# The biology of mental health and wellbeing

What are the processes in the brain that drive our mental health?

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## Introduction

For hundreds of years, possibly thousands, philosophers, psychologists, psychiatrists, and physiologists have dedicated their lives to discovering what keeps mankind well, especially when it comes to our mental health and wellbeing.

Today, we know many of the answers to this age-old elusive question. We can now confidently stand on the shoulders of those scientists, doctors and philosophers who came before us and take both their learnings and mistakes to give us the best possible chance of having a great life. There has never been a better time in the history of humanity to achieve this.

And yet depression, anxiety and other mental (ill) health symptoms are not only common but are running rampant. Our modern lifestyles are significantly more stressful and less natural than our forebears', and oftentimes medication is the go-to solution to treat these problems without looking at other factors in a person's life.

Before the scientific revolution of the 17th and 18th centuries (the Enlightenment), there were many rules and rituals, including religion and other beliefs, which helped place mankind in the universe and create some meaning and purpose in life. We're not debating whether or not these things were factually correct; they merely provided a framework that helped people live a life that they felt was worth living.

It's well known that cultural norms are an important part of how people interpret their feelings and end up with normal 'up and downs' or a psychiatric diagnosis. When we look back over history, we can see that mental ill health was more normalised in ancient society than it is today. Where modern medicine might have diagnosed someone as having depression, historically they might have been referred to as having a melancholic nature. In fact, many of the most productive and creative talents in history would today have been diagnosed and perhaps medicated for their psychiatric 'illnesses', like Beethoven (bipolar), Lincoln, Churchill, Nightingale, and van Gogh (depression), and Michelangelo (autism and Asperger's). It's plausible that today some of these outstanding achievers might have been medicated out of achieving anything.

But is prescribed medication the answer to common mental ill health issues like depression and anxiety, or are non-pharmacological solutions a better alternative? This essay outlines the history of medication that was designed to treat mental ill health symptoms and how in many cases it has failed to provide the results it set out to achieve, and instead proposes an alternative to the treatment of such symptoms by looking at the human body and brain more holistically.

## The serotonin hypothesis

The scientific and reductionist study of human health through the 19th and 20th century enjoyed spectacular success. Vaccines eradicated entire diseases (polio); anaesthesia allowed for surgery, even transplanting entire organs; antibiotics meant survival from surgery and other bacterial infections; and chemotherapy has evolved to put some cancers into remission.

The brain is part of the body so we should be able to apply the same scientific principles, right? That's exactly what psychiatry has tried to do.

In many ways the scientific study of mental (ill) health and wellbeing was reductionist, at least initially. That's because we found that the brain was the centre of our mental life. We discovered that perhaps different parts of the brain did different things so fixing that part might help improve health and wellbeing. We discovered that perhaps there were chemical imbalances for which we could find pharmaceutical solutions for.

Enter the serotonin hypothesis of depression and anxiety (also sometimes called the monoamine hypothesis). This has been the mainstay of clinical psychiatry, at least for mood problems, for the past few decades.

At the most basic level, the neurotransmitter serotonin is hypothesised to be low in people with depression. Resolving this through drugs like SSRIs (Selective Serotonin Reuptake Inhibitors) could increase serotonin levels and influence mood and mental health.

The trouble is that meta-analyses of the clinical trials show a very small and probably not clinically meaningful effect, especially compared to the placebo control which has some positive effect too. It was Irving Kirsch's work, especially his 2008 paper "Antidepressants and the placebo effect"[1] which claimed through rigorous meta-analysis that:

> *"[...] analyses of the published data and the unpublished data that were hidden by drug companies reveals that most (if not all) of the benefits are due to the placebo effect. Some antidepressants increase serotonin levels, some decrease it, and some have no effect at all on serotonin. Nevertheless, they all show the same [small] therapeutic benefit. Even the small statistical difference between antidepressants and placebos may be an enhanced placebo effect, due to the fact that most patients and doctors in clinical trials successfully break blind. The serotonin theory is as close as any theory in the history of science to having been proved wrong. Instead of curing depression, popular antidepressants may induce a biological vulnerability making people more likely to become depressed in the future."*

