to suffer because of society's prejudice in one form or another pre and post op.

It has nothing to do with mental illness, circumstances and powerlessness can make people feel depressed. Anti depressants won't change that. Getting a break will.

MexicanAl
29 September 2010 09:47AM

Recommend (17)
Responses (0)
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> We've all seen the commercials. There's a sad little white marshmallow, a person in a darkened room unable to attend the party, or unable to enjoy a beautiful day. And then a voice shouts out that here is hope. That depression of yours is a result of imbalances in chemicals in your brain and, if you can correct those chemicals, you will feel better. Easy!

Never have I seen an advert for antidepressants, or any other prescription drug for that matter.

Brant
29 September 2010 11:48AM

Recommend (5)
Responses (0)
Report
Clip | Link

@Humblelife

Shocking. And I hope you're keeping up the pressure! If you've found out, you should not let a person like this continue to influence susceptible people.

The only thing he should be allowed to retrain as is an oesteopath or physiotherapist.

Brant
29 September 2010 11:50AM

Recommend (11)
Responses (0)
Report
Clip | Link

@Humblelife
Do an expose on this guy.

@Guardian - investigate if this is true.

pocketshepherd
29 September 2010 12:08PM

Recommend (2)
Responses (0)
Report
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> We've all seen the commercials. There's a sad little white marshmallow, a person in a darkened room unable to attend the party, or unable to enjoy a beautiful day. And then a voice shouts out that here is hope. That depression of yours is a result of imbalances in chemicals in your brain and, if you can correct those chemicals, you

> will feel better. Easy!
>
> Never have I seen an advert for antidepressants, or any other prescription drug for that matter.

They're all over American television. Advertising selling prescription drugs doesn't sit quite right but it's there.

scortja
29 September 2010 12:13PM

Recommend (2)
Responses (0)
Report
Clip | Link

Humblelife - can you name or give clues? This is very serious.
Have you officially complained?

chaosmostly
29 September 2010 12:38PM

Recommend (2)
Responses (0)
Report
Clip | Link

The first signs of depression often go unnoticed.
Depression usually starts as recession.
Causes include Wall Street, its government quislings and religious fundamentalists.
Once these causes are eliminated, so too depression.

ursuppe
29 September 2010 12:47PM

Recommend (5)
Responses (0)
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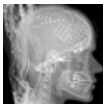
I had seen some suggestion of the neurogenesis theory before but it's interesting to find that it is the subject of some serious research. The time lag between anti-depressants being started and the effect has always struck me as the most convincing evidence that they are not working simply as placebo.

I would be interested to know how this theory relates to bipolar disorder where not only the depression but the highs need to be accounted for.



jkforde
29 September 2010 01:05PM

Recommend (8)
Responses (0)
Report
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http://en.wikipedia.org/wiki/Depressive_realism

While I do get down and utterly despair at the never changing human condition I nevertheless prefer my level of awareness and realism than the utter banality of our status quo 'head in the sand' measure of normality and success.

When we stop automatically labelling depression as a negative and just accept it as a necessary an welcome part of the spectrum of human madness then we might start getting somewhere.

MexicanAl
29 September 2010 02:12PM

Recommend (2)
Responses (0)
Report
Clip | Link

@Pocketshephard, I stand corrected. Still, it is a minor bête noir of mine when articles like this aren't adapted to where they are published. I should probably get out more.

sparclear
29 September 2010 04:13PM

Recommend (3)
Responses (0)
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@pocketshepherd & MexicanAl
HRT used to be advertised like this in its early days too and I know quite a few women who received it as a specific antidepressant.

Like all the other pharmaceutical approaches, there are side-effects and although the patients were grateful at the time, the depression resurfaced when they came off the drugs. Some by then had had gallstones or even the entire spleen removed and were

in receipt of yet more medication for high blood pressure and heart symptoms.

That is so often the price we pay, side-effects and unaddressed life problems once the medicine stops. It seems that few practitioners know truly how to boost the patient's own "brain growth" in a healthy direction, which offers them permanently the chance of adjusting their lives and becoming creative, expressive individuals....and yet, these are the very skills that good parents must possess.

Bliad
29 September 2010 05:52PM

Recommend (1)
Responses (0)
Report
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Happiness is having sex with a beautiful woman; misery is having to pay for it.

