HMNC Brain Health

Tailored Depression Therapy - The Future is now

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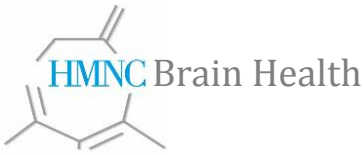

Florian Holsboer

The last two decades have seen a dramatic increase in public awareness of psychiatric disorders leaving us with the conjecture that depression and anxiety are modern times maladies. Whether they really increase is hard to know since we have no accepted laboratory measures. To make a diagnosis objective we must rely on verbal information.

What we can say proudly is that the fight against stigma and discrimination was successful and today many more people than in the past are accepting and communicating their psychiatric diagnoses.

What we also can say is that depression has to be taken very seriously. Depression has many socio-economic consequences let alone the individual suffering and the elevated risk for other diseases. And most importantly, depression is a potentially lethal disease, every year around one million people worldwide die from suicide.

Depression facts

Depression

is becoming the leading socio-economic burden in industrialized countries

and other mental brain disorders are the leading source of years lost to disability from ALL medical causes

is a risk factor for cardiovascular disorders, diabetes and dementia

is a potentially lethal disease, with 800.000 – 1 Mio suicides each year globally, nearly all of which are a consequence of a mental brain disorder (in Germany: 1-2 suicides every hour, 24/7)

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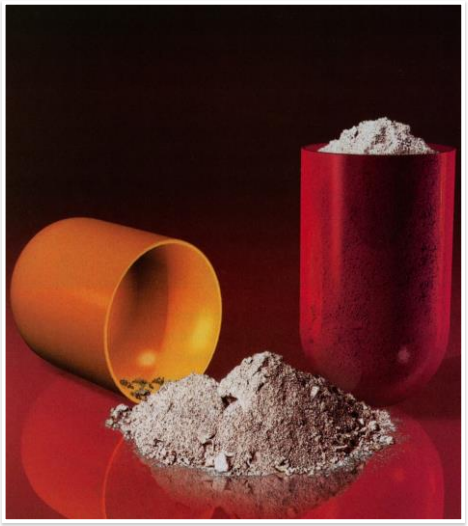
What is strange about depression, is that basic and clinical research have despite all efforts – not elucidated the mechanism that causes depression.

Despite that, we have treatments that work. In severe depression antidepressants are the first line treatment, and whenever feasible combined with a pragmatic form of psychotherapy.

Antidepressants are the first-line treatment of depression



- **Some patients have difficulty to accept that depression treatment need drugs**
  Antidepressants given to the right patients at the right dose in combination with augmentation result in 60-70 percent remission
- **But:**
  - It takes **too** long until they work
  - They work in **too** few patients
  - They have **too** many side effects
- **And:**
  Their mechanisms differ not fundamentally from each other.

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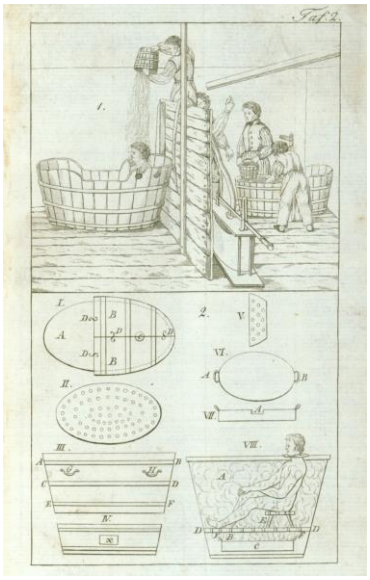
It is a sobering fact that patients are often reluctant to accept the physical or biological nature of their disease. Natural sciences may be successful in explaining a disease mechanism; they not even attempt to resolve the meaning of a disease for the individual. Patients ask the question of meaning and purpose of their individual disease. They are reluctant to consider their individual suffering as a deviation from the norm.

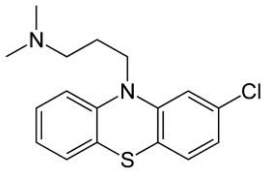
This general consideration that strongly demands a departure from a "one-size-fits-all" treatment is complemented by a number of other disadvantages in practice: it takes too long until antidepressants work, they work in too few patients and they have too many side effects.

Physical therapies in lunatic asylums

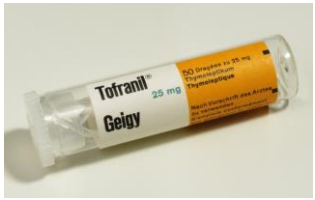


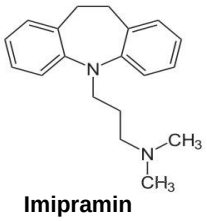
Nevertheless, the advantage of current treatments over treatments up to the 19th century is tremendous: 200 buckets of cold water were poured over the heads of the poor patients that were fixed in a bathtub. And even more brutal: patients were put in a kind of centrifuge and whirled until they felt giddy and vomited.