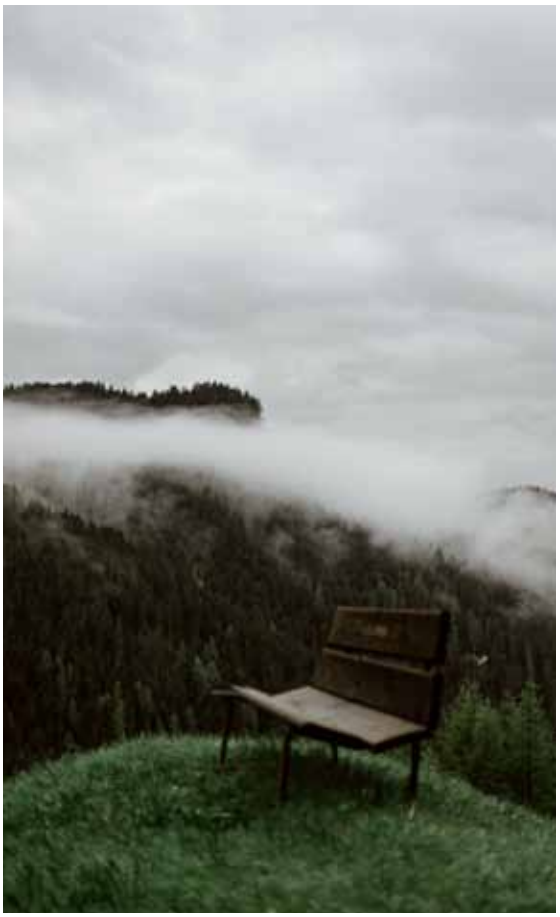
As you might imagine, Kirsch's work didn't land lightly. A new 2018 meta-analysis by Cipriani et al.[2] in *The Lancet* claims that:

> *"We found that the most commonly used antidepressants are more effective than placebo, with some more effective than others. Our findings are relevant for adults experiencing a first or second episode of depression—the typical population seen in general practice."*

The exact same data was reanalysed and published by another group in 2019 and they concluded that:

> *"The evidence does not support definitive conclusions regarding the benefits of antidepressants for depression in adults. It is unclear whether antidepressants are more efficacious than placebo."* [3]

A further review which again involved Irving Kirsch and meta-analysis expert Janus Jakobsen was published in late 2020 in *BMJ Evidence-based medicine*[4] which concluded that "*[the] benefits of antidepressants seem to be minimal and possibly without any importance to the average patient with major depressive disorder. Antidepressants should not be used for adults with major depressive disorder before valid evidence has shown that the potential beneficial effects outweigh the harmful effects*."



It is also questionable whether these drugs have any curative or long-term benefit, and they also cause some potential harm.[5]

Most of the side effects for adults are mild, but there are identified serious issues for adolescents and people 24 years of age and under.[6, 7] Boaden et al. showed in their 2020 paper that:

> *"Compared to placebo, selected antidepressants can be efficacious in the acute treatment of some common psychiatric disorders, although statistically significant differences do not always translate into clinically significant results."*

That's encouraging, yet the same analysis showed that there was weak evidence of increased suicidal ideation and attempt for one SSRI (venlafaxine).

A review of the evidence for suicide risk by the US Food and Drug Agency[8] has resulted in a black box warning on some SSRIs around the increased risk they pose to suicidality. They concluded that "[…]*there was a small increased risk of suicidal thoughts or behaviour in children and adolescents taking antidepressants compared with placebo (risk ratio 2.0, 95% CI 1.3-3.0)*." This now includes notes that depression of itself is the most important determinant. (It's worth noting that a risk ratio of 2.0 means double the risk.)

## Newer science points to non-pharmacological interventions

If serotonin isn't the answer, what is? Is there even a scientific answer to brain and mood health? Newer science shows robust clinical and subclinical effects of non-pharmacological interventions.

