ÜBERSICHT

ACCEPTED: January 2015
PUBLISHED ONLINE: February 2015
DOI: 10.5960/dzsm.2015.165

Reinsberger C. Of running mice and exercising humans – the quest for mechanisms and biomarkers of exercise induced neurogenesis and plasticity. Dtsch Z Sportmed. 2015; 66: 36-41.

Reinsberger C [1]

Of running mice and exercising humans – the quest for mechanisms and biomarkers of exercise induced neurogenesis and plasticity

Die Suche nach Mechanismen und Biomarkern für bewegungsinduzierte Neurogenese und Plastizität

1. UNIVERSITY OF PADERBORN, *Institute of Sports Medicine*

Summary

› **Sports and exercise** can influence brain structure and function on a variety of levels. Adult hippocampal neurogenesis, synaptic plasticity, dendritic complexity and angiogenesis are among the basic mechanisms that are induced by exercise in animal models. But how do these mechanisms translate into the human brain and provide the basis for many positive aspects of sports and exercise on neurological and even neurodegenerative diseases?

› **Knowledge** of exercise induced adult neurogenesis and plasticity on synaptic and cellular levels is primarily derived from rodent models. Evidence for similar effects in human brains are evident mainly at a macroscopic level and take into account the hierarchical and modular network organization of the human brain that can be assessed in vivo by a growing number of neuroimaging methods. Besides further elucidating the complexity of the basic mechanisms themselves, many studies lack a differentiated view on the intervention of exercise or sports.

› **It will be most interesting and helpful** to understand in the future, how adult neurogenesis and brain plasticity are influenced by type (e.g. cardiovascular, coordination, strength), volume and intensity of exercise. With this knowledge it would be possible to regard and utilize sports and exercise rather like a pharmacy than a single medication by designing disease specific exercise and sports specific training programs that may most effectively restore and/or enhance brain function, one of the great challenges of Sports Medicine in the years to come.

KEY WORDS:
neuroplasticity, adult neurogenesis, sports, exercise, neuroimaging

Zusammenfassung

› **Sport und Bewegung** beeinflusst die Struktur und Funktion des Gehirns auf verschiedenen Ebenen. Adulte hippokampale Neurogenese, synpatische Plastizität, Komplexität dendritischer Aufzweigungen und Angiogenese sind einige dieser Mechanismen, die im Tiermodell durch Bewegung induziert werden. Aber wie weit lassen sich diese Mechanismen auf das menschliche Gehirn übertragen? Wie können hierdurch die positiven Aspekte von Sport und Bewegung auf neurologische / neurodegenerative angewendet werden?

› **In diesem Artikel werden** bewegungsinduzierte adulte Neurogenese und Plastizität auf zellulärer Ebene, die sich vorwiegend in Tierversuchen nachweisen lassen, diskutiert. Der direkte Nachweis ähnlicher Effekte beim Menschen gelingt nur schwer und erfolgt nicht selten mit Hilfe einer wachsenden Zahl an Methoden hirnbildgebender Verfahren unter Berücksichtigung der hierarchisch-modularen Netzwerkarchitektur des Gehirns. Neben der Aufklärung dieser komplexen Zusammenhänge, wird Bewegung dabei nicht selten als uniforme Intervention angesehen.

› **In Zukunft wird es von großer Bedeutung sein,** wie adulte Neurogenese und Hirnplastizität durch Art (z. B. kardiovaskuläres Training, Koordinationstraining, Krafttraining), Volumen und Intensität des Trainings differenziert beeinflusst werden kann. Hieraus könnte es möglich sein, durch die Ausarbeitung von krankheits-spezifischen Interventionen Hirnfunktionen und -strukturen differenzialtherapeutisch gezielt zu beeinflussen und damit Bewegung und Sport eher als Apotheke denn als Medizin zu betrachten, was sicherlich eine der großen und spannenden zukünftigen Aufgaben der Sportmedizin darstellt.