Imipramin – unexpected success of a "me-too"-drug in the 1950ies

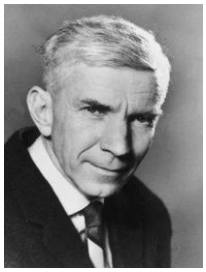


Chlorpromazin





Imipramin



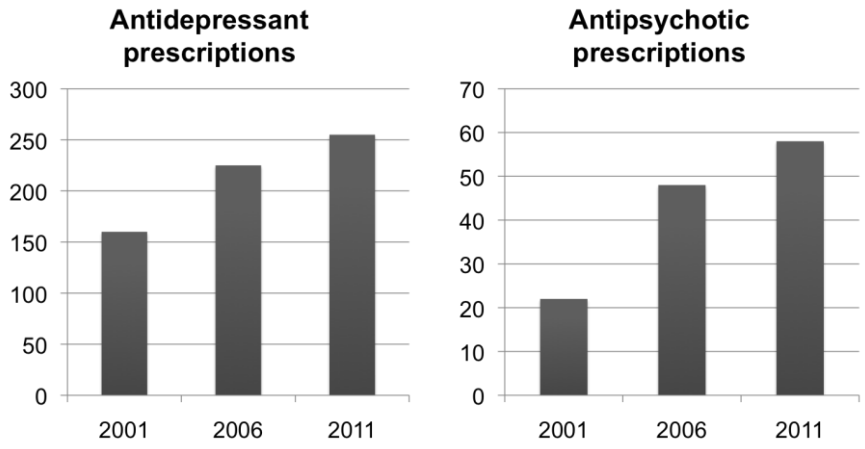
Roland Kuhn (*1912 - †2005)

Jules Angst (*1926)

The field had to wait until two Swiss psychiatrists, the late Roland Kuhn and Jules Angst, discovered that a drug called imipramine is an effective antidepressant. Up to now, all antidepressants that are prescribed follow the mode of action of this first antidepressant that is to enhance the signaling of certain transmitters such as serotonin between nerve cells.

Why am I telling you this? It is important to note that both clinician scientists knew nothing about specific gene variants underlying depression and at that time serotonin as a relevant transmitter was unidentified. It was careful clinical observation and smart interpretation by highly experienced, wise clinicians. These drug and all the followers changed our field radically. One important and most obvious result was a dramatic drop in suicides. We may ask what will be the next breakthrough, the next revolution in our field. Or, is there no need for that, is everything fine. I tell you upfront: I don't think so.

Treatment of mental disorders has increased over past 10 years



Millions of prescriptions in US market

Antidepressant prescriptions are increasing, so are those of antipsychotics that are often used to augment antidepressant effects.

Most big pharma companies have left depression R&D

Increased acceptance of mental disorders

→ **Markets grow**

Despite increased prescription

→ **Revenues decrease**
Market saturation with generics

Preclinical studies not predictive

→ **Too late moved to humans**

Late development failures

→ **Failed studies, not negative studies in phase III (needed for approval)**

In the light of this, it is surprising that most of the big pharmaceutical companies have left research and development of antidepressants. While markets grow, revenues decrease, because the markets are saturated with generics, that is drugs that have lost patent protection.

What has happened? There are two main scientific reasons: One is that the animal models used in basic science are not predictive for antidepressant effects in human. The other clinical reason is more complex: New drugs that were developed and were targeting more specific mechanisms were tested as if they would become new age blockbusters.

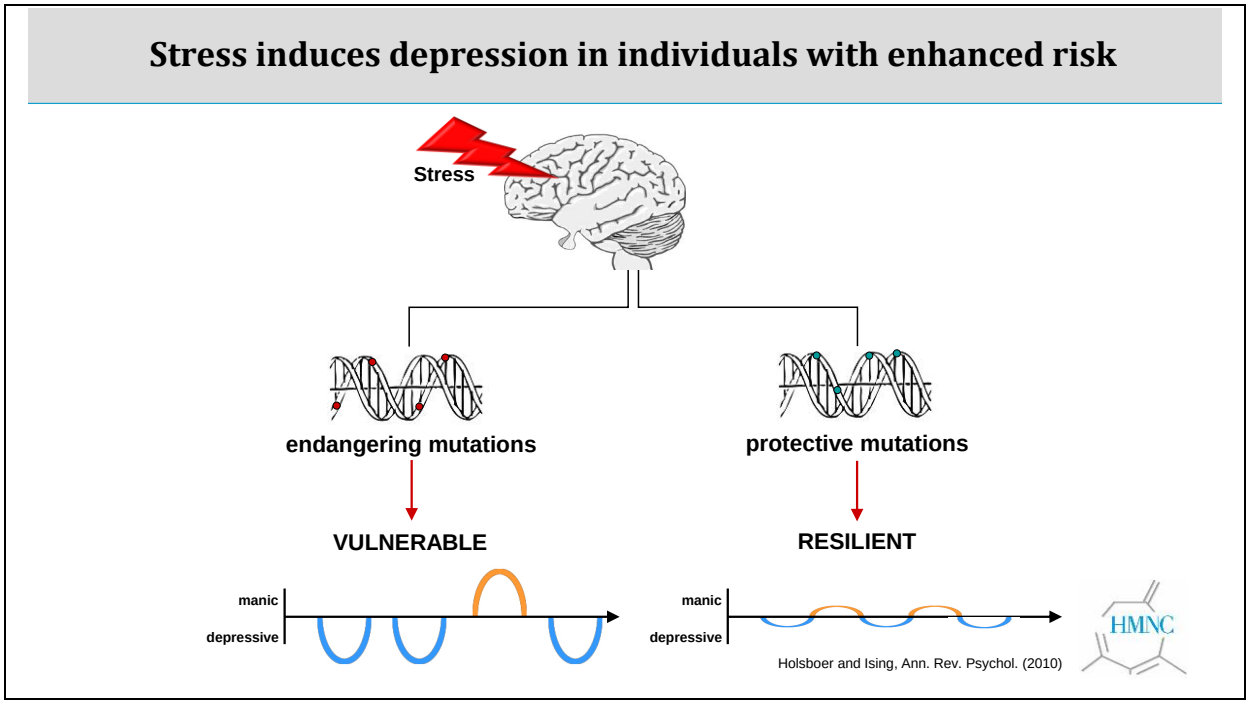
The problem of that strategy is obvious. If you do not know the exact mechanism that underlies your depression, you better take a drug that is unspecific and works on all possible pathways. Only if you know, which specific mechanism underlies the depression in an individual patient a specifically acting drug is superior to an unspecific drug. “The more specific your drug is, the more you need to know about your individual patient” that is the fundament of tailored medicine.