Bliad

cmreveley
29 September 2010 06:10PM

Recommend (5)
Responses (0)
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I should precis my comments by saying that I don't buy the notion that serotonin is the whole story. I think AD's are over prescribed and depression not well understood and overdiagnosed.
Nonetheless, there are serious errors in what you say. First, "antidepressants" by which you mean "selective serotonin reuptake inhibitors" like prozac DONT increase serotonin levels. what they do is prevent the afferent cell from removing too much from the cleft after an action potential (re-uptake). re-uptake is normal. excess molecules that didn't bind efferently are pulled back up to save costs. the idea is that depressives (SOME depressives) have a re-uptake pathology. so not enough serotonin gets to the efferent cell. So, you introduce a compound that slows re-uptake by changing the cell's metabolism. UPSHOT: serotonin isn't increased or decreased. it's just put in the right place. Changing a cell's metabolism takes time. Hence: SSRI's take a while to have an effect. but see how you feel if you discontinue abruptly..finally: If you take MDMA most of your serotinergic vesicles get released (pathologically of course) at a huge rate. You feel very much not depressed. But: you're now out of vesicles. So later on you feel low. later still, cells have had time to make more. You're ok again.

I made clear in precis that I don't think SSRI's are for everyone. They are very effective for people who are very depressed, and are depressed because they exhibit a re-uptake pathology or can be helped by inhibiting serotonin re-uptake.

I think there's more to neuro-pathological depression than the serotoninergic system. Multi causal likely, and in many cases just different pathologies.

I think that, as I said, "depression" is overdiagnosed. Often it is "sadness". Often, very often maybe, it is a result of life circumstances to which the patient isn't reacting in a pathological way in physiological terms. Drugs won't help that. Life is very sad sometimes. All the time for some. So they are sad. But their brain is not malfunctioning, so introducing a compound (that doesn't itself induce pathology like MDMA does) can't help.

But SSRI's have their place all the same. Serotoninergic patholgy happens. The drugs work for that. But in general, not that many people probably have that pathology.

Anway, SSRI's aren't about more or less of this neurotransmitter. And a person with the pathology I mentioned would not necessarily show less serotonin under MR spectroscopy (I can't think how else you'd measure it in a human non-invasively. Maybe someone else knows. I don't even know if MR spec can pick up serotonin). But it would all be hoarded up inside the cells' vesicle pools. Not being used to transmit effectively.

cmreveley
29 September 2010 06:48PM

Recommend (3)
Responses (0)
Report
Clip | Link

sorry, terms:

AFFERENT : the cell transmitting (behind).
EFFERENT : the cell recieving.
VESICLE : a little ball of membrane with transmitter molecules (serotonin in this case) inside. They live in neurons. Some are kept in reserve, some ready to go.
ACTION POTENTIAL: a neuron "firing" which causes the vesicle membranes to

merge with the end of the nuron's membrane releasing the molecules into...
CLEFT: the "synaptic cleft" a gap between neurons over which transmitters diffuse, and bind to receptors on the efferent. This changes the voltage on the efferent, making it more (or less, but more for serotonin) likely to emit an action potential itself.

REUPTAKE: it takes energy from food (which for a neuron is a chemical called ATP) to make serotonin. If there is some left over in the cleft the afferent mops it up to save for later:

So the pathology: too much reuptake too fast, not enough transmitter binds @ efferent, the vesicles are stored for later.

Same amount of serotonin on aggregate. possibly *more* in a depressive.

"selective serotonin reuptake inhibitor"

didn't do me much good. Life's a bitch as I said. I derive more enjoyment from studying the brain.

alan111d
29 September 2010 09:48PM

Recommend (8)
Responses (0)
Report
Clip | Link

Depression is a disorder of mood. There may well be a correlation between this and brain chemistry or neurology, but even if there is, that is only correlation, and correlation does not prove cause and effect.

The logical thing is to look first at how our moods change. We have a number of non-drug treatments that work well in treating depression, without side-effects, and without addiction. This doesn't mean we shouldn't look for drug treatments, but neither should we focus on drugs so much that we fail to invest in, and research adequately, the treatments that don't make the drug industry rich. There has been too much money taken from the public for something of little benefit to sufferers, while non-drug treatments have battled to get noticed.

It's got to change.

Equalityforall
29 September 2010 10:15PM

Recommend (3)
Responses (0)
Report
Clip | Link

As others point out, it is potentially the desire to find one cause and thus cure for depression that may mean that we still only partially get to treat it.

