# Wetware Hacking or Artificial Means of Cognition Enhancement

# What is this talk all about?

- **There will be numerous and inevitable generalisations and assumptions**
- **I can't cover the entire vast area and will have to concentrate on its segments that**
  - **I had hands-on experience with, or interesting personal communications about, or can offer limited availability sources (mostly in Russian)**
  - **I prefer and like more than the rest :-)**
- **There will be quite a lot of «garage science» which has to be taken with a bit of salt but does, nevertheless, provide food for thought**
- **After all, «hacking» is in the title!**

# The overall problems/issues

- (mostly medieval) ethics and «fair competition» nonsense
  - See prof. Nick Bostrom's "Three Ways to Advance Science"
- Reluctance towards «healthy human pharmacology»/biophysical intervention
  - However, what is a (psychologically) «healthy human»? (test the audience!)
  - Are we evolutionary capable of handling the volumes of information we are immersed in nowadays whether we want it or not? Do we not suffer from a kind of «information obesity»?
  - Nootropics are presumed to be adaptogenic, ergo/acto and stress-protective!
  - In the USSR they were at the front-line of treating neurotic conditions, and for good reasons (and some substances classified as such do have weak anxiolythic or antidepressant effects)
- Grant-based vs state sponsored research funding
  - The key difference between «East» and «West»
  - Recent developments on nootropics research were funded by DARPA in the US — google for «The Night of the Living Meds»
  - Try getting a grant for anything to do with the «healthy human pharmacology» or equivalent

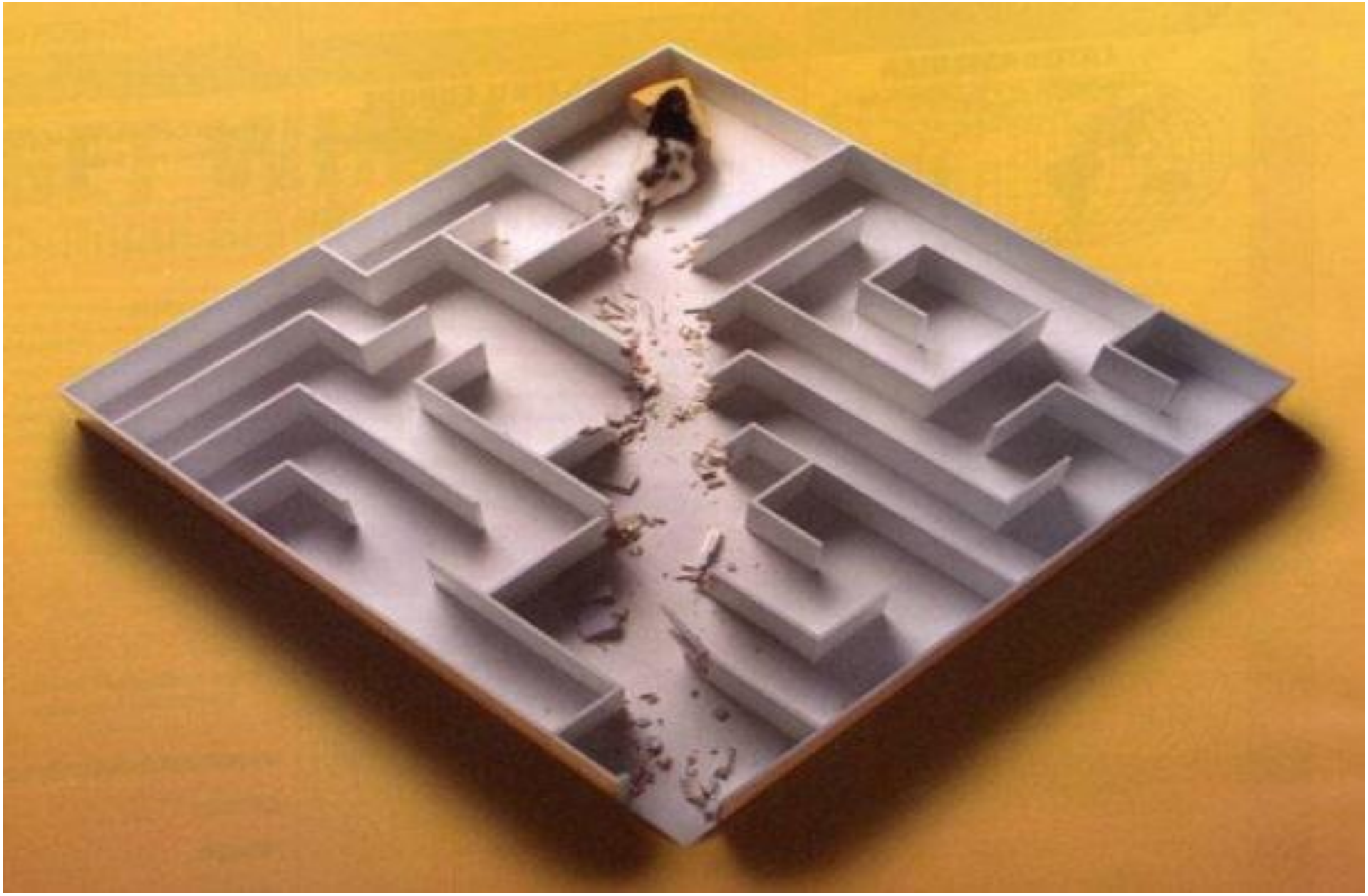
# «Philosophical» problems

- **How do we clearly define the criteria of being «nootropic»?**
- **In this talk, by «cognition» I primarily mean «learning and memory». To which extent do we include/exclude attention, concentration, motivation, anxiety, stress, fatigue and other emotional and "visceral" factors influencing it?**
- **Considering the complexity and numerous levels at which «cognition» can be looked at, how reductionist can we really get?**
  - **On the one hand, the issues in question can be reduced down to the Ohms law and similar basic laws of physics, chemistry and physiology**
  - **On the other hand, the estimated number of states of the neuronal network of human brain exceeds the estimated number of all elementary particles in the known Universe by more than a 100 orders of magnitude (V. I. Binhi, 2011)**
  - **«there is a huge «black box» between events at the molecular level studied in model systems and actual behaviour of the real cells or entire organisms» (Schmidt, 1961)**
  - **«functions of a higher system are not the sum of the functions of the lower systems it consists of, but their integration. Every higher system has its own qualitative uniqueness created only by the organisation of this higher system" (Schmalhausen, 1964)**
  - **NEVERTHELESS, A MODEL SHOULD BE SIMPLE ENOUGH TO BE USABLE**