The field has seen a myriad of studies with new specific drugs, but all the trials were negative, that is, the new drugs were not superior to placebo. In reality the studies were not negative but failed, as they failed to stratify the patients according to their underlying mechanism

Impediments for innovation in antidepressant research and development

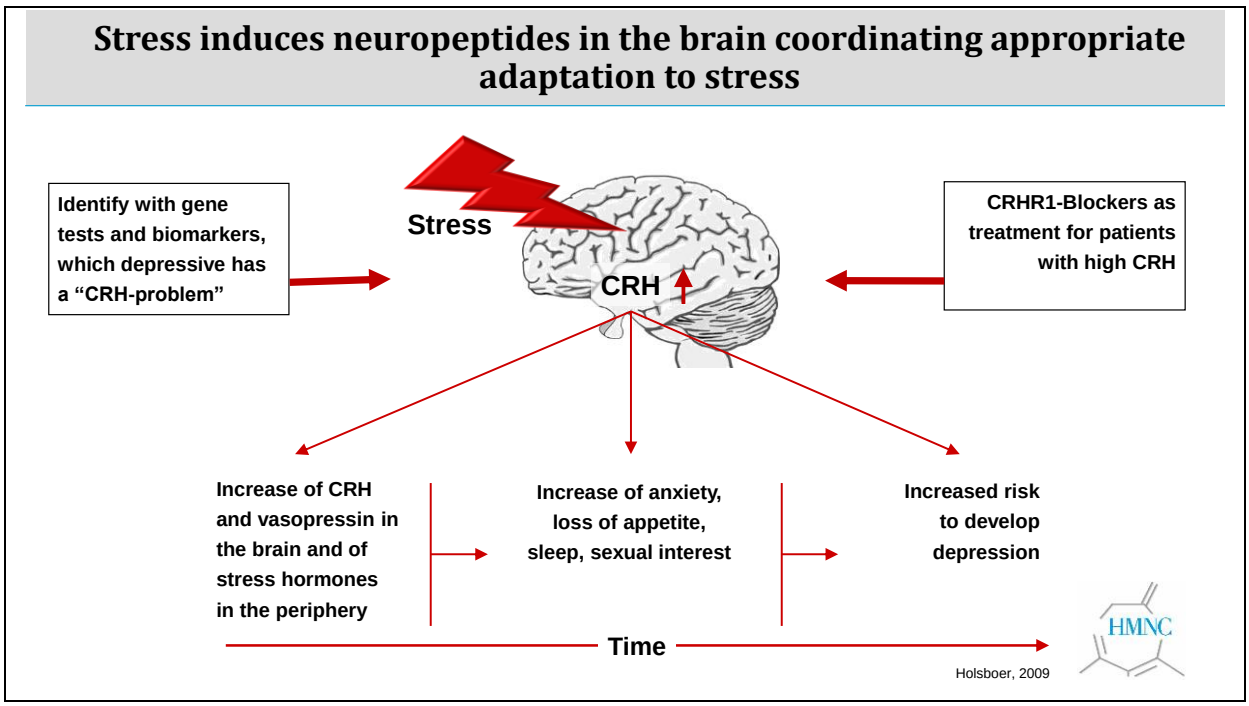
- **Economic success:**
  - **Phenomenal returns of investment in the past**
  - **20 billion Euro per year in 2005**
    - → **Risk aversiveness**
    - → **Adherence to blockbusters**
- **Therapeutic drug unspecific:**
  - → **„One size fits all”**
- **Diagnostic uncertainty:**
  - **Diagnosis based upon verbally transmitted information**
  - **DSM V does not contain neuroscience**
    - → **Diagnoses unspecific**

Other impediments were related to this failure but more on the economic side. They relate to the risk aversiveness because of the phenomenal returns in the past, and also to our inability to apply biomarkers that allow to attribute the right drug to the right patient. That is already possible in other medical specialties, primarily in oncology where diseases like leukemia can be broken down with biomarkers to a number of mechanistically different diseases that respond differentially to diverse drugs.