In other words, there is strong evidence of things that work to improve brain health that aren't drug-based. These work on depression and mental wellbeing, and across a range of other brain and mental health issues, from anxiety to Alzheimer's disease. They also have few negative side effects and many other positive effects on the body.

For these reasons, most countries, including Australia and New Zealand (from the NZ Best Practice Clinical Guidelines for depression)[9] recommend non-pharmacological interventions as the 'go to' for best practice (Table 1).

**TABLE 1: Best practice guidelines for depression treatment**

1. Non-pharmacological interventions are essential in the management of patients with depression and should be continued if medicines are initiated.
2. Anti-depressants are generally reserved for patients with moderate to severe depression.
3. There is little evidence separating the classes of antidepressants in terms of efficacy; adverse effects, safety and patient preference are used to guide treatment decisions.

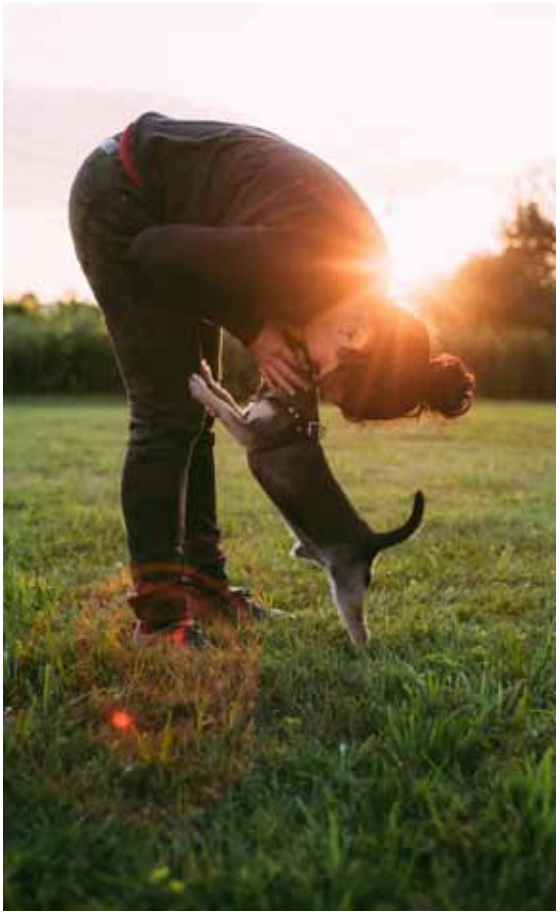
Non-pharmacological interventions for depression are centred on building mental strength and resilience. These include:

1. Cognitive behavioural therapy
2. Relaxation techniques, e.g. mindfulness
3. Education about depression, e.g. depression is not a sign of weakness; it is a serious medical condition experienced by one in six people at some stage in their life
4. Social support from whānau/family and friends
5. Maintaining cultural, religious or spiritual connections
6. Regular exercise, including group activities
7. A healthy diet
8. Addressing alcohol or drug intake
9. Sleep hygiene

So, we are on track, at least with the guidelines. But in practice this isn't what usually happens. SSRI medications are still the first line treatment in many cases. And there is virtually no health infrastructure to help us eat better, sleep better, exercise more, drink less, and connect with others, including talk therapy.

To makes things more complicated, there isn't yet a coherent explanation as to why these different things are all effective either.

## The biology of wellbeing



Let's take a step deeper into biology and brain chemistry and attempt to explain why these all work. Let's move beyond the serotonin hypothesis of mood and create a more coherent explanation which tells us more precisely why sleep, exercise, nutrients, and other practices keep us well, and return us to health when we are out of whack.

Such an understanding is critical because the details matter. They inform us, convince us, and guide us into more and more detail about exactly what we should do, when, and for whom.

Firstly, let's remember that the brain is complicated … really complicated. For a start, it's not actually separate from the rest of the body. The brain takes and sends neural and hormonal signals to and from the rest of the body constantly. In every way, the brain extends throughout the body.