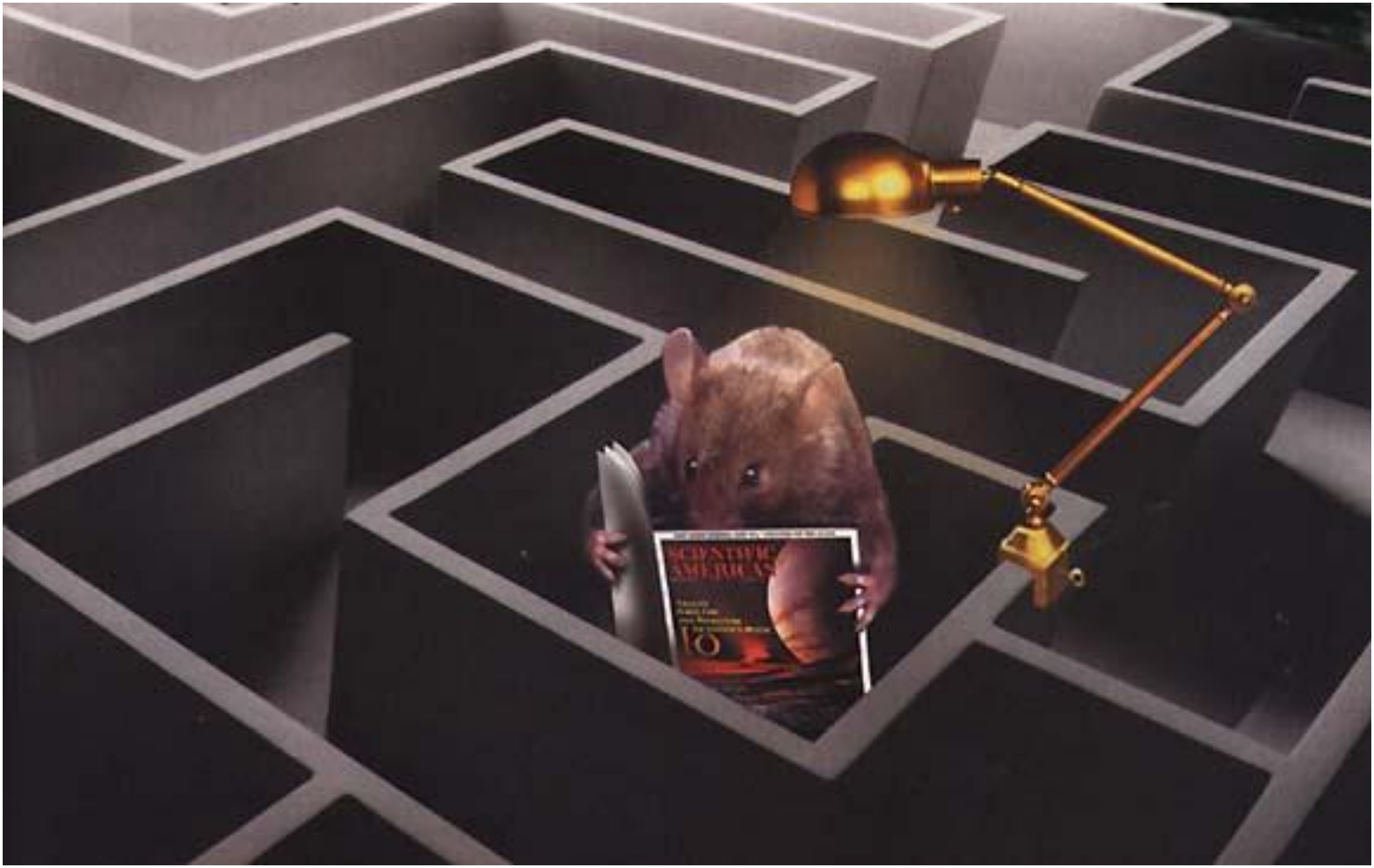
# «Technical» problems

- Transfer from in vitro models to in vivo
- Transfer from animal models to human
- Transfer from dementia etc. patients to healthy humans and vice versa
- Objectivity and specificity of psychological tests
- Lack of fully objective physical/chemical correlates
- Modeling memory/learning insufficiency
- Taking into account age, gender, individual differences and environmental conditions

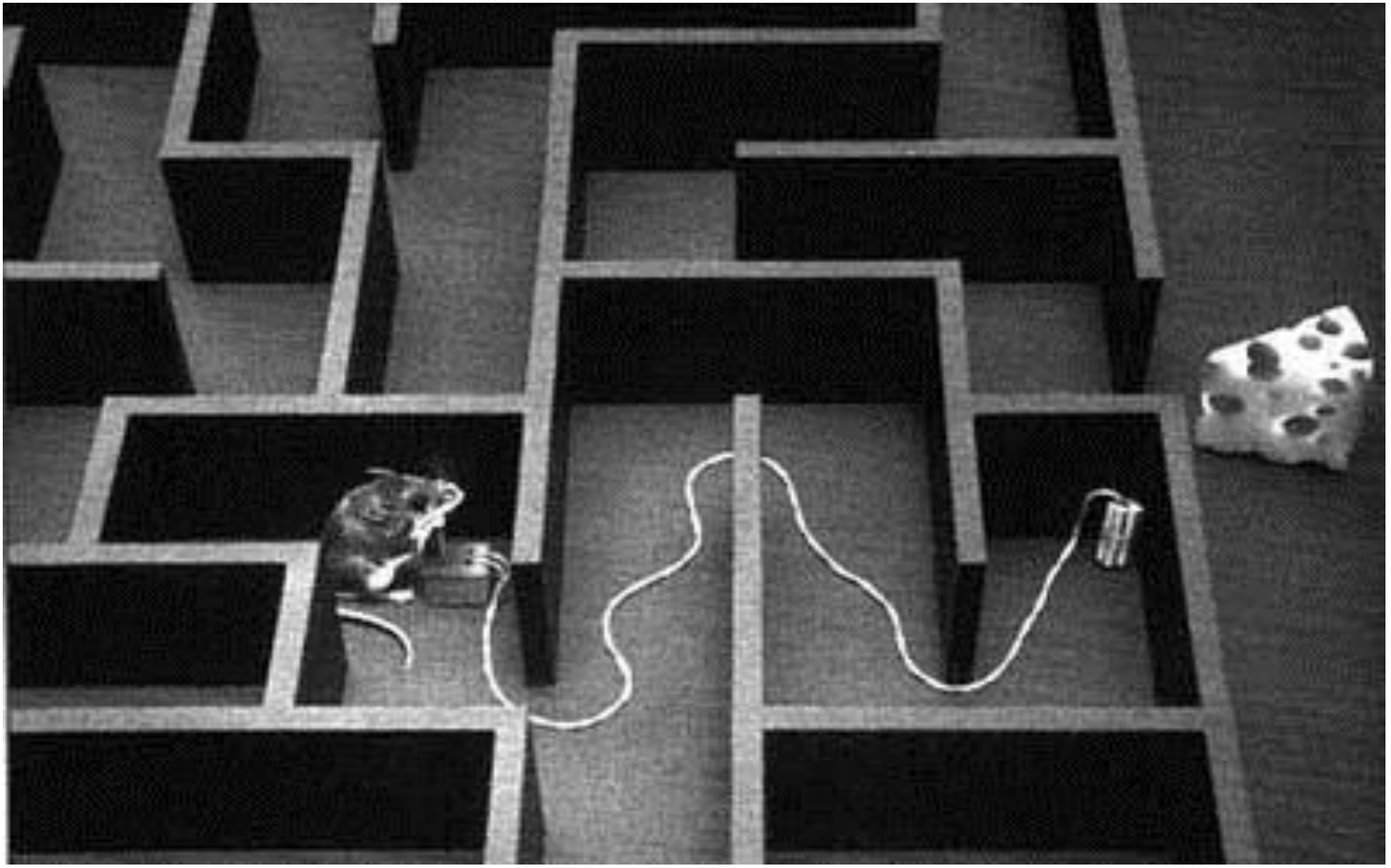
# This could be psychostimulation...



# This clearly is a nootropic effect



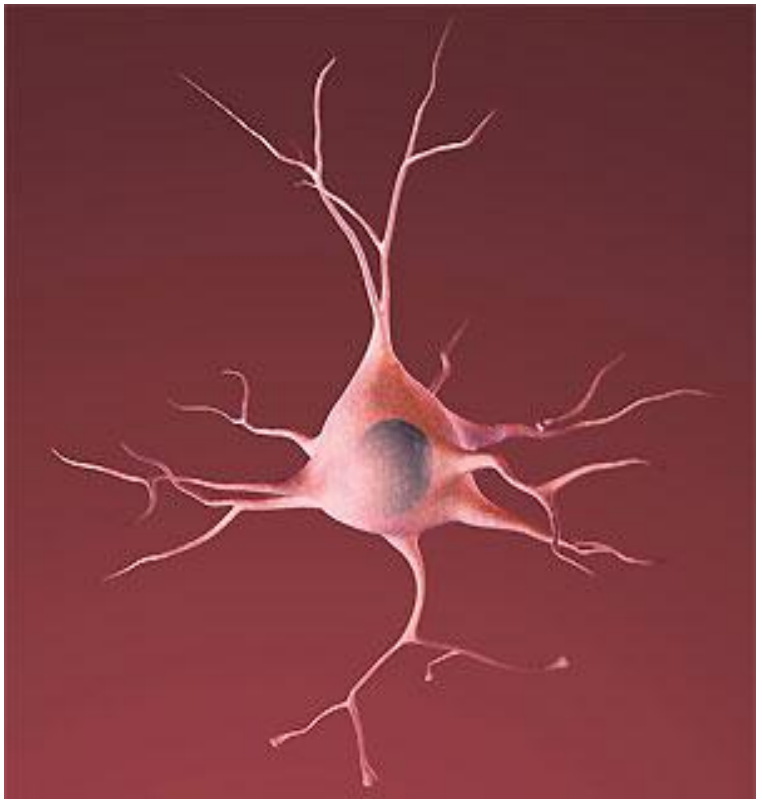
# … and its practical outcome



# Wetware Networks 101

- Human brain = network of about a trillion hosts (100 billions of them are neurones, but not only neurones are involved in memory/learning)
- Completely separate neuron forgets what happened to it 10 milliseconds ago
- So, what can it really learn outside the network?
- Processing power of the whole network is down to the number of interconnection updates per second
- In a nutshell, the main tasks of a neuron is finding, establishing and maintaining communication routes to other neurons

?