SCHLÜSSELWÖRTER:
Neuroplastizität, adulte Neurogenese, Sport, Training, neuronale Bildgebung

Introduction and nomenclature

Positive effects of sports and exercise on brain functions have become apparent on a large and growing number of behavioral and neurobiologic scales on transmitter, cellular, synaptic, meso and macroscopic levels. The common denominator of these observations across all levels is the informed assumption that exercise may induce brain plasticity that encompasses a variety of morphological changes that have functional consequences. With the growing number of neurobiologic methods and broadening the possibilities to investigate plastic brain changes on all of these levels, it is crucial (and possible) to differentiate specific effects, which, on the other hand, allows a comprehensive view of brain function in health and disease. Synaptic brain plasticity, for example, refers to changes in the strength of synaptic connections in response to either an environmental stimulus (eg physical exercise) or an alteration in synaptic activity in a network (4), which then contributes to adaptive large scale network changes (28). Adult neurogenesis (among others) undoubtedly provides a basis for plastic changes and refers to the birth of new neurons from stem cells in defined locations of the (mammalian) brain. These cells may then have the potential to migrate, differentiate, and mature into functional nerve cells (39). Many factors

QR-Code scannen und Artikel online lesen.

CORRESPONDING AUTHOR:
Claus Reinsberger, MD PhD, Professor of Sports Medicine (Chair), Institute of Sports Medicine, Department of Sports and Health Faculty of Science, Universität Paderborn, Warburgerstr. 100, 33098 Paderborn
✉: Reinsberger@sportmed.upb.de

have been shown to regulate neurogenesis, such as stress, aging, drugs, environmental enrichment and physical activity (overview in (37)). The following article aims to provide a brief overview of the current knowledge and concepts of exercise induced neurogenesis and plasticity on several scales.

Neurogenesis in the adult brain

Generations of physicians and scientists were educated in the belief that all adult human neurons are post-mitotic. Therefore neurogenesis in the adult brain was not felt to be possible. It was rather assumed that during the embryonic and early post-natal period maturation of the brain occurs through the formation of neuronal circuits and networks of existing cells.

As early as in the sixties, however, it was already demonstrated that the mammalian brain contained neurons that could be dated postnatally in origin (1). Injecting rats with tritiated thymidine led to the expected autoradiographic detection of labeled glia cells, but also of neuronal nuclei, specifically in the dentate gyrus of the hippocampus (1). Further reports and laboratory techniques were then still insufficient to cause a shift in paradigmatic thinking about adult neurogenesis. Even the demonstration of variable seizes of thalamic nuclei of in the canary brain in relation to seasons (and singing behavior) 16 years later could not fully convince the community of the phenomenon of adult neurogenesis (21). One of the major methodological advances came with the observation that bromodeoxyuridine (BrdU) as an analogue of thymidine is used in DNA-replication and can be used a biomarker for cell proliferation. Immunohistochemical staining of BrdU-binding antibodies (after denaturation of DNA) revealed in various animal models that the hippocampus and the olfactory bulb may contain neurons that were generated after birth (15, 18, 32).

In 1998, it was shown for the first time that human hippocampal neurons also have the ability to originate after birth: Five patients with laryngeal or pharyngeal carcinoma received BrdU for intraoperative guidance of tumor resection. Post mortem, neuronal cells in the dentate gyrus and subventricular zones were found to be BrdU-positive, therefore must have originated between the time of surgery and passing of the patient (8). A more recent, complex and sophisticated technique of radioactively labeled carbon (^{14}C) measurements allows precise dating of biological tissue without pre-labeling (27). ^{14}C concentrations in the atmosphere vary depending on many influences, mainly on nuclear bombing and testing during the cold war in the 1950s – 1970s. During these years ^{14}C concentrations were exponentially elevated in the atmosphere with their peak in the late 1960ies. As ^{14}C is used as a substrate for photosynthesis and incorporated into the DNA during mitosis, ^{14}C concentration for each year can retrospectively be determined by analyzing annual rings of trees. Using this technique, the determination of ^{14}C concentrations in human tissues has been reported to allow dating of the tissue origin with a precision of +/- 1.5 years (27). Not surprisingly, cells from tissue with the ability to regenerate itself (e.g. intestine) revealed a variety of old and newly generated cells. Examination of brain tissue led to surprising results: hippocampal neurons, specifically in the dentate gyrus, could also be dated post-natally (26). Quantification of these findings allowed the application of mathematical models with the result that adult human brains are capable of building approximately 700 new hippocampal neurons per day and each year a turnover of 1.75 % of the pool of hippocampal neurons occurs. Using this method, it has been demonstrated that no other brain region (including the subependymic zone and the olfactory bulb) contained neurons that were originating after the first years of life.