Secondly, the brain itself is a self-modifying distributed neural network capable of more processing and more complexity than any supercomputer. We have nearly 100 billion neurons, each synapsing with up to 7000 other neurons. Each synapse has a weighted strength of connection (like a probability gate) and often both excitatory and inhibitory connections. Neurons grow and are pruned off, and synapse connection and strength are constantly changing. This 'neuroplasticity' is how we think, decide, act, and feel.

Our wellbeing is biological. Formulating a theory that is simple enough yet complicated enough, but true across a range of scenarios, is the hard part. We are looking for parsimony.

Some would say this is the holy grail of physiology. Others say that it's philosophically impossible for something (our brain) to figure out how itself works.

Here's what I think the totality of the current (and evolving) science says. It says that there is a linchpin of the neurological system. It's the fine balance between the two neurotransmitters GABA and glutamate. It's called the glutamate hypothesis.

Understanding this could be the most important thing you ever do for your mental health and wellbeing.

## The glutamate hypothesis

By far the most prevalent neurotransmitter is glutamate. It is excitatory (as in, it is released when you are excited), and it is fine-tuned by an accompanying inhibitory neurotransmitter called GABA. GABA and glutamate act as a sort of neurological homeostasis. The levels do need to balance out.

The glutamate hypothesis refers to when glutamate gets over-released, and the GABA-glutamate homeostasis (or balance) is affected. It's not the only factor in brain health, for sure, but the evidence is that it is a central component of being mentally well.

Let's try to simplify what is a more complex, yet more scientifically coherent, theory of what keeps us mentally well.

Because glutamate is excitatory and directly related to excitement, when you are stressed it floods out. In evolutionary terms this was the occasional short burst of 'fight or flight' when the sympathetic nervous system gave you all the tools to survive in that few minutes when life was at stake.

In the modern world, our 'better safe than sorry' brain is biased towards ramping this fight or flight system up even when it isn't necessarily life threatening. This means that we can have this system turned up for hours, days, weeks, and even months at a time.

This, combined with our modern world which condones poorer sleep, nutrient deficiencies, ultra-processed food, low exercise and fitness, and poorer social connections, makes it hard to get the glutamate and GABA balance right.

How does that affect us? Well, when glutamate is constantly high, it over-stimulates a receptor on the next neuron called the NMDA receptor. This has two effects. First, that receptor starts to get dialled down (attenuated) and needs more and more glutamate to get activated. Second, all this extra glutamate spills over outside the cells. This glutamate is toxic and damages the nerves, synapses, and supporting cells (glial cells and astrocytes).

Under normal conditions, glutamate is needed to make GABA. This means that the process is circular and in constant flux of these neurotransmitters changing from one form to another, with glutamine an intermediate form. In other words, there are processes for managing glutamate and removing and recycling it in the brain when things are working as they should.

This whole process of the system getting out of whack, not cycling properly and glutamate getting too high, is called excitotoxicity [10].

## Glutamate excitotoxicity – a downward spiral

Glutamate excitotoxicity drives a physiological cascade with feedback which continues to make things worse and worse.

During glutamate excitotoxity, glutamate continues to be overproduced and continues to spill over. Sometimes cells end up dying and the high concentrations of glutamate inside the cell are released creating even more excitotoxicity, killing more cells, and releasing more glutamate … and the cycle continues.

So, what over-stimulates glutamate, reduces glutamate removal, or gets high glutamate around neurons?

