Neurogenesis in the Brain
the death of a dogma

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Neurogenesis and Exercise
- Exercise is one of the most important ‘primers’ for neurogenesis
- The Overtraining Syndrome: facts and fiction
  - The hormonal disturbance due to NFO or OTS can be detected using a ‘double exercise protocol’
- Cryotherapy
  - Recovery: From exercise: should we cool the body?

Cognition declines with age

Cross sectional Longitudinal evidence

Cognition of ‘fit’ elderly better?

Does training improve cognition in sedentary elderly?

Meta analysis: effect exc training on cognition in elderly

Exercise has positive treatment effects in older patients with dementia & cognitive impairments

Heyn et al Arch Phys Med Rehabil 2004
Exercise & Cognition
- Most studies are ‘observational’
- Not easy to perform an intervention study
- Many influencing factors
- Most recent studies indicate an improvement of cognition in elderly caused by exercise training

Mechanisms?
- Cerebral circulation
- Neuronal efficiency
- Glucose regulation
- ... Neurotrophic factors

Brain cells die – and do not get replaced

1960s: Joseph Altman
- Series on papers in high level journals:
  - J Comparative Neurology, Science, Nature
  - evidence for new neurons
  - Results were ignored

Nottebohm (late 1960s)
- Neuronal basis for song learning in birds!
- Seasonal and song related changes in volume of specific brain nuclei
- Due to change in actual number of neurons
- 1980s they showed that thousands of new neurons are added every day to the avian brain!
- These cells responded with an action potential to sound
- These studies were viewed as irrelevant to the primate or even to the mammalian brain

Electron microscopy: BrdU
- This substance (BrdU) is taken up by cells and is a marker of proliferating cells
- Can be visualised with immunocytochemical techniques
- BrdU (5-bromo-3’-deoxyuridine)
Early 1990s

Altman’s claims that new neurons were added to the adult *dendate gyrus* had been confirmed several times.

But also the opposite ➔ decreased number of adult neurons:
- acute and chronic stress
- ageing
- Increased glucocorticoid levels
- Chronic administration of morphine or heroin
- ...

Every day *thousands of new cells* are added to the mammalian brain

➔ % wise little compared to total of brain cells, but it shows that there is considerable structural change possible

New brain cells

Cells live from a few days to the lifetime of the animal
➔ These adult generated cells have a role in **learning and memory**

➔ Hippocampus
➔ But also other brain areas

Brain derived neurotrophic factor (BDNF)

Is the most abundant **neurotrophin** in the brain
➔ most widely distributed **growth factor** within the brain

It enhances the growth and maintenance of several neural systems
Serves as a neurotransmitter modulator
Participates in use-dependent plasticity mechanisms such as long-term potentiation (LTP) and learning

Hippocampus
BDNF is transported retrogradely and anterogradely to synapses. It potentiates synaptic transmission. Released BDNF binds to its receptor (TrkB) presynaptically to modify transmitter release, and postsynaptically to modify postsynaptic sensitivity. BDNF is responsive to a variety of stimuli which enhances neuronal activity. It supports the survival and growth of many neuronal subtypes. BDNF expression is diminished in Alzheimer’s disease.

Van Praag et al (Salk institute La Jolla California)

Wheel running enhances:
- Dentate gyrus LTP* 
- Dentate gyrus neurogenesis
- Spatial learning
- New neurons are required for some computational theories of learning

* = physiological model of certain forms of learning and memory

Enriched environment

Standard Housing: rats housed as groups. ➔ social interaction
Enriched environment: Tools, running wheels, larger cages, ...
Enriched environment

Environmental stimulation elicits various plastic responses in the adult brain. But also in the ‘old’ brain:

- Also in birds (in cages and let free) show signs of enrichment (free)
- Wild birds captured ⇒ impoverishment

Voluntary running

Enhances the survival of ‘newborn’ neurons = cell proliferation
Or in neurogenesis (4 weeks old cells)