Both hippocampal tissue derived from animal models and humans have been shown to be capable of generating new neurons post-natally. Although many mechanisms, including determination of the function of these newly build cells, still have to be fully elucidated, this important and replicated observations are a necessary basis to understand exercise induced neurogenesis and plasticity.

Exercise induced neuroplasticity in animal models

Application of BrdU-staining offers a biomarker to investigate effectors of neurogenesis in rodent models. Enriched environments consisting of cages with paper/plastic tubes, nesting material and tunnels to resemble social stimulation and to encompass experience have been shown to induce significantly more neurogenesis in the dentate gyrus than in animals in empty cages with a more isolated and sedentary lifestyle (Fig. 1) (15, 33). It was recognized that part of the enrichment effects may have been due to exercise and a few years later it was demon- ›

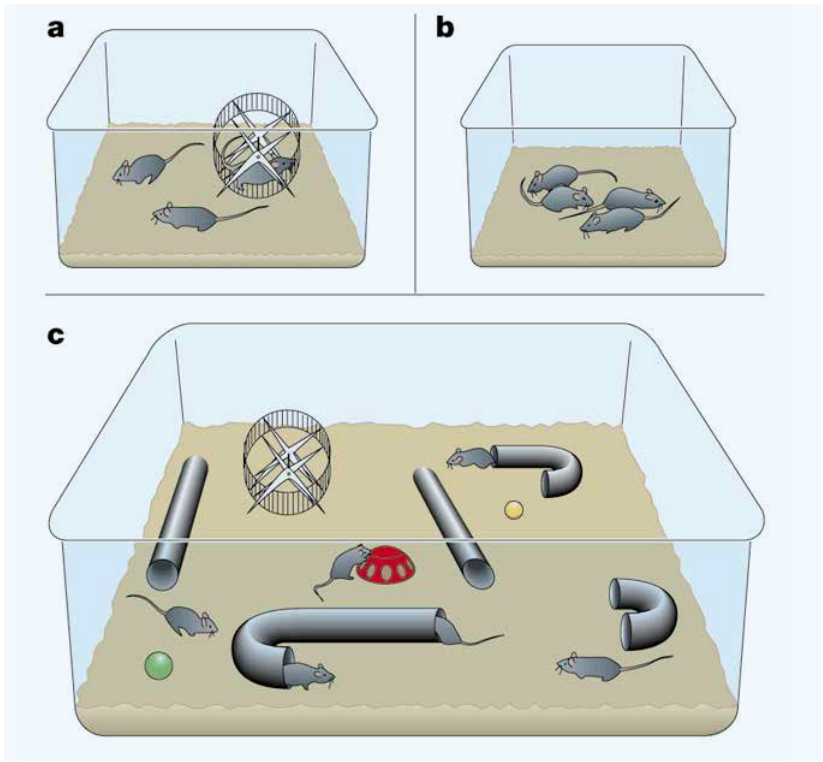

Fig. 1

a) A cage containing a running wheel for voluntary physical exercise (48 times 26 cm). b) A standard housing cage (30 times 18 cm). c) Cage for an enriched environment (86 times 76 cm). Enrichment consisted of social interaction (14 mice in the cage), stimulation of exploratory behaviour with objects such as toys and a set of tunnels, and a running wheel for exercise. With permission from Van Praag H, Kempermann G, Gage FH, Neural consequences of environmental enrichement. Nature Rev Neurosci. 2000.