Here's a list:

1. Chronic stress is excitatory.[11]
2. Psychological trauma is excitatory.[12]
3. Chronic inflammation[13] means glutamate cannot be removed easily. Glutamate is itself inflammatory. This could be caused by a high ultra-processed food diet (high glucose and insulin), nutrient deficiency (magnesium, and various others including zinc and Vitamins D and C), poor sleep, alcohol, stress, and lack of exercise.
4. Brain cell death through traumatic brain injury, ischemia (lack of oxygen to the brain) from a heart attack, stroke, or hypoxia at birth.[14]
5. Brain cell death through neurodegenerative disease such as Alzheimer's disease, Parkinson's disease, and multiple sclerosis. For other reasons, these all cause neuronal death and then the release of glutamate and this starts the downward spiral of excitotoxicity.[15]

Glutamate excitotoxicity is linked to causal effects in:

1. Depression and anxiety[16]
2. Diabetic retinopathy[17]
3. Neuro-cognitive issues including migraines and brain fog[18]
4. Epilepsy[19]

Glutamate excitotoxicity can exacerbate issues with the following:

1. Neuropsychiatric disorders including schizophrenia and bipolar disorder[20]
2. Neurodegenerative diseases including Alzheimer's disease, Parkinson's disease, and multiple sclerosis[21]
3. Neurotrauma, including TBI, stroke, and hypoxia[22]

## What can we do to reduce glutamate?

The following are thought to be protective or helpful in reducing glutamate by either helping with removal or reducing stimulation.

### 1. What we eat

Any nutrient which reduces inflammation in the brain is helpful to the glutamine-GABA balance. What is known to reduce inflammation?

- Antioxidants like Vitamin D, Vitamin C, and B complex vitamins[23, 24]
- Omega 3 fats, e.g. fish oil[24]
- Having ketones present in the brain[25]
- Keeping blood sugar and insulin under control, which usually means not eating too much ultra-processed food, and avoiding refined carbohydrates
- Avoiding MSG (monosodium glutamate) which can directly raise glutamate levels[26]
- Avoiding the artificial sweetener aspartame[27]
- Alcohol can stimulate GABA acutely in small doses, giving a calming feeling, and is implicated in neuronal damage in chronic high use through glutamate excitotoxicity (although this is controversial).[28]
- Magnesium (which we will come back to later) is an NMDA receptor antagonist. This means it stimulates the receptor site for glutamate. Paradoxically this works because too much glutamate tells the receptor to dial down its sensitivity to glutamate and you produce even more to get the signals across. Magnesium has been shown to be effective in reducing mild to moderate depression well in clinical trials.[29]
- Non-steroidal anti-inflammatories have also been shown to reduce depression in several consistent clinical trials.[30] Remember, lower inflammation means better glutamate levels, which can help move us out of a vicious cycle.

### 2. How much we exercise

Exercise is a highly effective mood modulator. It is also highly effective and curative in managing brain health, including depression and anxiety.

There are several plausible ways this could happen, which modulates the glutamine-GABA balance.[31]

- Aerobic exercise is anti-inflammatory.
- All exercise helps improve glucose and insulin sensitivity.
- Exercise helps produce high levels of BDNF in the brain. This improves neuroplasticity,
  a process reduced by high glutamate.

### 3. Sleep

Sleep is anti-inflammatory. Deep non-REM sleep activates the glymphatic system which removes waste products and reduces inflammation in the brain. Good sleep is the cornerstone of a healthy brain. Sleep deprivation induces glutamate excitotoxicity in the brain.[32]

### 4. Cold

There is evidence that cold water immersion is effective in changing mood and reducing anxiety and depression. A reason for this may be because this cold exposure upregulates glutamate removal.[33]

Consistent with this is how patients who have suffered brain damage are treated.[34] For example, you might lose some brain cells through a traumatic brain injury, a stroke, a heart attack where you lose oxygen in the brain, a spinal cord injury, or hypoxia at birth. Interestingly, a common treatment in intensive care units across all these conditions, is induced hypothermia with magnesium infusion. These are effective in reducing the ongoing cascade of extra cell death through glutamate toxicity. The cold helps reduce and remove glutamate, and the magnesium helps reset the glutamate receptors. Without such intervention the newly dead brain cells release glutamate which kills more cells, and the downward spiral means a worse outcome from an already bad situation. An induced coma with an ice blanket is therefore used to get the body temperature down to 30-32C.