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# The mechanisms involved

- If we don't know the mechanisms involved we easily get lost in the flood of empiric observations
- And then we can fall prey to snake oil pushers and «overenthusiastic» marketing that can be «economical with truth»
- Those familiar with neuroscience please bear with the following part of the talk as it will be very boring for you
- Yet this is the bare minimum one should be aware of prior to understand the rest of it

# What and how do we «route»?

- **Our ”network traffic” is simply electrical current**
- **It flows in accordance with the conservation rule: least resistance = maximum conductance**
- **Is the connection present (”cable” plugged)?**
- **Is the conductance (Siemens, $Ohm^{-1}$) favourable?**
- **This is our wetware «routing metric», it determines where and how the ”traffic” will flow (the artists amongst you can envision a flow of water that takes available, suitable path)**
- **Between neurones it depends on the neuronal membranes polarisation as neurones are not wires directly connected to each other: ~ -60 mV = resting membrane potential, depolarisation = current, hyperpolarisation = no current**
- **$Na^+$, $Ca^{2+}$ in -> current, $K^+$ out or $Cl^-$ in -> no current. Hence it is an electrochemical rather than just electrical process**

# The «ping!»

- **The low frequency ”pairing protocol” constantly operates between the connected neurones**
- **It is a steady, constant flow of low frequency stimulation**
- **It indicates two interconnected neurones that functional connection is in place**
- **It does not determine where the major higher frequency traffic flow goes**
- **But is still important for maintaining the connections = neurite outgrowth and synapse formation**
- **Here we will predominantly deal with the higher frequency flow**

# Neurone-to-neurone interactions

- Feedback modulation: other neurones are informed about any traffic flow route change:
  - Via direct coupling to neighbouring neurons
  - Via highly diffuse chemical modulators (NO, CO etc.)
- The feedback is propagated further down the neuronal chain
- Neuronal chains: where «-» and «-» do give «+»
- Synaptic gating: a ”gatekeeper” neurone at junction plays the role of a transistor
  - ***Inhibitory gating (biological noise filters)***
  - ***Permissive gating (biological AND gate)***
  - Some neurones will fire simply when freed from inhibition

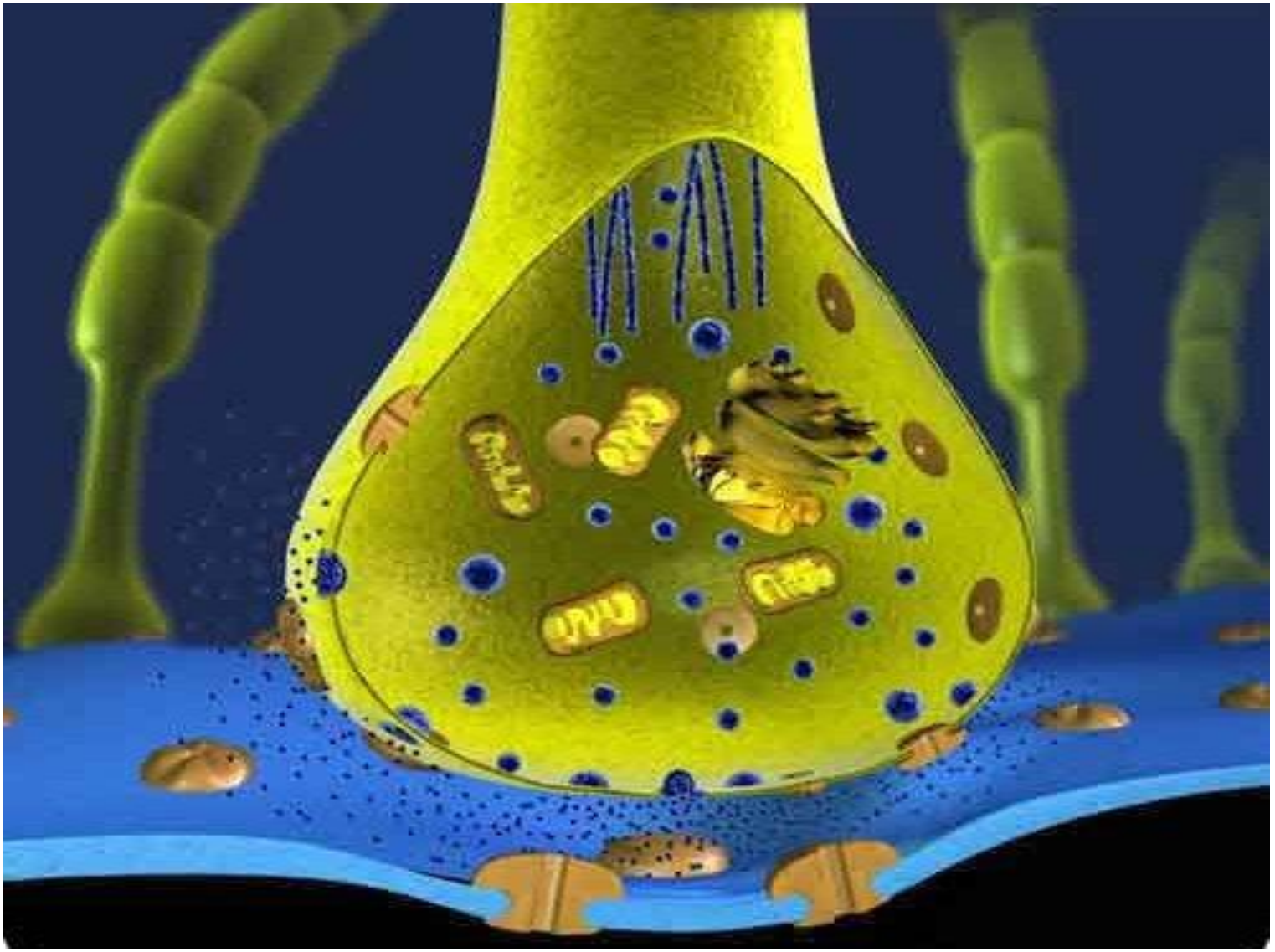
# ...and on a more global scale

- Neural pathways in the brain have different local learning rules, depending on
  - Neurons location
  - Neurons types
- Hierarchical zones with variations in assigned path (”route”) importance
- Specificity of effects depending on these zones
- Coherence (phase!) and covariance (time!) between zones and entire brain areas (seen on EEG)
- The «binding problem/factor»: how is this all effectively integrated into the whole? (we will return to it later on numerous times)

# The hebbian learning theory

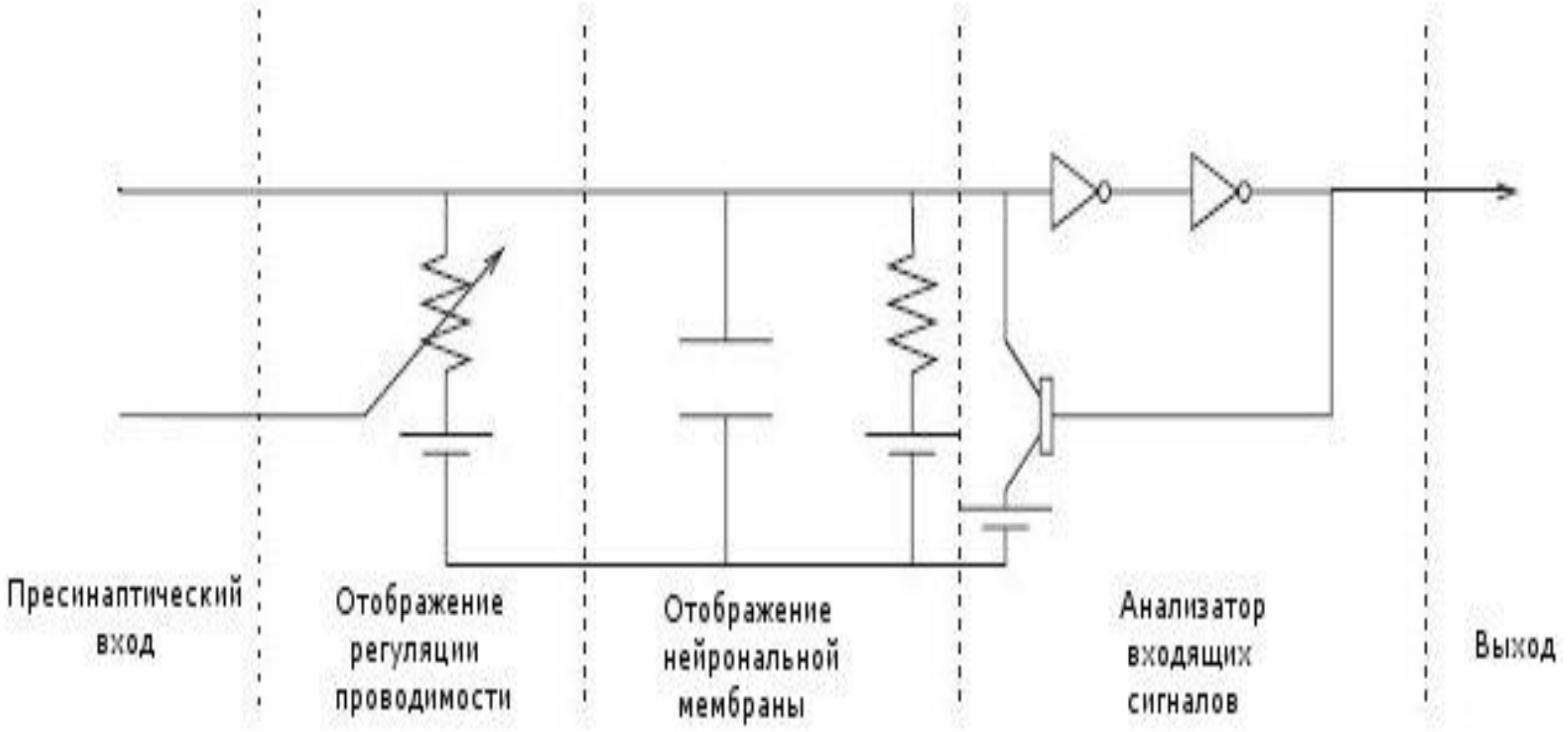
- Donald Hebb (1949): **if the firing of two neurons is associated the synaptic strength between them must increase (so-called Hebbian learning rule) - «neurones that fire together wire together»**
- Synaptic weight of connection between neurons ”i” and ”j” is $\Delta W_{ij} = k*r_i*r_j$. (r – firing rates, k – the learning rate constant)
- Neurons body R ~ constant => could be viewed as a “plain boring wire” for the purpose of this talk!
- It's the synapses where the interesting “routing” decisions are really made, and it is synaptic activity (changes of membranes potentials) that mainly reflects on EEG readings
- Neuronal plasticity (adaptability) is largely determined by the synaptic plasticity (synaptogenesis, synapses reshaping, etc.)