strated that exercise alone is also indeed associated with cell proliferation and neurogenesis, specifically in the subgranular zone of the dentate gyrus (32). It is still debated whether physical activity is indeed the crucial or sole component to stimulate neurogenesis in enriched environments or whether (and how) both conditions may even be used complimentary to enhance effects, as hippocampal neurogenesis and increased BDNF levels may only be achieved when running wheels are part of the enriched environment (16), where as enriched environment alone may still induce synaptic plasticity and increased dendritic complexity (in type 1 diabetic mice) (2). It seems also possible that physical activity may fulfill the role of a primer and neurogenesis is stimulated subsequently by other aspects of enriched environments (e.g. cognitive stimuli) (10). Another very interesting point of debate is the optimal quantity (volume and intensity) of exercise to stimulate neurogenesis most effectively (overview in (37)), a crucial step if one intends to derive exercise recommendations for humans in health and disease. While it has been shown that neurogenesis occurs as early as 3 days after the onset of running (17), it is not entirely clear, how long this effects lasts, whether different aspects of exercise (cardiovascular, coordination or strength) may induce different changes and, most importantly, whether and how this refers to human neurophysiology.

In addition to the generation of new neuronal cells, dendritic sprouting is also affected by exercise: although granule cells of mice engaging in voluntary exercise seemed to have fewer primary dendrites, the overall length of the dendritic network is longer and its complexity is larger (23). It is also notable that exercise may increase dendritic spine density in other hippocampal regions than the dentate gyrus (CA 1 pyramidal neurons, layer III pyramidal neurons of the entorhinal cortex) (29). Although these findings have not been demonstrated in humans, it is fair to assume that not only the genesis, but also the maturation and development of granule cells of the dentate gyrus can be influenced by exercise.

Tab. 1

EXAMPLES OF PLASTIC MECHANISMS INDUCED BY EXERCISE (ANIMAL MODEL) (AFTER VIVAR ET AL., 2013) (34):
- (adult) neurogenesis (dentate gyrus, supependymal zone / olfactory bulb)
- synaptic plasticity (e.g. long term potentiation)
- increase of spinal density
- increase of neurotrophic factors (e.g. BDNF, FGF-2, NGF)
- increased angiogenesis (e.g. by incerased VEGF, IGF-1)

BDNF: Brain derived neurotrophic factor, FGF-2: fibroblast growth factor 2, NGF: nerve growth factor, VEGF: vascular endothelial grorth factor, IGF-1: insulin like growth factor 1.

Similarly, many other mechanisms influencing neurogenesis have been identified to be sensitive to exercise in the mammalian brain (tab 1, overview in (34)). Besides neurogenesis in the hippocampal and olfactory system, synaptic plasticity and increasing spine density are enhanced by exercise and contribute to a more complex neuronal network. Hippocampal longterm potentiation (in the dentate gyrus) as a model of learning and memory has been shown to be enhanced in running mice (31). Not surprisingly, it is also well documented that concomitantly concentrations of neurotrophic factors are also increased by exercise. Among those, Brain derived neurotrophic factor (BDNF) is probably described best (eg (14, 20)). It binds on tyrosine kinase receptors and reaches (induced by exercise) high concentrations in the hippocampus, but also other areas of the brain. It has been shown to mediate synpatogenesis, synaptic plasticity and enhanced learning and memory (34). In addition, exercise induced plastic changes of the brain may also be mediated by other growth factors such as Insulin like Growth factor 1 (IGF1) or increased angiogenesis stimulated through increasing concentrations of vascular endolthelial growth factor (VEGF) and others (34). While the existence of exercise induced neuronal plasticity (in the hippocampus, subependymal zone and bulbus olfactorius) in the mammalian brain has consistently be demonstrated, its full, most likely complex and heterogeneous development remains to be elucidated. Relevant mechanisms in rodent models include the generation of transit amplifying precursor cells of neural stem cells in cytogenic niches of the brain (13). These assemblies of astrocytes and neuroblasts around blood vessels are found adjacently to the subependymal cell layer (of the lateral ventricles) and the subgranular zone of the dentate gyrus (of the hippocampus), but it is currently investigated, which role similar mechanisms and locations may or may not play in human adult neurogenesis and how these mechanisms are sensitive to exercise.