\textbf{One day} \hspace{1cm} \textbf{4 weeks}

\begin{itemize}
  \item \textbf{a} \hspace{1cm} \textbf{b} \hspace{1cm} \textbf{c} \hspace{1cm} \textbf{d} \hspace{1cm} \textbf{e}
\end{itemize}

\begin{itemize}
  \item \textbf{f} \hspace{1cm} \textbf{g} \hspace{1cm} \textbf{h} \hspace{1cm} \textbf{i}
\end{itemize}

Effect of exercise on hippocampal BDNF mRNA

7 day of voluntary wheel running

\begin{itemize}
  \item \textbf{a}
  \item \textbf{b}
\end{itemize}

\textbf{sedentary}

BDNF expression correlates with the distance run per night

\begin{itemize}
  \item \textbf{d}
  \item \textbf{c}
\end{itemize}

Enrichment

Enhances memory function in various learning tasks:

Voluntary wheel running and treadmill training ⇒ enhance spatial learning
Anatomical changes

The number of new neurons are enhanced by enrichment and exc

Neuronal survival is enhanced by exc

Not only neurons but also gliogenesis, synaptogenesis, and angiogenesis

Increased brain weight and size

Motor skill learning

Dendrite branching

Increases cortical thickness and synaptogenesis

But also the number of synapses per neuron

And increased capillary density

Mechanism influence of exc on BDNF

Exercise primes the hippocampus to respond to environmental stimuli, and ensures the viability of neurons to resist insult

Multiple factors control BDNF expression

IGF-1 = potent survival factor for neurons

Peripheral IGF-1 initiates growth factors cascades in the brain

Is there a limit?

27 generations of selective breeding

Genetic determined runners

Neurogenesis increased more in animals bred for increased running behaviour than in control runners

But …
Is there a limit?

There seems to be a plateau. Neurogenesis correlated with the distance run in the 'normal' animals. But...

Levelled off in the animals bred for increased running behaviour.

Also in learning?

Access to a running wheel enhanced learning in control, but not in selectively bred animals.

Rhodes et al. Behavioral Neuroscience 2003

There is a strong positive correlation between running distance and neurogenesis in normal animals. There might be a limit in exercise induced neurogenesis. Despite the high levels of exercise in specific bred animals, spacial learning was not improved.

Consequences for damaged or diseased brains

Effects seem to be beneficial. Recovery from stroke or brain lesions -> 2hr of running each day: performance on the 'maze test' improved.

Neuroplasticity

Creating new networks.

Measuring BDNF in humans

Barrière Hémato-Méningée
Blood-brain barrier (BBB)

- In animals
  - BDNF crosses BBB bi-directionally
  - Correlation (at rest) between cortical and serum BDNF concentrations

- In humans
  - Release of BDNF from human brain

Human study

- Well trained cyclists
- Age (yrs) = 22.9 ± 4.3
- Weight (kg) = 73.6 ± 8.4
- Height (cm) = 177.7 ± 7.0
- VO$_{2max}$ = 73.5 ± 6.4 ml/kg/min

- 60 min à 55% Watt$_{max}$
- 30 min Time trial à 75% Watt$_{max}$

BDNF increases in peripheral blood due to exercise

**REBOXETINE**
(Noradrenaline re-uptake inhibitor)

**CITALOPRAM**
(Serotonin re-uptake inhibitor)

Results SSRI study

BDNF levels higher in 30°C

Consequences for damaged or diseased brains

- Voluntary running provide protection against ischemia
- Huntington’s disease rats delays the onset of behavioral deficits = loss of motor coordination
- Spinal cord cells
  - Behavioral training can enhance the survival and functional consequences of foetal tissue implants
  - And that training enhances motor response

Example experiment

N = 57 male rats
- Occlusion n. cerebri media (microinjection ET-1=Ischemia) or Sham surgery

4 groups (surgery + rehabilitation)
- Ischemia + “Enriched rehabilitation” (IE)
- Ischemia + “Standard housing” (IS)
- Sham + “Enriched rehabilitation” (SE)
- Sham + “Standard housing” (SS)
Infarction induced