# Wetware Networks 101



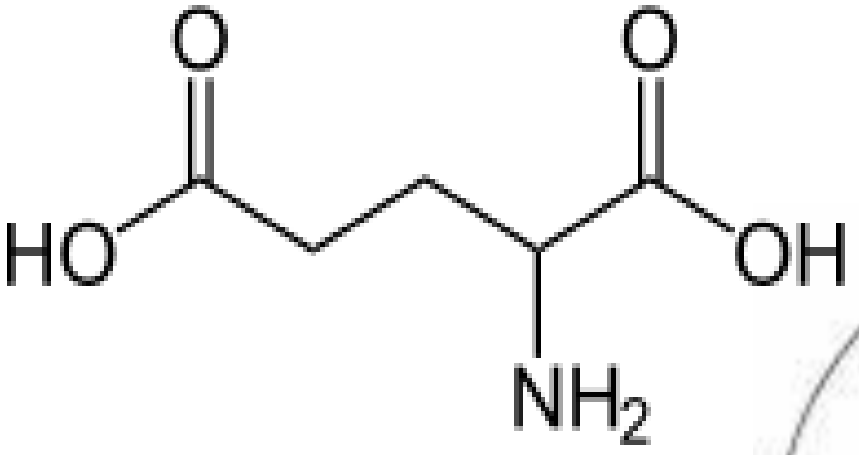
”A receptor is somewhat similar to a daemon listening to a port»

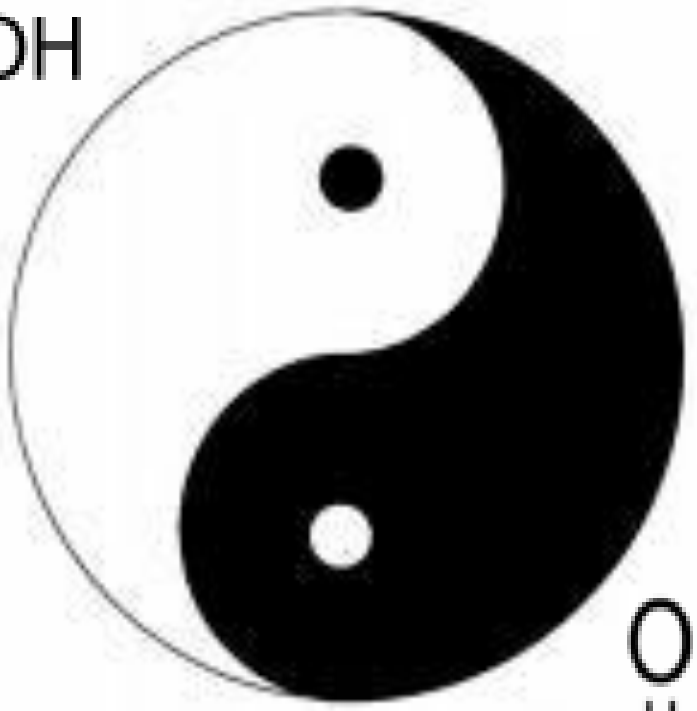
# The synapse as a simple electronic scheme

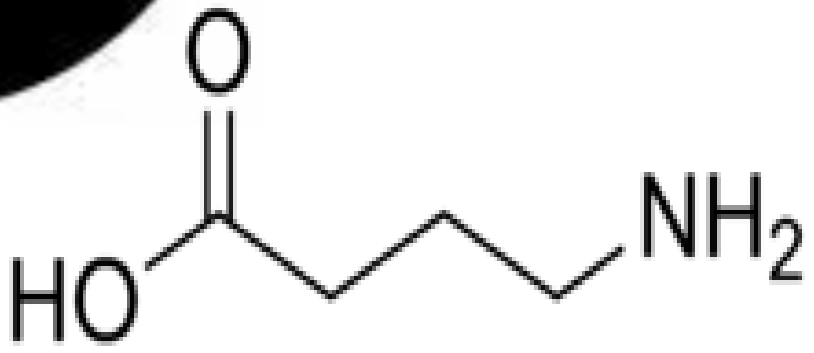



- Presynaptic Input → Conductance Regulation → Neuronal Membrane → Input Analyser → Output

# Glutamate vs GABA



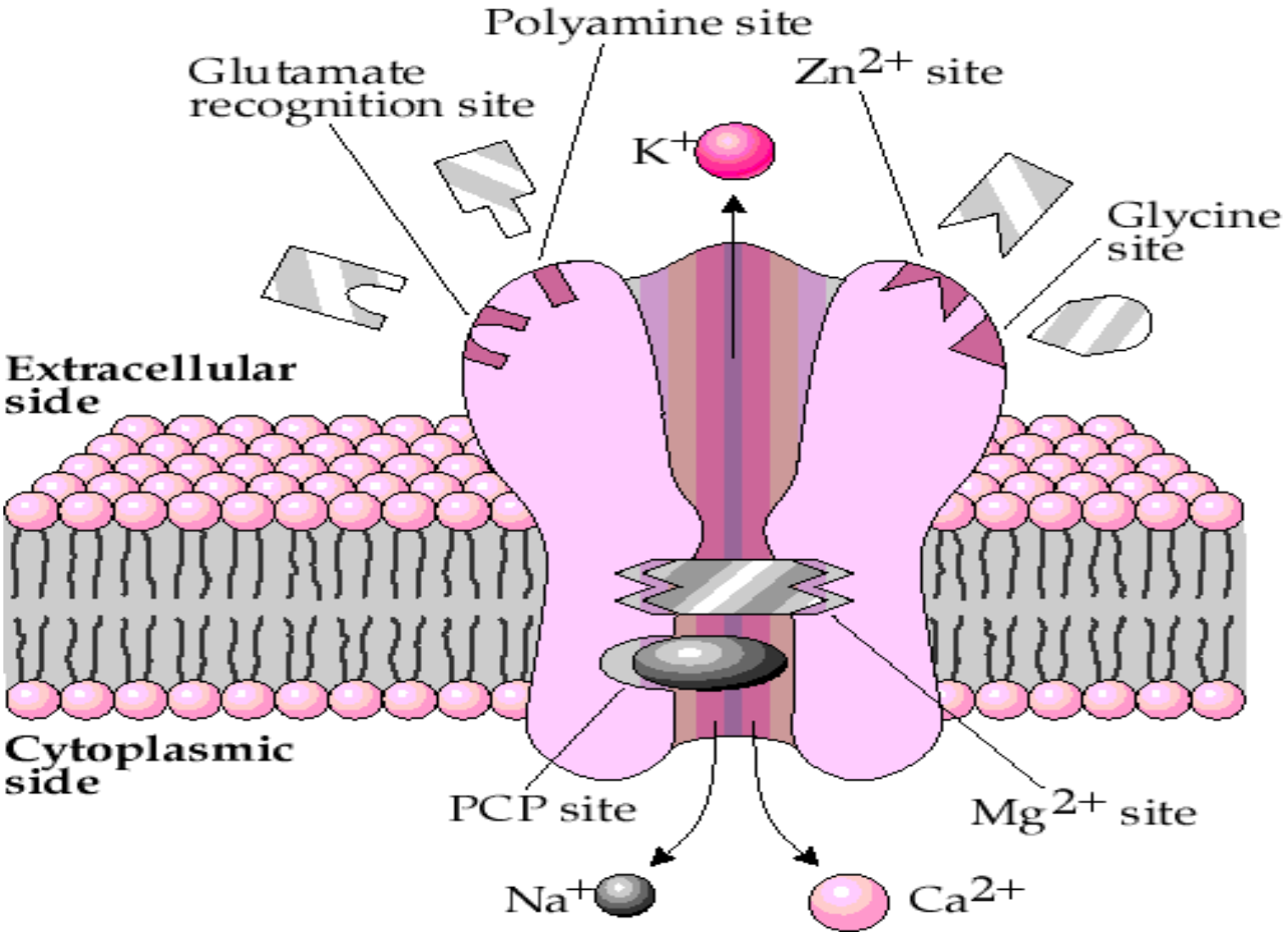





# Glutamate & GABA receptors

- Ionotropic vs metabotropic receptors
- Ionotropic receptor is a chemically activated ion channel (there are also voltage-activated ones)
- Metabotropic receptors couple to enzymes
- Glutamate-activated ion channels form our neuronal coincidence detection units
- It takes a pair of these receptors to do the job
- They belong to two different types called NMDA and AMPA (there are also Kainate receptors)
- GABA A receptors are ionotropic, they let $Cl^-$ in
- GABA B receptors are metabotropic / inhibitory