Exercise induced neuroplasticity in humans

Over the past decades it became clear that despite several similarities mechanisms of adult neurogenesis may differ distinctly between the rodent and human brain. This may be due to the more complex organization of the human brain, but also on different analysis techniques that are utilized to investigate exercise induced brain plasticity or neurogenesis in general. It is, for example, still unclear, whether adult neurogenesis in humans occurs both in the dentate gyrus and subependymal zone with a differentiation along the olfactory bulb (as suggested by studies utilizing BrdU, eg (8)) or in the dentate gyrus alone, as the ^{14}C method was not able to detect neurogenesis in the olfactory bulb or subependymal zone (26). Surrogate markers are needed to investigate exercise induced plastic changes of the human brain. These usually refer to a sum effect of variable amounts of neuronal activity or a priori assumptions of neuronal effects resulting in behavioral performances or observations. The dentate gyrus, for example, may rather be involved in pattern separation than encoding or completion (which is believed to occur in the hippocampal regions CA1 and CA3 instead) (19). Based on this assumption and utilizing a pattern separation test, it was possible to demonstrate a positive correlation between the effects of a high intensity interval training (HIIT), expressed in the change of peak oxygen uptake, and the change in the mean % of correct pattern separation, albeit in a small number of subjects (n=12) (5).

A more unbiased approach to investigate structural brain plasticity is offered by quantitative neuroimaging techniques, for example magnetic resonance imaging (MRI). One of the first studies investigating brain changes in relation to sports activities revealed increases in cortical thickness in bilateral mid-temporal and left posterior-parietal regions after juggling (7). The utilized method of voxel based morphometry (VBM) has since become widely available and been implemented in a variety of studies investigating brain plasticity induced by sports and exercise, such as juggling, aerobics, balancing or even golf (overview in (30)). Pooling of VBM data across studies has become possible to increase sample sizes and perform meta-analyses, but, for example in juggling, results are not uniform: When comparing VBM results of 5 studies, the right occipito-temporal region was the only area that was consistently affected by structural changes of the grey matter induced by juggling, but the analysis was rather dominated by a high variability of other locations of the induced changes (30). The