Do the SSRI's, as a single treatment option, only work for some people because previous researchers had focused too tightly on finding just the one main cause/solution.

I liked the way that your approach was explained so clearly, but I couldn't come to the same conclusions as you did, with each of your three strikes - but I recognise that you know far more about your work than I do.

Humans are complex, our lives are somewhat chaotic, with the only certainty being our birth and death. We won't all have the same response to identical stimuli, potenitally at every level of our bodies, whether this is conscious peception or the impact that living has on our bodies. It thus seems somewhat facile to expect that a complex problem, such as depression, which is experienced very differently by people, could be targeted with one solution. I dearly would love it to be the case, as this would help a higher proption of those people who may have the misfortune to experience this devilitating condition.

Equalityforall
29 September 2010 10:17PM

Recommend (0)
Responses (0)
Report
Clip | Link

debilitating condition, sorry for the lack of spell checking.

DrHemp
30 September 2010 02:53AM

Recommend (1)
Responses (0)
Report
Clip | Link

I thought MDMA, aka ecstasy, had been discovered years ago :-)

IndependentLady
30 September 2010 03:06AM

Recommend (5)
Responses (0)
Report
Clip | Link

It would be nice if society actually understood what clinical depression and anxiety were, before worrying about if and how the treatments work. If you don't understand the condition, how the hell do you understand the treatment?

TheGrayCat
30 September 2010 05:43AM

Recommend (5)
Responses (0)
Report
Clip | Link

There's absolutely nothing new in this.

Serotonin levels in the brain can vary widely between individuals, without any ill effects.

Serotonin and dopamine are the two major neurotransmitters. But, there's over a 120 more transmitters. Each Anti-depressant has a slightly different action to the others. And the mechanisms of these actions are not understood.

Mostly they're as effective as smoking dope, drinking alcohol, or insufflating cocaine, to beat the blues.

Speed and cocaine boosts dopamine. For some people they're effective anti-depressants - for others they're effective disasters.

I've heard recently that small doses of LSD - may be a very effective anti-depressant.

Drug companies say things like - oh yeah, this stuff boosts serotonin, blah blah blah. Truth is they don't know, they're just dope dealers.

But what's wrong with a little dope, to pick you up when you feel down.

KesterRatcliff
30 September 2010 08:41AM

Recommend (4)
Responses (0)
Report
Clip | Link

I found this article and some of the comments really, really interesting.

I'm no expert but I have a small suspicion which I've aired with a friend who is a PhD in neuropsychopharmacology, and he thought it wasn't too wacky:

Oxytocin and testosterone both have mood improving effects too. Supposing there are different kinds of depression with different neurochemicals associated with them, it may be that some kinds of depression are more related to oxytocin or testosterone levels.

Oxytocin is probably completely safe, risk-free, totally good -aka. 'the cuddle hormone', it's also the down regulator for the HPA axis which correlates with c-PTSD and depression associated with social anxiety disorders. So in some countries, USA and maybe Australia, they're testing oxytocin inhalers as a treatment for anxiety disorders and c-PTSD. Because I couldn't get an oxytocin inhaler on prescription here, I tried the old herbal way with raspberry leaf tincture which apparently has been proved to work on the oxytocin receptors in a similar way to SSRIs to indirectly increase levels of oxytocin.

Testosterone is much more interesting as a mood-regulator -obviously, people's first association is with men behaving badly, but -it does many other things besides correlate with aggression and sex-drive. I've tried out the idea on several people who know a lot about these things and they basically thought it was due to litigiousness about risks and prejudice about the cultural connotations of treating depressed people with testosterone gel or patches to just raise their levels to the the upper limit of the normal range.

sparclear
30 September 2010 09:52AM

Recommend (4)
Responses (0)
Report
Clip | Link

@KesterRatcliff
neither am I altogether an expert, but fairly basic (A-level) human physiology study shows that the problem with hormone treatments generally is getting the dosage right, the range of what's normal is so variable, and the consequences of overdose can be so catastrophic. It is true that their fluctuations can influence mood radically - as every

woman suffering from PMT knows.

witchburner
30 September 2010 10:14AM

Recommend (1)
Responses (0)
Report
Clip | Link

"If low serotonin levels aren't responsible for depression, what is?"