# NMDA basics




- NMDA receptor is probably the most sophisticated receptor ever to evolve, AMPA is tidbit simpler

# Coincidence detection 101

- NMDA has some rather unique peculiarities
- It can let both $Na^+$ and $Ca^{2+}$ through
- It is voltage-gated, but only for $Ca^{2+}$ (the reason being $Mg^{2+}$ stuck in the bottleneck)
- Activation of NMDA on it's own does not ”provide enough voltage”, so only $Na^+$ can pass
- Simultaneous co-activation of neighbouring NMDA and AMPA allows $Ca^{2+}$ to pass as well
- This is our coincidence, based upon the phenomenon of NMDA being both ligand and voltage-gated ion channel
- Multiple regulatory sites enforce local rules/fine tune

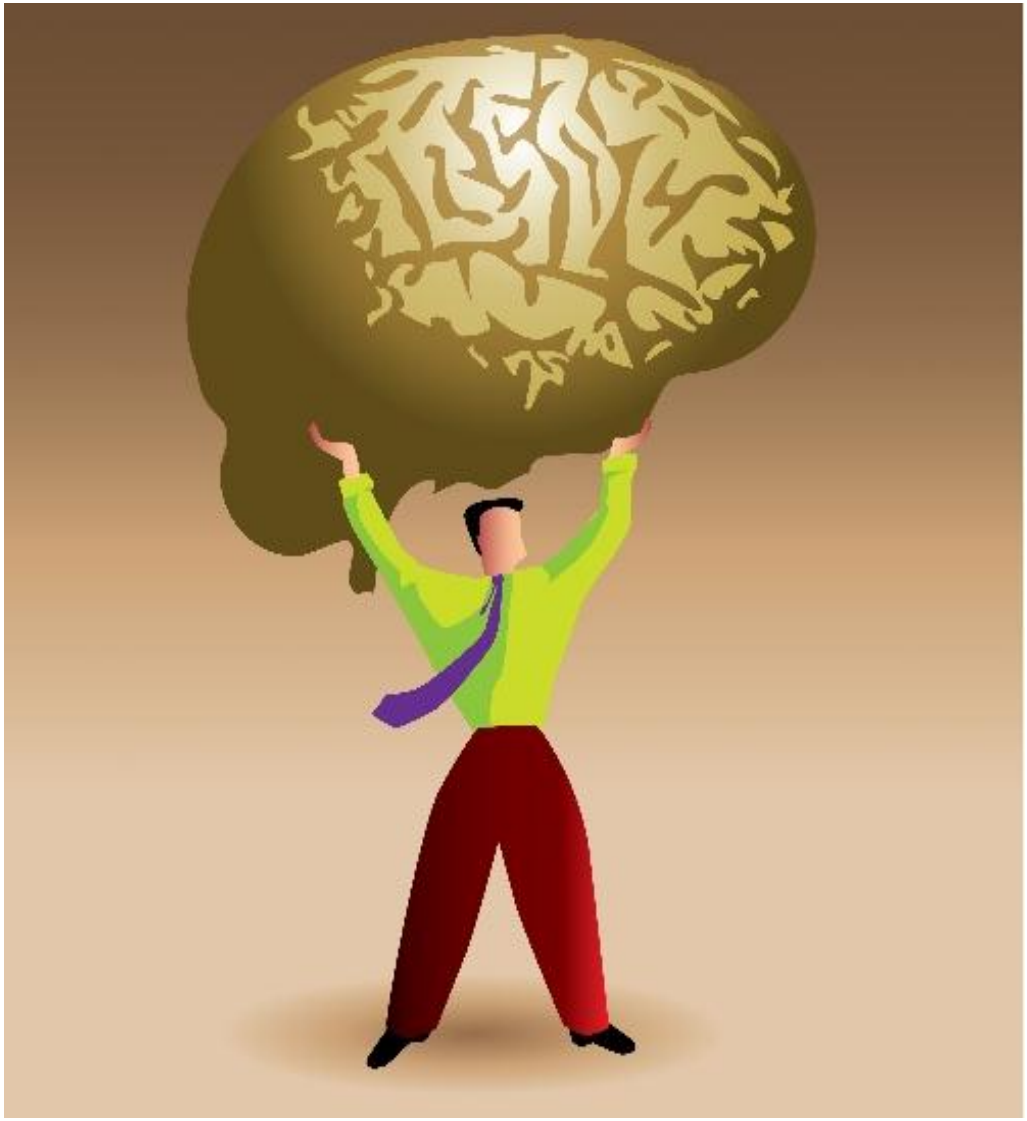
# All right, how do we overclock our wetware?

# Wetware Overclocking 101

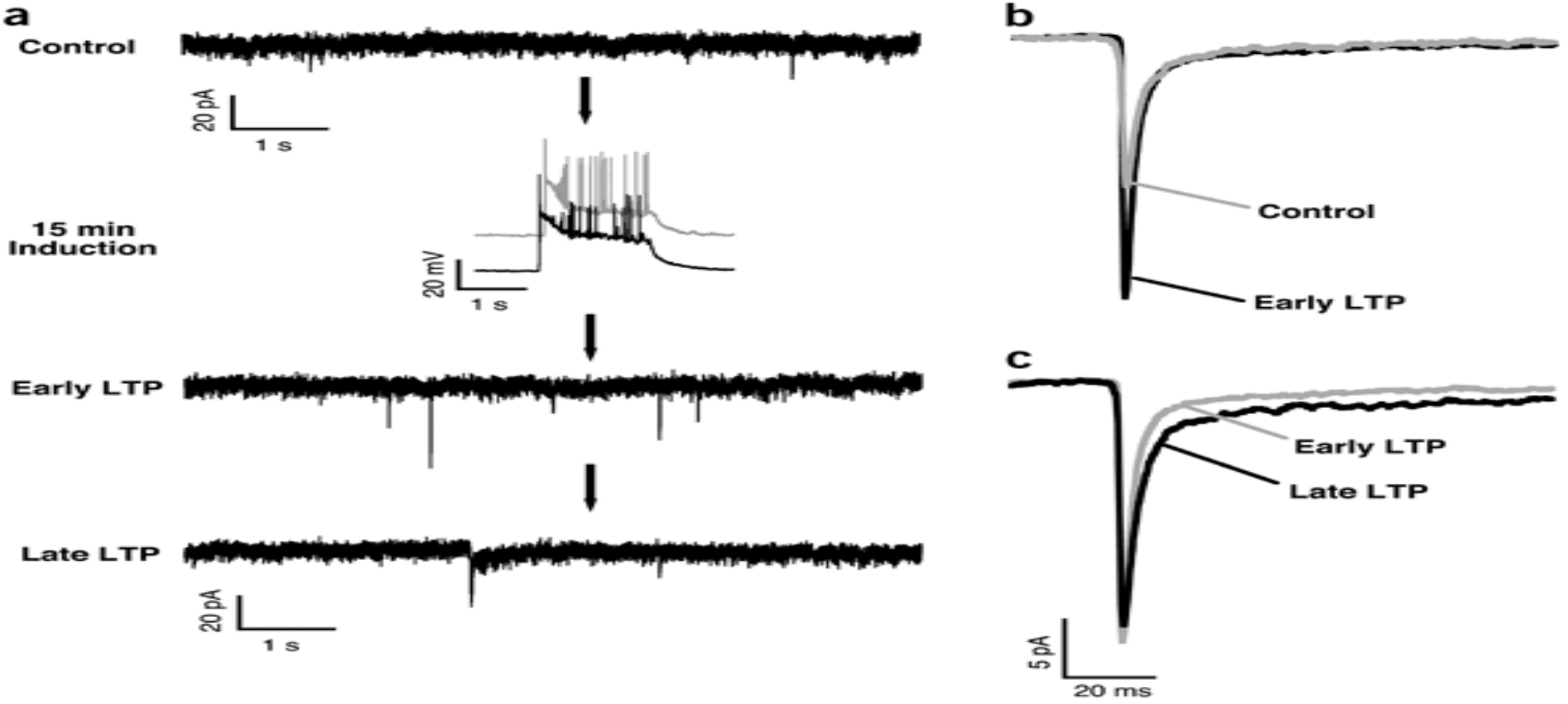
- increase the amount of connections between neurons (neuronal sprouting) so that there are more routes and links for our ”traffic” to go through
- increase conductance through the connections to provide a "fatter pipe" and stabilize new routes
- both approaches are directly correlated and depend on each other!
- At higher levels we have to look at activating *or inhibiting* specific neuronal pathways or entire brain areas
- Coherence, covariance and the «binding factor» heavily come into the play