How can psychiatry catch up with oncology?

From my view, the most promising repository for innovative drugs is the stress hormone system. We all know that we respond differentially to stressors. Some patients that carry genomic risk factors are susceptible to depression when exposed to enduring stress. Others have changes on their genome that make them resilient. These are not likely to get a stress-induced depression. But it cannot be ruled out that they nevertheless get a depression. The underlying mechanism in this case would be different from that among stress-susceptible patients.



With gene tests and biomarkers, we are currently able to separate patients where stress hormones play a causal role for depression from those where the stress system plays no role.

One prominent candidate is a so-called neuropeptide whose long name we abbreviate with CRH. This molecule is produced in the brain and is the master hormone that coordinates behavioral and metabolic adaptation to stress. If stress endures, a CRH-dependent depression emerges and here - and only here – a CRH-blocker would be the right drug.

In all past studies with CRHR1-blockers this possibility, that is the objective identification of those where CRH is causing the disease, was missed. It was given to everyone with depression. The result was that outcome of the studies was negative and further development was put on hold.

In the wake of this disappointment, the future of personalized, individualized or precision medicine was challenged culminating in the question: can society afford personalized medicine for the individual?

Can society afford personalized medicine for the individual?

Yes, it can!

Common error: Personalized medicine is expensive, its added value for patients questionable and returns of investment for industry are poor

The truth is: Development of a „blockbuster“ is extremely expensive and failed for the last decade

Development of personalized medicine is much less expensive, because phase III trials are different, requiring less patients

→ **High return of investment!**

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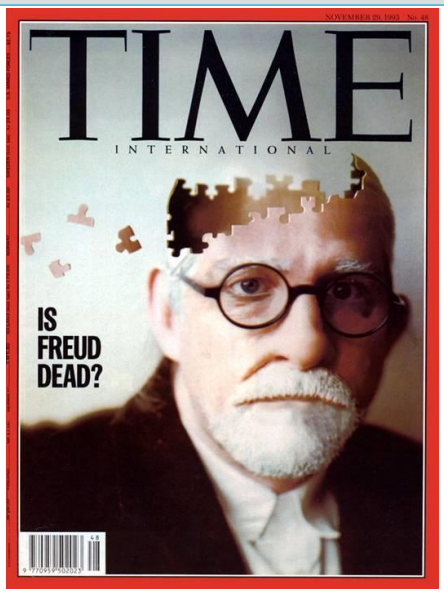
As outlined in that slide the straightforward clear answer is: Yes it can.

Individualized medicine is the departure from statistical medicine



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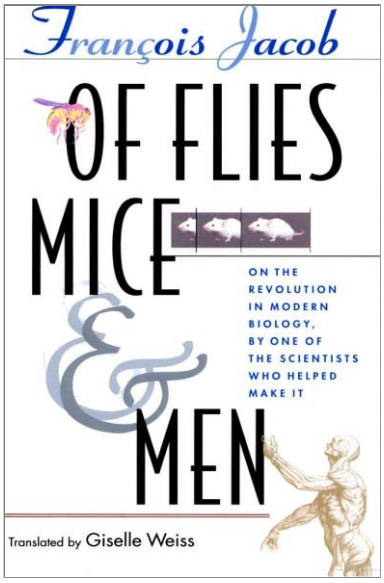
I said in the beginning that the individual patient and the practicing doctors became reluctant to accept that neuroscience-based discoveries for better treatments are also attending to patients individual needs. In fact, tailored, personalized medicine picks up some of Freud’s perceptions.

It takes on board the individual perspective, however, on the basis of neuroscience not on exploration of human mind. The most important change is that individualized medicine is the departure from “statistical medicine”, where patients assembled under a diagnostic category are viewed as being equal regarding causal mechanism and treatment condition.

Individualized medicine is also much more quickly addressing the ill human being and discourages endless sticking to animal experiments.

Depression in animals?



„Research is the art to solve a soluble problem“

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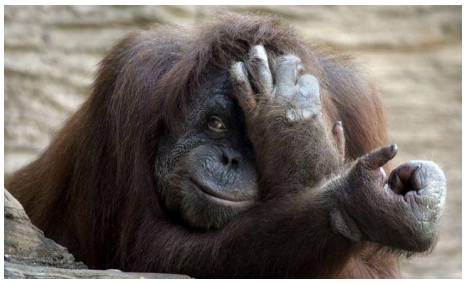
It is understandable that the young scientist interested in such complex behavioral traits as depression, but having a time-limited contract during which he has to finalize a doctoral thesis is also interested to complete his work in the given time. The eminent scientist François Jacob addressed that in a wonderful book “Of flies, mice and men” and concluded “research is the art to solve a soluble problem”. A complex trait in a mouse clearly seems to be more easily resolved than human depression and that is one reason why we see overabundant animal experiments targeting depression.