Narwhals.

the soluion is to buy an anti-Narwhal rock from me, ownership of this rock guarantees that no Narwhal shall ever come within 20 feet of your house.

The basic package (1 anti Narwhal rock, "Narwhals go home" t-shirt): £49.99
The Deluxe package (3 rocks, 3 t-shirts, a harpoon gun): £199.99

Orlando98
30 September 2010 10:57AM

Recommend (1)
Responses (0)
Report
Clip | Link

For 30 years I was miserable and anxious. I couldn't be positive about anything. I just presumed it was cos I'm Scottish.

Then my GP said "you have low levels of serotonin in your brain - take prozac twice a day and you'll be fine".

Within a month I was a completely different person. I haven't looked back. So whatever my problem actually is, whether it's depression and anxiety or soemthing else entirely, prozac works amazingly well. I would urge anyone who's depressed to try it. It changed my life and it saved it too.

Pumellhorne
30 September 2010 11:56AM

Recommend (2)
Responses (0)
Report
Clip | Link

A lot of people missing the point here. No simple answer and not one solution to fit everyone, no matter what personal experiences you've had.

To quote from the Neurotic Physiology blog linked in the article:

> Prozac still works in a significant number of patients. So what does this mean? Is the serotonin theory of depression totally wrong? Well, probably not entirely. The brain is a complicated place, and it's most likely that depression is a combination of factors, such as changes in neuronal growth and death, changes in neuronal connections, and changes in the biochemistry of neurotransmitters such as serotonin. Additionally, it is very possible that all of these changes feed back and influence each other. So serotonin may still play a role in depression, but it is probably not the main cause, and in fact there may not be one main cause of depression.

And from the paper 'The effect of age on proliferation-regulating factors in human adult neurogenic regions' also linked to the article:

> These findings suggest regulation of the adult neurogenic environment in the human brain may differ over time from that in other species.

The human brain and its systems (including the body, of which it is an inseperable part, the Brain of Morbius and Dr Hfuhruhurr notwithstanding) are 2-way streets and there is no simple answer that fits everyone. If there were they wouldn't need to do fully conscious brain surgery. But then, I suspect, humans wouldn't be able to adapt as we do and such things as brain surgery and comments threads wouldn't exist.

Pumellhorne
30 September 2010 01:00PM

Recommend (3)
Responses (0)
Report
Clip | Link

Significantly, in the abstract to 'Regulation of adult neurogenesis by stress, sleep disruption, exercise and inflammation: Implications for depression and antidepressant action' it uses...

> ...recent studies investigating factors that regulate neurogenesis with special emphasis on effects of stress, sleep disruption, exercise and

> inflammation, a group of seemingly unrelated factors that share at least two unifying properties, namely that they all regulate adult hippocampal neurogenesis and have all been implicated in the pathophysiology of mood disorders. We conclude that although neurogenesis has been implicated in cognitive function and is stimulated by antidepressant drugs, its functional impact and contribution to the etiology of depression remains unclear. A lasting reduction in neurogenesis following severe or chronic stress exposure, either in adult or early life, may represent impaired hippocampal plasticity and can contribute to the cognitive symptoms of depression, but is, by itself, unlikely to produce the full mood disorder. Normalization of reductions in neurogenesis appears at least partly, implicated in antidepressant action.

http://www.ncbi.nlm.nih.gov/pubmed/19748235

So maybe a fix for depression doesn't require neurogenesis-inducing pills, it may come down to living a 'better' lifestyle and being lucky enough not to experience extreme stress in early life of protracted stress in later life.

Of course opinions will differ on what a 'better' life would be, but I'll bet one day studies will agree that the pursuit of money, recognition and influence in an anonymous, crowded and often selfish urban society isn't it.

Pumellhorne
30 September 2010 01:07PM

Recommend (5)
Responses (0)
Report
Clip | Link

Of course for those unlucky enough to have experienced extreme and/or protracted stress, especially in childhood, a fix of some kind is required. Any kind of drug or supplement is a less than perfect solution so maybe we need to look at the social, not just the physiological, elements of the issue.

From my own observations I'd suggest bouts of chronic depression often follow times of perceived failure and occur during times of great demand with little opportunity to manage the situation or to succeed in obtaining the desired outcomes.

Is it any coincidence that in an increasingly aspirational society depression has become an epidemic?