# Brainbuilding?

- Neuronal Plasticity: the higher is the traffic load the more our neuronal networks are used to it
- ... and the higher is their capacity for data processing and storing
- Thus, ”brainbuilding” is not much different from muscle building in principle



# LTP and LTD

- Long Term Potentiation (LTP) and Long Term Depression (LTD) underline Hebbian Learning Rule
- Can last for months (”memory engrams” formation!)
- 

# The pharmacological approaches

# Setting criteria for a ”true” nootropic?

- Should promote neuronal sprouting
  - Cellular foundation for higher data throughput and retention
  - Resilient and redundant connectivity links
- Should promote LTP
  - Electrochemical foundation for higher data throughput and retention
- Should not overstimulate glutamatergic transmission to cause excitotoxicity
- Should not have any significant effects outside the brain

# Getting emotional?

- Noradrenaline and dopamine signalling can promote LTP formation, serotonin also can affect it
- Emotional arousal, excitement, motivation, reward
- When present while learning, they indicate positive cooperation between glutamatergic and catecholamin-ergic (dopamine, noradrenaline etc.) signalling
- However, the key transmitter for LTP maintenance and promotion is still Glutamate (”controlled” by GABA)
- The same applies to LTD: «unlearning/forgetting» is largely active and must be done in a right way

# The rule of a thumb (in my opinion, anyway)

- Caffeine, Cocaine, Amphetamines, Amphetamine-like ”soft” stimulants (Ritalin etc.) are ***not*** nootropic
- In search for nootropic effects do not mess with the reward/punishment system (dopamine/serotonin)
- Psychostimulants are not nootropic...
- Psychostimulants are not nootropic...
- Psychostimulants are not nootropic...
- All work and no play makes Jack a dull boy...
- All work and no play makes Jack a dull boy...
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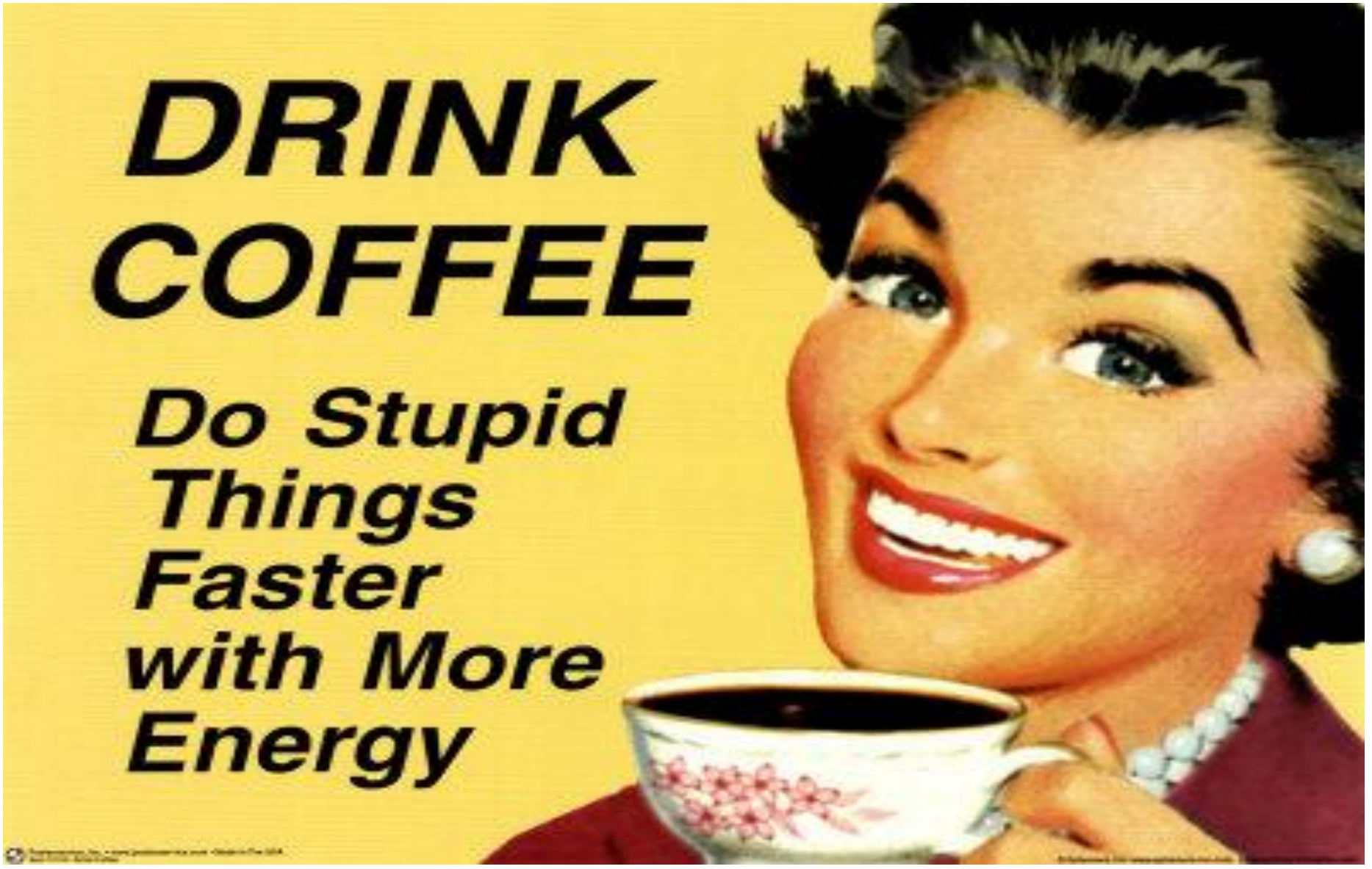

DRINK
COFFEE
Do Stupid
Things
Faster
with More
Energy

# Smoking?!

- Nicotine. Ouch....!
- Increases release of glutamate in the brain
- Receptors, on which it acts are important in memory formation
- Septohippocampal pathway stimulation
- Attention & memory «+»
- Even neuroprotection
- But can we replace it?