Do animals suffer from depression?



We learned the hard way that extrapolation of „depression-like“ behavior from animals to humans is of limited value for understanding causality and discovering new treatments

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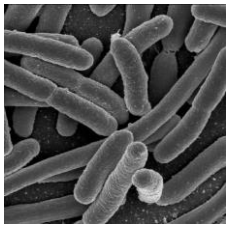
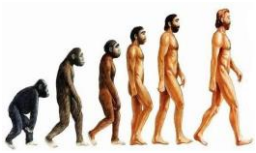
In fact, we learned it the hard way that extrapolation of “depression-like” behavior from animals to humans is of limited value. That includes unfortunately discovery of innovative treatments.

The DNA → Protein dogma

„What is true for E. coli is also true for elephant“ **... and human,**

Jacques Monod (1975)





It is (unfortunately) not that simple

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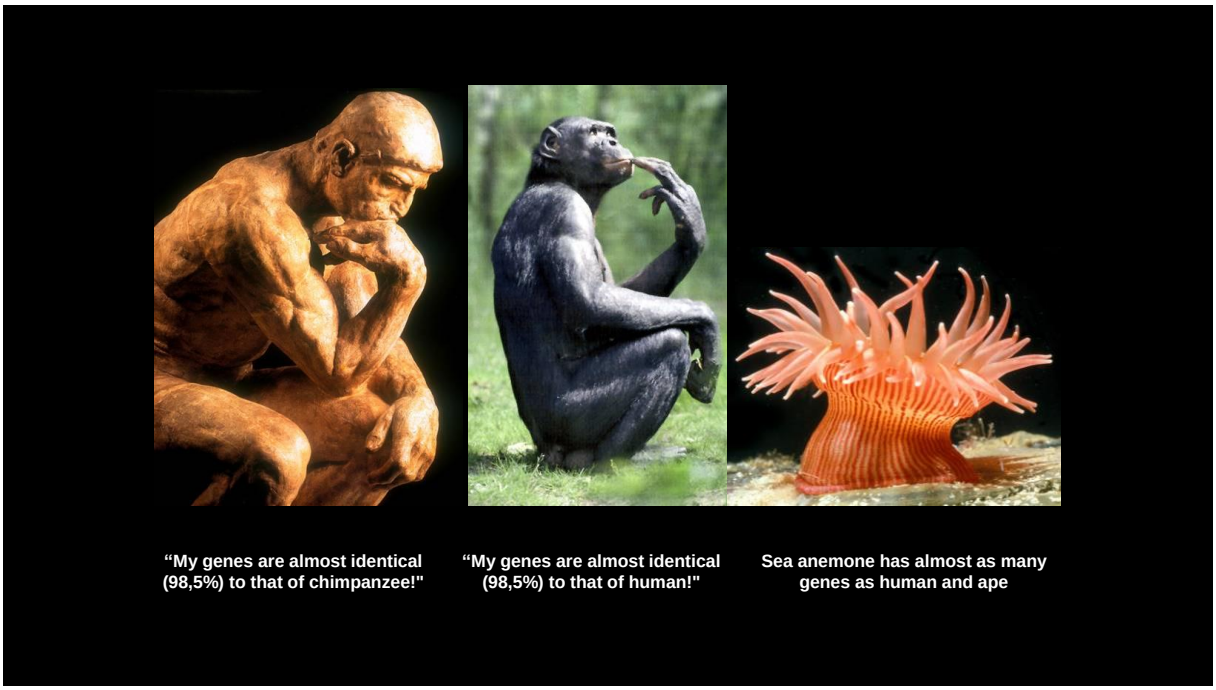
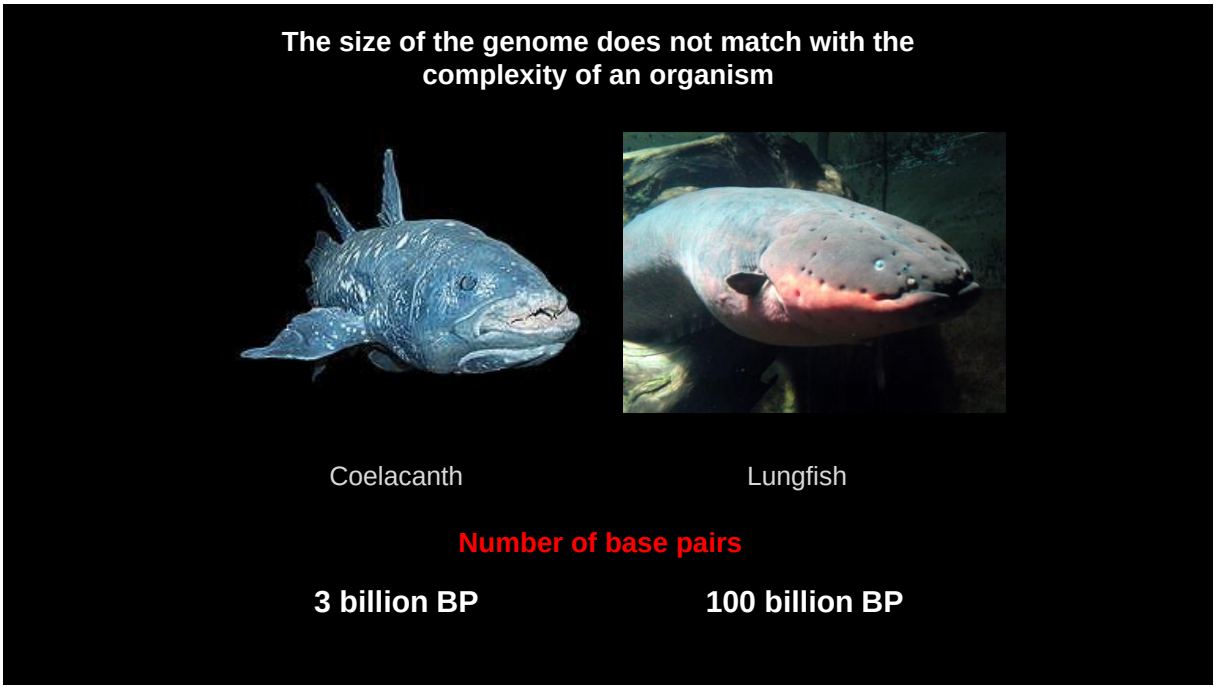
Also the dogma from the famous Jacques Monod: “Anything found to be true of E. coli must also be true of elephants”. This has lead us astray and we see many studies in worm, fish, fly and mice published in prestigious journals with little meaning for clinical science and practice.