DBDouble
30 September 2010 01:23PM

Recommend (1)
Responses (0)
Report
Clip | Link

Comment on the Critical Psychiatry blog.

cmreveley
30 September 2010 08:37PM

Recommend (3)
Responses (0)
Report
Clip | Link

Actually, GABA, gluatamate and to a lesser extent acetylcholine are the main neurotransmitters in the brain. glutanate excites, GABA unexcites. Too little GABA = epilepsy. Benzodiazapines increase susceptibility of cells to GABA. So it stops siezures (anti-convulsant(for epileptics) and chills you out (just calms that brain down; anxiolytic/sedative.

But dopamine is the main one that has an effect on *reward* (the dopaminergic system indeed is what makes coke so fun. Dopamine and the reward circuit are associated especially with the substantia nigra. Reward is associated with learning, (getting it right, strengthen circuits, wrong dont strengthen), (getting it right=getting food, f***, fight or whatever you prefer) and hence addiction. Cokes heavily dopanineric effect is why you feel like you're a cool dude and in the right, and also why you get addicted.

Serotonin is more complex (dopamine is too obviously). It has effects on mood, and intense pleasure and displeasure. but MDMA is not addicitve. Serontonin isn't so much in the reward circuit (nor is it wholly divorced - these are not simple issues).

There are in fact not very many distinct substances that serve as neurotransmitters. Each of them is involved in many circuits, mostly your "old" brain influencing your "new" "human" brain (neocortex, which internally uses mostly GABA, glutamate and acetylchonelene. Or nothing (a direct link called a gap junction) osccasionally).

the fact that there aren't many transmitters means that messing about with them *globally* (which is all drugs can do, you can't put the drugs action only in one

anatomical area) is going to have side effects. the fact that they interact, and we dont know how means that we (they in fact, I don't make this stuff) don't know how they work.

The drugs are found via trial and error. Really. The results of trials are rigged etc (read Dr. Goldacre's book "bad science").

Drugs can work if you have a distinct pathology, and usually are VERY sick. way to sick to write on this blog. And you suffer terribly from the side effects, because huge doses are required for e.g. a really, really ill schizophrenic to benefit from drug therapy.

but they *do* stop hearing the voices.

Like I say, I think the vast majority of SSRI prescriptions are unecessary and harmful. but its cheap and easy for a doctor to write a script. Drug companies encourage them to. So they do. They are busy and stressed.

alan111b you say: "Depression is a disorder of mood. There may well be a correlation between this and brain chemistry or neurology, but even if there is, that is only correlation, and correlation does not prove cause and effect. "

would you say there is a correlation between your having a brain and being able to write?

You're referring to the fact that correlation does not imply causation. It doesn't. Though in context of supporting evidence often it does suggest it strongly.

So, obviously Alan what we scientists do is try to find causal links via testing and logical inference. Soctrates is a man. All men a are mortal - > Soctrates is mortal. That *is* science. Not "correlations" chucked about. you check if socrates is a man. then you know he's mortal. you CHECK.

Statistics are only part of the story, when changing something (the only way to establish a causal effect) isn't an option (that's why we use animals for experimentation : we can change their brains) or as an adjunct.

you realise correltation is mathematically defined, and that statistics is a branch of maths right? It's not just a word. It has a *meaning*

depression is a mood disorder. Yup. LOTS of mood disorders. And I'd argue only a small number helped by SSRI's. Those helped by SSRI's are helped because the neuropathology is the right one. If you want to come to brighton, I'll find your bregma, drill a hole in your head and we can establish whether there's causation via immunohistochemistry. Also, I'll have to murder you aftterwards to analyse your brain.

No?

cmreveley
30 September 2010 09:31PM

Recommend (2)

Responses (0)

Report

Clip | Link

Incidentally, while it is not possible (or allowed anyway) to drill a hole in Alan's head, inject a tracer into a site, wait two weeks (he could use the time to get his affairs in order; bonus!), put hum in a MASSIVE JAR full of ether, inject him with a massive dose of ketamine (the isomer of the street drug, not the street drug) to be sure he's out, crack open his ribcage, inject saline solution into his heart's left (I think, push up and left) ventricle to flush the blood from top of his body, then switch from saline to a fixative, then chop his head off, throw his body in the biohazard bin, crack his skull, pull out his brain, put it in a jar full of sugarwater, put that in the fridge for a while, take it out, freeze his brain with dry ice, slice it finely over a period of weeks (v boring), spend a year or two looking at the slices under a microscope(v v v v boring) and establish a

CAUSAL rather than merely CORRELATIONAL connection between whatever he has reported and the results of the serotonin (or whatever, his choice, let's give him that much) tracer study,

it IS possible to do it with rhesus macaques. Or legal at any rate. Lets not go there.