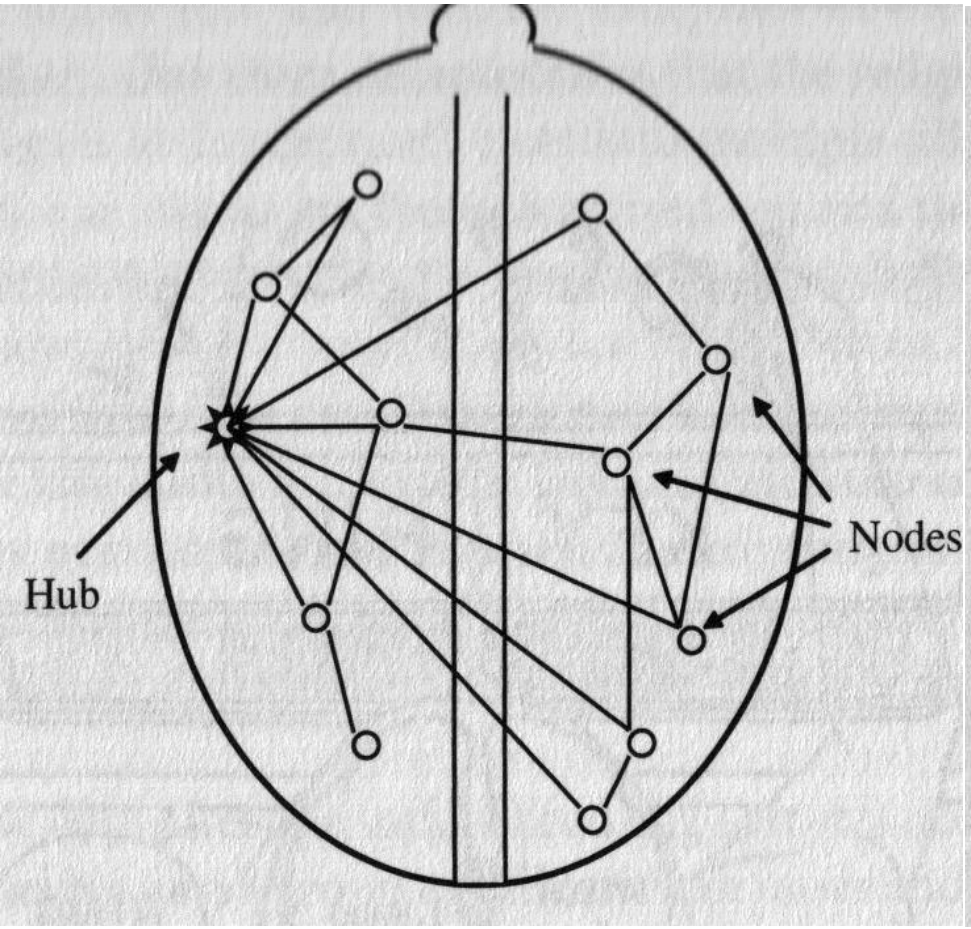
# Replacing nicotine

- **Antialzheimers drugs like Tacrine affect cholinergic transmission but have too many side effects for healthy human use being close relatives of carbamate insecticides**
- **Choline precusor supplementation**
  - **Choline chloride + Niacin + Zinc**
  - **Or DMAE (dimethylaminoethanol) as a precusor**
- **In my experience only good at removing the ”memory block”**
- **Not ”true” nootropes by the definition used in this talk**
- **Effects of nicotine outside the brain are significant**
- **But some do use nicotine patches for memory improvement**

# Piracetam and Ko

- The first (since 1972) nootropes: ampakines
- Bind to a modulatory site on AMPA receptors
- Increase the time of these ion channels staying open, thus the conductance is enhanced
- Do not open the channels by themselves – so no excitotoxicity can happen
- Do promote neuronal sprouting
- Piracetam, pramiracetam, aniracetam, oxiracetam, nefiracetam, feniracetam, noopept and so on
- Newer experimental ampakines from Cortex Pharmaceuticals: CX717, CX1739, Ampalex etc.

# The «superconnection» state



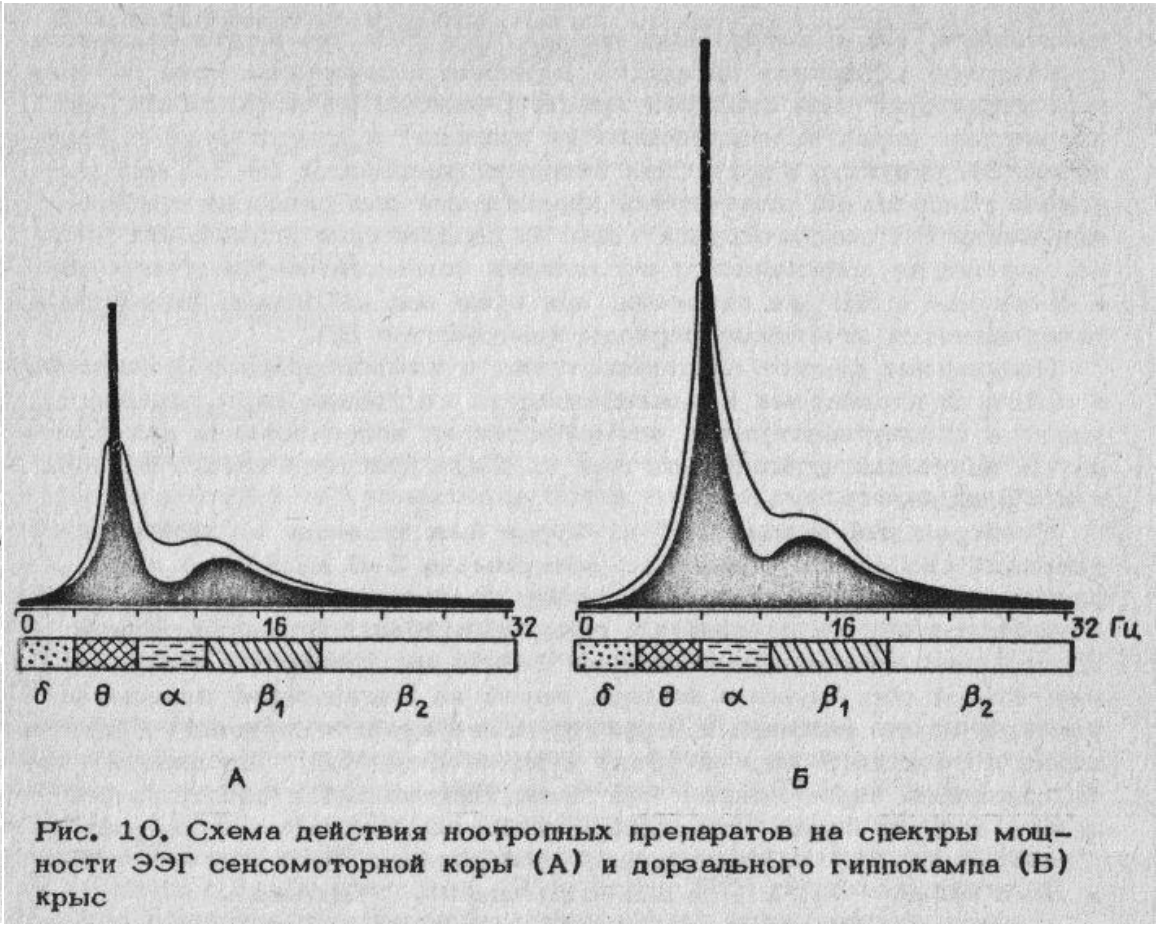
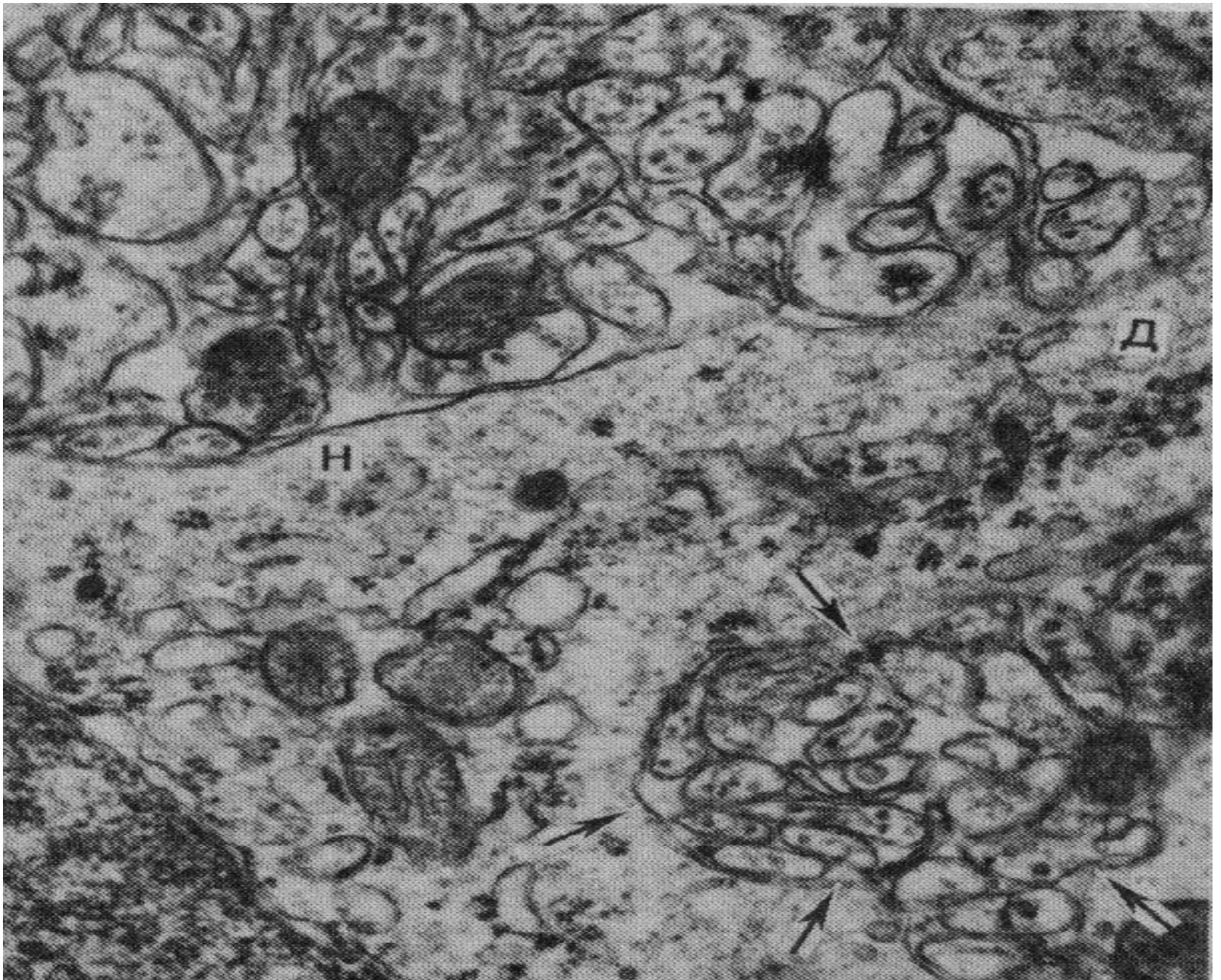