Currently we witness the genomic revolution, every day we learn about newly discovered genes that help us to understand, why we are how we are, what helps us to stay healthy and which genes convey the risk to get sick. We also learned how complex the interplay between genes is and that genes contribute only a fraction to complex behavior.



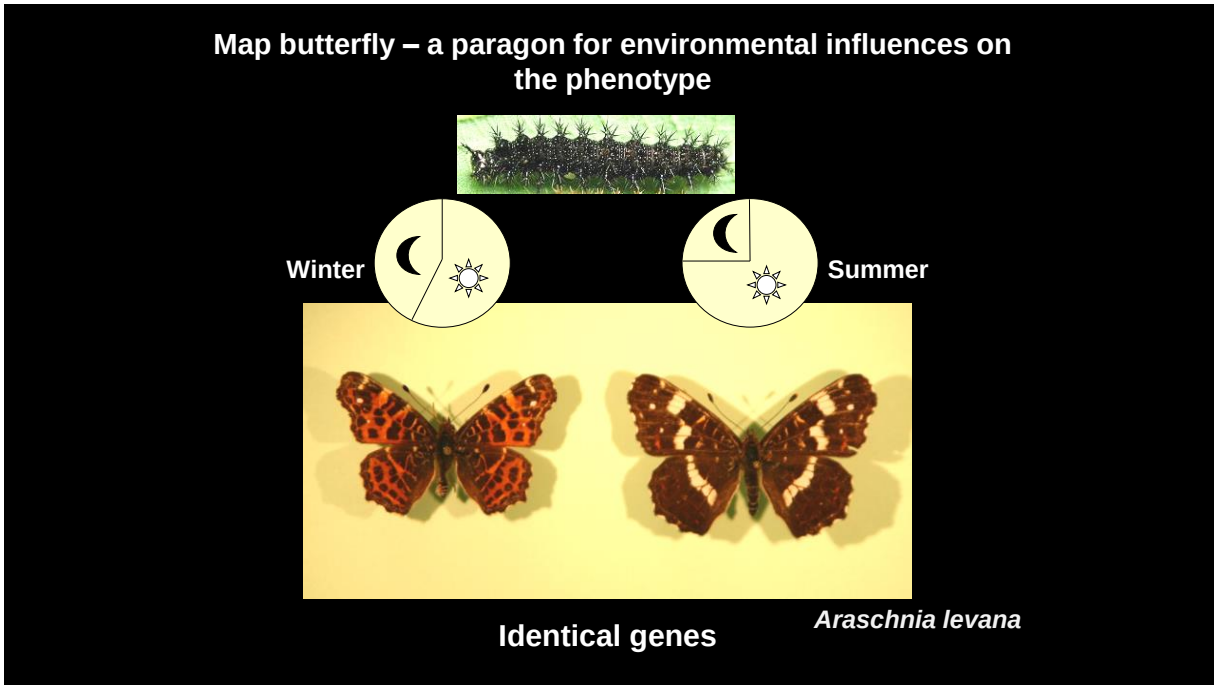
The genetic endowment of a chimpanzee is not much different from human. The fact that the seeanemona – not bigger than a fingertip – has as many genes as human and ape is surprising and a bit disturbing.



The famous fish coelacanth which has not changed the phenotype over millions of years has as many base pairs on his genome as the human. The lungfish, the fish predating all animals that walk on land has a genome comprising not less than 100 billion base pairs. Remember the human has only 3 billion base pairs.

Apparently, the sheer number of genes is not very informative and we should not be too gene-centric.