### 5. Being calm

Fixing the sympathetic fight or flight response is often quite easy. Breathing slowly and deeply through the nose results in the baroreflex being invoked. The baroreflex simply means that slow, deep nose breathing turns the sympathetic nervous system off.[35]

This breathing technique reduces glutamate transmission and increases GABA. It's actually that simple.

### 6. NMDA receptor antagonists

If glutamate-GABA balance is a linchpin and causal in brain health, then drugs which help return the receptor to normal should have an immediate effect on symptoms. Ketamine, a drug in anaesthesia and also an NMDA receptor antagonist, has been shown to have an immediate effect on even intractable major depressive disorders.[36]

Psychedelics like LSD, MDMA, and Psilocybin are also NMDA receptor antagonists. This may be part of the reason they are promising as single treatment effects on long-term depression and other psychiatric issues. They have other brain effects as well, including widespread neuroplasticity, which might be hard to separate. At this stage it's hard to tell exactly how these drugs impact the brain, but it's interesting to follow this space.[37]

### 7. Oestrogen

It's a curious thing that women are almost twice as likely to experience depression and anxiety as men. The same is true for Alzheimer's disease. But men have more schizophrenia, autism and ADHD.

It may be to do with how we process glutamate in the brain, along with different parts of the brain. Do glutamate system differences explain this?

Women have higher blood glutamate levels than men in general, and they get worse at clearing them as they age compared to men. However, women with good levels of oestrogen may have superior stress coping mechanisms.

One reason is how women use oestrogen to help manage glutamate and transport it into astrocytes for conversion to glutamine, then to GABA. It's long been known that men and women have some different pathways in stress management.

For women, oestrogen is neuroprotective. That's a known scientific fact. Low oestrogen is a risk factor for depression, poor brain health, including Alzheimer's disease, and brain fog. It's highly likely that the major positive effect of oestrogen in the brain is helping balance glutamate and GABA through facilitating the NMDA receptor function, which helps better balance glutamate and GABA and enhance neuroplasticity, learning, memory and mood.

Let's think about some scenarios in women's lives when oestrogen is low:

- Straight after giving birth. Depression and anxiety are low during pregnancy when oestrogen is high, and postnatal depression is associated with higher levels of glutamate in the medial prefrontal cortex.[38]
- In the three days prior to menstruation in normal cycles. This is consistent with PMS and the more serious PMDD which are associated with abnormalities in the glutamate system.[39, 40]
- Oral contraceptives may upset the normal oestrogen and progesterone cycling and therefore the glutamate-GABA system balance. This may be one reason a prospective study of more than a million women on oral contraception showed a 23% higher rate of antidepressant prescription.[41] It's also likely that early (adolescent) use of such contraception may be an added risk factor.[42]
- Oestrogen and progesterone levels can change rapidly throughout peri-menopause and drop right off into menopause. Glutamate excitotoxicity is a plausible reason for both the symptoms of brain fog during the perimenopause, and why hormonal replacement therapy is protective against Alzheimer's disease development in post-menopausal women.[43]

## Bringing it all together

Non-pharmacological solutions to mental ill health work together to make the human brain feel and function better. For example, eating better helps you sleep better, but a good night's sleep helps you make better food choices and be more likely to exercise. Exercise makes you tired and you will sleep better. Exercising outside lifts Vitamin D levels and properly regulates melatonin, the sleep hormone, which helps everything in your brain.

One way of getting the best bang for your buck is to package up activities together and to do several of the things that are helpful for reducing glutamate in the brain at once.

You might decide exercise is really going to help you. But what about doing it outside and with someone else, and choosing an activity and place that really brings you joy (like a walk at the beach with your best friend)? How about trying some cold water immersion, but practicing your nose breathing and positive mantra at the same time?

The more non-pharmacological interventions that support mental health you can implement in your daily life, the healthier and more resilient your body and mind will become, and the more other positive benefits you will enjoy. Instead of immediately resorting to medical intervention which may or may not work, why not consider a series of non-pharmacological interventions that can work together to give you an array of benefits? Your mind, body and soul will thank you.

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