Enriched rehabilitation

Rehabilitation

Start 15 d. post-op

“Enriched rehabilitation” ↔ Control
5d/w, 6u training on reaching apparatus for impaired limb & digits

Test protocol

Testing post-op: d. 10-15 (pre-treatment) and 4 & 9 wk after 1st treatment

Physical tests
Staircase skilled-reaching test (training pre-op)
- Asymmetrical forelimb use
- Beam-traversing task (training pre-op)

Enriched rehabilitation (IE) significantly elevated dendritic length

Enriched rehabilitation (IE) resulted in a significantly greater number of branches
Exposure to enriched living conditions in combination with daily forelimb rehabilitation after MCA occlusion:
- greatly enhanced the function of the impaired forelimb.
- greater functionality (i.e., the ability to retrieve more pellets and reduced impairment in limb placement)

Injured adult rat brain remains sensitive to specific behavioral therapy weeks after the injury.
Enriched rehabilitation is capable of augmenting brain plasticity.

**Exercise as antidepressant**

Several theories exist on what happens in the brain that might cause depression
Therapeutic interventions or re-establishing several possible improvements:
- pharmacological treatments
- psychotherapy
- ...

Is exercise a valid anti-depressant therapy?

**Exercise as antidepressant**

Most exercise intervention studies:
- aerobic exercise
- Cross sectional & Prospective studies

Exercise training in healthy subjects:
- Compared to controls: decreases in depressive symptomatology
- But, ... not real significant
- Logic: subjects were not depressed

**Exercise as antidepressant**

Exercise training in patients with chronic medical conditions:
Cardiac, Pulmonary, Neuromuscular disorders, Rheumatoid arthritis, osteoarthritis rehabilitation programmes
Cancer patients
Other: CFS, Fibromyalgia, Multiple Sclerosis

Although study designs (e.g., poor randomisation, small sample size, ...) were not always perfect
- Psychological benefits of regular Physical Activity

**Exercise as antidepressant**

Effectiveness of exc training compared with standard antidepressant medication:
- Exc is more effective than No treatment
- Exc is as effective as psychotherapy or medication

!! Studies suffer from methodological shortcomings

**Therapeutic effect of Exercise - Depression**

Exercise is used as a therapy for mental and neurodegenerative disorders
What prove is there for this exercise therapy?
If applied how should we do this?
Which studies have there been performed?
Participants were randomized to one of four aerobic exercise treatment groups (Lab controlled) for 12 weeks:
- total energy expenditure (7.0 kcal/kg/week or 17.5 kcal/kg/week)
- frequency (3 days/week or 5 days/week)
- exercise placebo control (3 days/week flexibility exercise)

The 17.5-kcal/kg/week dose “public health dose” (PHD)
The 7.0-kcal/kg/week dose “low dose” (LD)

All groups Depression symptoms decreased

No diff between control, 3 or 5d/wk

The major finding was that the public health dose (PHD) of exercise is an effective monotherapy for mild to moderate MDD

Conclusions
Before 1990: doubt that brain could make new cells
Labelling of cells with BrdU increased our knowledge and broadened our ‘vision’
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What stimulates BDNF?
- Enriched environment
- Exercise

Exercise enhances neogenesis
BDNF expression correlates with the distance run

Conclusions

Exercise and enriched environment have shown to
- Induce anatomical changes in the brain
- Increases motor skill learning

But there is a limit

These findings open new insights into the therapeutic effects of exercise

Conclusions

Brain plasticity exists
Enriched environment is important
Brain damage (e.g., stroke)
- Improved motor performance
- Sign elevated dendritic length
- Increase brain plasticity
- Needs to be started ASAP

Conclusions

Exercise is used as a therapy for mental and neurodegenerative disorders:
- Depression
- Alzheimer Disease
- Parkinson’s Disease
- Multiple Sclerosis
- ...

Conclusions

What prove is there for exercise therapy?

There is need for Randomised Clinical Trials and Controlled Clinical Trials
Most studies show improvements in symptoms that might be associated with the ‘positive’ physiological effects of exercise

Thank you