Рис. 10. Схема действия ноотропных препаратов на спектры мощности ЭЭГ сенсомоторной коры (А) и дорзального гиппокампа (Б) крыс

- Transcallosal potentials increase (Giurgea)
- Increase in EEG coherence between brain hemispheres
- Increase in the amplitude of the dominant brain wave, theta burst (rat), alpha/beta (?)
- Visual discrimination studies with functional ipsilateral hemisphere suppression in rats — memory loss/learning impairment due to supression effectively countered
- All points to the enhancement of the «binding factor» (so-called «superconnection»)

# Sprouting under the microscope



# «Good things come to those who wait» (TM)

- It takes quite a lot of new connections to be formed and stabilised to feel the difference
- It takes time for new ”routes” to go through the new connections and become useful
- Thus it works very slowly and needs ”brain training”
- The concentration plateau must be maintained
- The effect is long lasting and stable
- Artifacts I have personally observed
  - ”piracetam priming” after long regular intake
  - Hangover elimination or reduction

# What about Growth Factors?

- Nerve Growth Factor (NGF) and Brain-Derived Nootrophic Factor (BDNF) preparations
- Only started to be investigated in the West in relatively recent times
- Cerebrolizin
  - Extract of porcine brain rich in NGF etc.
  - Used in the USSR since 1952 (long before Rita Levi-Montalcini got her Nobel Prize for NGF in 1986)
  - Goddamn efficient (in my experience, anyway :-)
- Semax (stimulates BDNF release)
- Drawback: both drugs need to be injected i.m.
- Preparations that can be snorted are promising

# Coming close?

- Idebenone, Hydergine, Nicegroline (Sermion)
  - Do they really increase production or release of NGF?
  - Peripheral side effects for the last two!
- Vasopressine
  - Does participate in long term memory formation
  - Too many peripheral side effects
- Fragments of Vasopressine and Adrenocorticotropine (Semax!) deprived of hormonal activity
- Metabolic supplementation ??
  - Glucose (Insulin effects!) and Pyritinol (Merck, 1961)
  - Cavinton (Vinpocetine) and other cerebrovascular drugs

# Glutamate and glycine?

- The Great Holy War: the use of Glutamate itself
- Umami taste. Adzi no moto. Monosodium Glutamate.
- Would it not be all-consumed in the periphery?
- Would it really cross the blood-brain barrier?
- Would it not be toxic to ingest in large quantities?
  - ”Chinese restaraunt syndrome” versus diarrhetic shellfish poisoning

- Sublingual Glycine: placebo or not?

- Positive modulation of NMDA receptors by glycine
- But does it actually get there even if taken sublingually?
- And is ambient glycine not enough?
- Inhibiting glycine neuronal uptake could be the way to go
- I made a simple ”glycine delivery” compound back in 93 but it was never tested as everything has collapsed

# What about GABA?

- If we can increase glutamatergic transmission, why not to decrease gabaergic?
- However, blocking the «safety valve» is generally a bad idea, equally as bad as direct activation of NMDA, AMPA and Kainate receptors by agonists (“modulate, not activate!”)
- It can lead to seizures, spasticity, hyperalgesia, neuronal damage and loss due to excitotoxicity
- Non-competitive GABA A receptors agonists (e.g. Picrotoxin) and even the competitive ones (e.g. Bicuculline) are more suitable for murder than cognition enhancement. Some weak partial GABA agonists are considered for use, though
- However, GABA itself, as well as its agonists were included within the nootropics group in the USSR
- Complete nonsense?! Only at the first sight!

# GABA-based nootropics?!

- GABA itself *(badly crosses the blood-brain barrier!*), Phenibut, Picamilon, Pantogam...
- Weak anxiolythics without side effects of benzodiazepines, in particular sedation and addiction, used to treat neurotic states with success
- **«remove what obstructs rather than enhance what promotes» approach?**
- **To improve the SNR (signal-to-noise ratio) you can either increase signal or decrease noise (and optimally you do the both simultaneously!)**
- **Do weak GABA agonists promote inhibitory gating, thus increasing noise filtering and decreasing «information stress»? Sounds plausible!**
- **Also, a neuronal chain "inhibition of inhibition" mechanism type may be involved (a la neoclassical excitotoxicity)**

# Reaching the right balance?

- Should effective nootropic intervention combine both «signal increase» and «noise reduction» (e.g. Ampakines + weak GABA agonists?)
- At this point it is worth mentioning that ~10% of piracetam in the brain is metabolised into GABA
- Would they not cancel each other effects? Not obviously. In a similar manner, it is possible to combine psychostimulants and benzodiazepines to decrease their side effects while preserving the main ones
- *I would not define weak GABA agonists as «nootropic»*
- But the original Soviet definition of «anxiolytics with a nootropic effect component» makes perfect sense

# «Smart drugs» summary

- to reach any desirable effects the use of ”true” nootropics must be taken seriously (doses, intervals, continuity)
- mixtures of such compounds could be more effective than the compounds on their own
- there are supplements that could indirectly improve cognitive performance via providing higher energy supply when needed. These may not work alone and are auxiliary to the “true” nootropics
- There are tons of snake oil marketing of “smart drugs & nutrients”. Think about action mechanisms we've discussed. Question everything.

# «Nootropic» gene insertion?

- Cognition enchancement via genetic engineering?
- Altering the levels of expression of receptors and other proteins participating in LTP/LTD formation
- Altering their subunit composition and shifting the subtype balance towards promoting conductance
- Doogie mice aka the Supermice (Dr. Tsien's group)
  - Higher levels of GluN2B NMDA receptor subunit
  - Extra copies of GluN2B gene increase activity with age
  - Learn ~2 times faster, perform wonders in tests
  - The problem: hyperalgesia to certain types of pain was observed in a long term

# A way forward?

- The general algorithm of such manipulations is quite simple:
  - Find out which receptor subunit composition is more effective in LTP/LTD formation or more responsive to activating drugs
  - Insert a gene for the specific subunit(s) so that more of it is produced
  - Test the resulting effects in a variety of learning and memory tests, electrophysiologically etc., watch out for undesirable effects
  - This may apply to non-glutamate receptors too, for example nicotinic acetylcholine receptors subunit compositions
  - Targeting affector enzymes may be a bad idea due to their lower specificity
- Spatial distribution of specific receptor compositions and splice forms can make it all more interesting — you can potentially engineer brains with higher or lower activity in a specific brain lobe, smaller area or pathway
- It is also possible to engineer receptors that do not differ from the physiological norm but are more succeptible to ampakines and other modulating drugs
- Or the changes of subunut compositon with age can be taken into account and countered (already done with Doogie mice, as GluN2B/GluN2A ratio shifts towards GluN2A with age, and GluN2B permits larger charge transfer, since more Ca ions go through as such receptors take longer to desensitize)
- Note than GluN2A/GluN2B ratio could be a molecular level noise filter

# Other ways and potential limits

Other valid targets for genetic intervention could be:

- CNS-specific growth factors (NGF, BDNF)
- Favouring ApoE 2/2 vs ApoE 4/4 in neuronal membranes plasticity
- CNS-specific isoforms of affector enzymes, such as adenylyl cyclase or CaMKII
- Proteins that bind to and regulate Glu or GABA receptors activity
- *Proteins regulating neuronal programmed cell death, especially in development: do all neurones eliminated neonatally have to be eliminated, especially if we stimulate such pathways?*
- However, while there is a large number of genetic variations affecting individual human intelligence, each accounts for only a very small fraction (<1%) of the variance between individuals
- So, genetic enhancement of intelligence through direct insertion of a few beneficial alleles is unlikely to have a large effect
- … unless it is an artificial variation to which the statistical observation on variance stated above simply does not apply!

# «Paragenetic» means

- Choline supplementation to pregnant rats improved performance of their pups as a result of changes in neural development in turn due to changes in gene expession (Meck and Williams 2003; Mellott et al. 2004)
- Supplementation of mother's diet during late pregnancy and 3 months postpartum with long-chained fatty acids has also been demonstrated to improve cognitive performance in human children (Helland et al. 2003)
- ***By all means, gene and protein mapping of different receptors subunits of the entire brain will allow design of subunit-selective nootropics that target specific brain areas more than other areas of the brain***