I mentioned that genes do not act alone and our phenotype, the observable characteristic of our organism is at any given time resulting from gene-environment interactions, which we are only beginning to understand.



That is why I am showing you this picture of a little butterfly that looks totally different in winter and in summer. The only factor that changes over time are seasons. The genes have not changed but the environmental effect on the phenotype is huge.

That again is a reason why extrapolation of animal experiments to humans are of limited value if we deal with such extremely complex traits as depression. That slide gives you a few facts on the human brain that illustrates its uniqueness.

Brain Facts

The human brain

contains 90-100 billion nerve cells, where each cell interconnects with other ten thousand cells

has so many neurons that when put together would result in a string of 5.8 million kilometers (145 turns around the globe)

has a cerebral cortex that is much more complex than in any other animal, possibly due to a human-specific gene.

is crossed by small blood vessels at a total length of 640 kilometers

weighs 1.5 kg, but burns up 20% of all energy we consume

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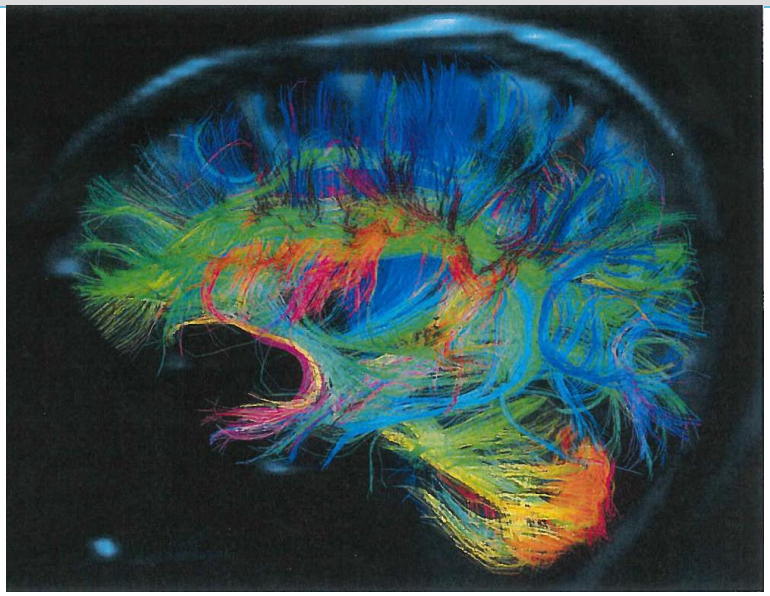
These facts also explain that it is not only the apparatus of individual nerve cells that makes us so unique. It is the resulting connectivity between cells that determine our phenotype, the risk to get ill and the way we respond to a given drug.

What makes the human brain unique?

From brain health to brain disease



From connectivity to dysconnectivity

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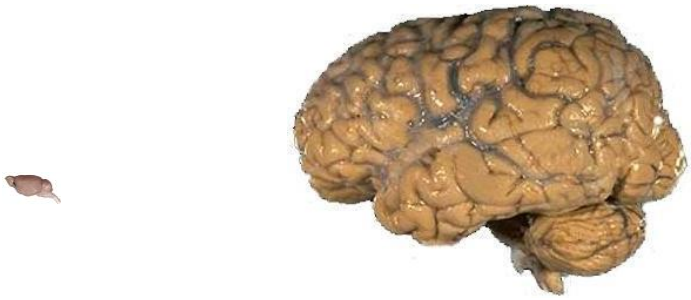
The consequences become also obvious when looking at the different brain sizes, especially that of the cortex, the area where we suspect that most of the neuropathology of depression takes place. Having shown you all these complexities you may ask: will we ever be able to understand how the human brain works.

I am skeptical and believe a full 1:1 understanding of our human brain with our human brain is illusionary.

However, any pessimism that we will be unable to translate certain neuroscience findings into clinical practice is totally inappropriate.

Brain size differences between mammalian species are enormous

Mouse	Human
0,4 g, 70 million neurons	1500 g, 90 billion neurons

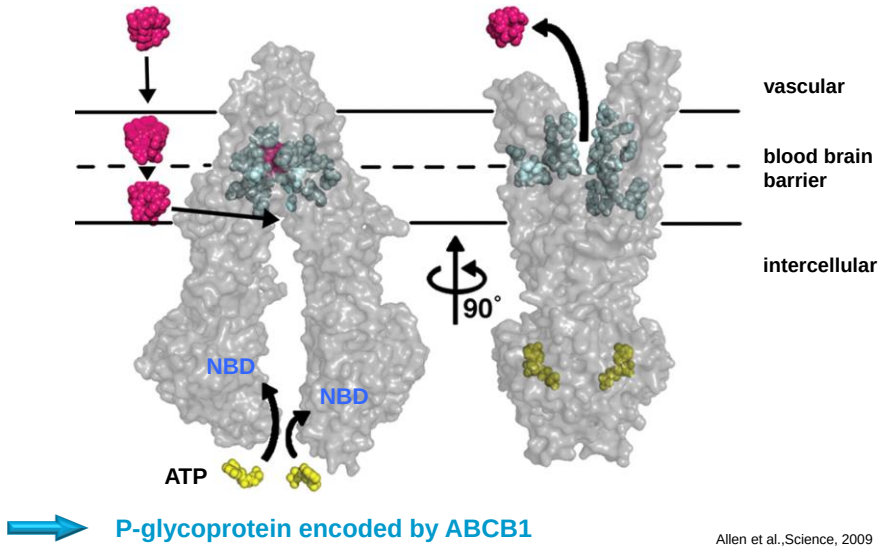


Human vs mouse > 1000- fold difference in size and neurons

In the last few moments of my discourse I will share with you an example that tailored treatment of depression is not something that occurs in remote future, it is happening right now:

Our brain is crossed by capillaries at a total length of 400 miles, essential to provide sufficient nutrients. Remember the brain, not more than 1.5 kg in weight burns up 20% of the energy we consume with eating and drinking. The brain is not able to regenerate in a way we know it for example from our skin. Therefore, it has to protect itself from all possible endangerments. One such protective mechanism is carried out by molecules that sit in the walls of the small blood vessels, where they act as “custodian” molecules. Their task is to bind molecules which are “foreign” not belonging to the bodies physiological apparatus. Also antidepressants are “foreigners” caught by the ”custodians” and exported back into the blood stream.

Structure of P-glycoprotein reveals a molecular basis for polyspecific drug binding



Now comes the big thing: The molecules that work as “pump” preventing the entry of antidepressants into the brain are encoded by a gene which we name ABCB1-gene. That gene may vary from patient to patient. This variance determines the efficiency of the “custodian” molecule. In other words: there exist gene variants were the “custodian” molecules are very efficient. In this case less antidepressant can enter into the brain. These patients respond much worse than other patients that carry a gene that makes an inefficient “custodian” molecule.

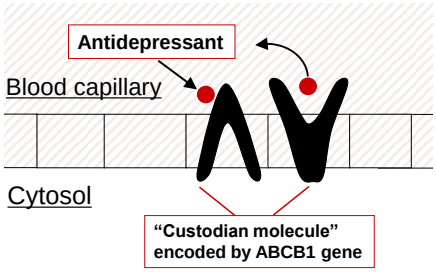
The twist in the story is that not all antidepressants are recognized by the “custodian” molecule in the same way. An antidepressant that is recognized by the “custodian” may not sufficiently work if the “custodian” is very efficient. A drug that is not recognized might be the better alternative. The consequences are enormous. For the clinician, this is the first time in psychiatry that a gene test allows to make a decision with huge clinical impact. Today I am happy to announce that this test is now on the market in Germany and soon also in Switzerland.

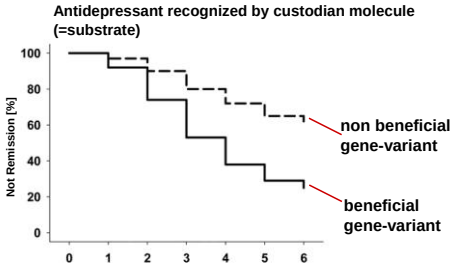
To cut a long story short: The patient benefits that he receives the right drug at the right dose and responds much earlier than with a randomly chosen drug. The doctor benefits, because he is informed how a genotype-based therapy can maximize treatment outcome and minimize side effect. And last but not least, the insurance companies benefit because patients have shorter depression episodes, and less days of sick leave.

Moreover studies showed that the genotyped patient has less risk to relapse into a new depressive episode.

That success was enabled by a joint effort of the Max-Planck-Society and our company, which I now represent after more than 25 years at the helm of the Max-Planck-Institute of Psychiatry.

Genotype of the „custodian molecule“ determines clinical efficacy of antidepressants





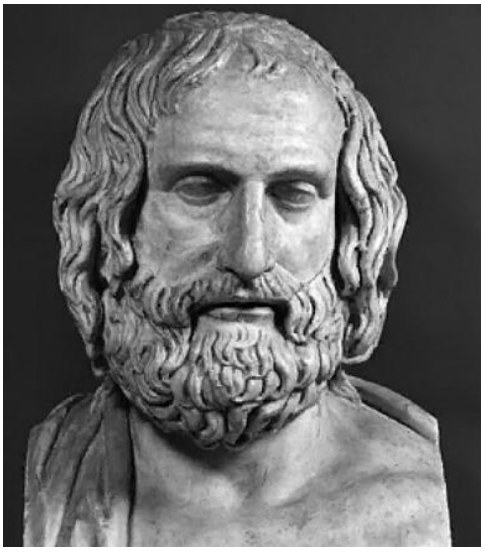
Custodian molecules prevent penetration of many chemical compounds into the brain

→ **also of many antidepressants**

An ABCB1 gene test informs about efficiency of custodian molecule (P-Glycoprotein)

→ **The more efficient the custodian molecule the less efficient the therapy**

The key message here again is that this success was only possible because we closely adhered to the human patient, following the statement by Protagoras 2500 years ago: “Man is the measure of all means”.



MAN IS THE MEASURE OF ALL MEANS

Protagoras (490-411 B.C.)

THANK YOU FOR YOUR INTEREST!