People have been doing it for 4 or 5 decades.

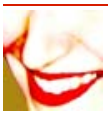
A man named Rolf Kotter, who has just died, took the trouble to collate every single study ever into a huge database of what connects to what in a monkey brain, what tracers, what transmitters etc.

Free to look at. Bit technical. Not the best bit of software engineering (can be slow),

But Rolf was the greatest. RIP.

www.cocomac.org

Please give generously, the project's future is uncertain because of Dr. Kotter's recent death.



hedgesparrow
1 October 2010 12:47AM

Recommend (0)
Responses (0)
Report
Clip | Link

alan111b

> Depression is a disorder of mood. There may well be a correlation between this and brain chemistry or neurology, but even if there is, that is only correlation, and correlation does not prove cause and effect.

cmreveley

> Would you say there is a correlation between your having a brain and being able to write?

Snigger.

hedgesparrow
1 October 2010 01:40AM

Recommend (1)
Responses (0)
Report
Clip | Link

So to summarize:

TheGrayCat
Antidepressants are as effective as smoking dope. Or drinking. Or taking LSD. So people should do those things instead.

alan111b
This article is focusing to much on the brain. How does that help depressed people?

McNultyReloaded
There is no such thing as depression. It's a Capitalist conspiracy.

Actually I'm really impressed we haven't had any of the "I was sad once, but felt better once I'd gone for a walk, depressed people should do that instead" brigade yet*.

Look. People. Anti depressants do work. They stop some people, like me, wanting to literally bang my head against a wall. They have stopped me wanting to do this for a number of years now, so I'm thinking it's probably not a placebo.

But I think the problem is that for some people anti depressants will always be a bit of a cheat. A cheat to mental health. To them recovery should either involve a painful examining of ones inner demons, the ingesting or smoking of, possibly illegal, but always 'natural' drugs and remedies or for some, as we've seen here, the entire restructuring of western civilization as we know it*.

When people wail "But, they worked for me!", we're given a condescending look, and reassured that we just 'think' they worked for us. That the fact we don't want to kill ourselves anymore is just the placebo effect. And what do we know anyway? After all, we're a bit mental.

*I'll get right on that, shall I?

Equalityforall
1 October 2010 08:46AM

Recommend (1)
Responses (0)
Report
Clip | Link

Thanks KesterRatcliff and Sparclear - when we're able to think outside of the box, even just a little, we may find more of the answers that we're looking for.

It's the one stop shop of SSRI or just CBT that is straight jacketing us in the UK at present. Not that there's anything wrong with either of these, but they clearly have limitations.

I like the concept of Oxytocin or something like Ecstasy, if helping people become more loved-up allows them to become healthier. Again, this type of approach is possibly limited to work for just some people,. but we shouldn't overlook it.

WinnieOfOz
1 October 2010 12:29PM

Recommend (1)
Responses (0)

Report

Clip | Link

Okay, first of all, must admit I haven't read the article, and given it's one of my pet hates (people commenting on a heading) I stand accused, and plead guilty.

But I DID skim though, and I DID skim through the comments to see if there were any relevant.

Please, please, please folks, if you're suffering from depression, have your Vitamin D levels checked.

I had them checked for a completely different reason; they were severely low - even with them since being tripled i only just scrape into the normal range.

Mood? No comparison. When I first found out the results I consulted Dr Google who told me the connection between Vitamin D and depression. Sure, I thought. Me, who's been on and off anti-d now for a few years.

For those who have experienced depression: you know how you wake, and even though you've been blessed with decent income, family etc etc all you can think is 'oh god, not another day to be got through'?

~~~~~~~

@ dirbruere

Absolutely. Of course we're shattered when life sticks the knife in, but as you've suggested, genuine depression is when there's no reason, or trivial reasons send us crashing. The guilt involved when we're financially better of than the vast majority of the world's population, when our health is good, when our family is happy, just aggravates the situation. How can I feel like crap when 90% of the world's population would give their right arm to trade places with me?

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