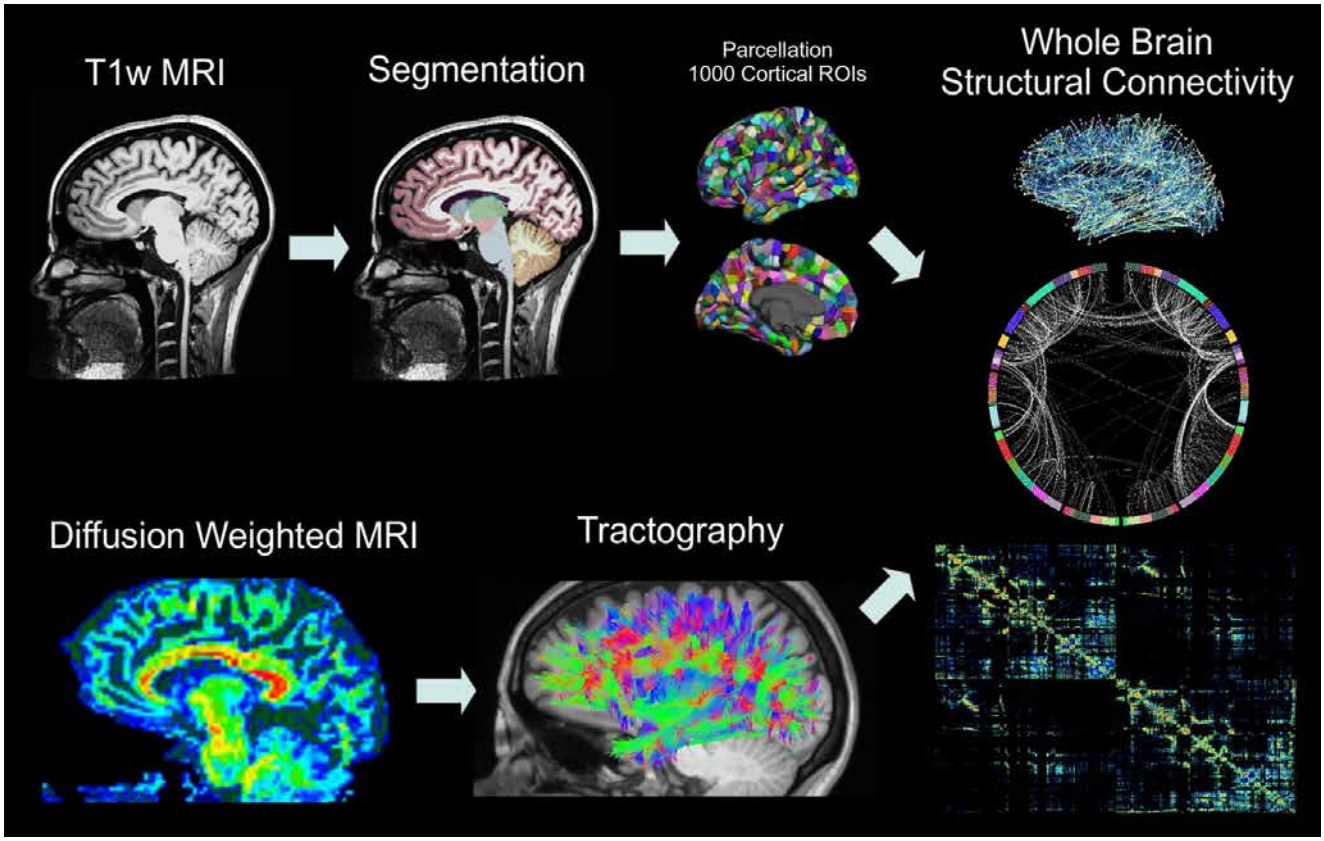

Fig. 2

Analysis of structural connectivity to investigate plastic brain changes in vivo. MP-RAGE volumes are segmented into 83 ROIs, which are further parcellated into 1000 cortical and 15 subcortical ROIs. Whole-brain white matter tractography is performed after voxelwise tensor calculation, and the density of fibers that connect each pair of cortical ROIs is used to calculate structural connectivity. (with permission from DeSalvo MN, Douw L, Tanaka N, Reinsberger C, and Stufflebeam SM. Altered structural connectome in temporal lobe epilepsy. Radiology. 2014;270(3):842-8.) T1w = T1-weighted, ROI: region of interest

reasons for the lack of reproducibility of a robust effect may be due to differences in study protocols, statistical techniques and morphometric algorithms. Modifications of MRI scanner settings resulting in higher signal to noise ratios, especially for grey-white matter boundaries, as well as different and more sophisticated algorithms to calculate brain volumes, grey/white matter volumes, cortical thickness or surface areas are used to provide more robust biomarkers of brain anatomy (38). Overall, surfaced based approaches seem favorable, because they allow separate determination of cortical thickness and surface area, which are independently determined by genetic factors, possibly explaining some of the diverging results of previous studies. They may also allow geometric inter subject registration with consideration of anatomical characteristics of the individual brain and independent registration of grey and white matter to facilitate group comparisons without a priori assumptions and with a very high resolution. While certain sports interventions are capable of inducing increases in grey matter volumes, others may lead to regional atrophic changes. In a recent VBM study, ultra marathon runners displayed cortical atrophy in the bilateral posterior temporal and occipito-parietal cortices, the anterior cingulate and caudate nucleus. Although these changes may be due to cerebral energy preservation processes, the exact clinical and functional implications of these findings remain to be elucidated. It was also noted that these changes normalized 8 months after the intervention (11).

Modern views on the brain and its organization understand the brain as a hierarchy of structural and functional networks (fig. 2) (28). On a structural level, the ‚connectome' approach is focused on quantifying and formally analyzing properties of complex large-scale connectivity networks, integrating MRI scans that are modified to investigate grey matter (eg T1 3D magnetization-prepared rapid gradient-echo (MP-RAGE), spoiled gradient echo (SPGR) or others) and white matter (Diffusion tensor imaging, DTI) signals. In this context, brain regions are regarded as nodes of a graph with connecting edges, based on measures of structural connectivity. Tools of network description, e.g. based on graph theory, offer the possibility to describe brain function by characterization of small-worlds and scale-free patterns, hierarchical modularity, hubs and rich clubs. Several neurological and neurodegenerative disorders, such as Alzheimer's Disease or Temporal Lobe Epilepsy, have been shown to be associated with significant network changes visualized by the mentioned methods (6). So far, this approach has not been applied to investigate plastic effects on the brain induced by sports and exercise. As with studies investigating plastic changes at different (cellular or meso-) levels, functional effects of the structural changes need to be elucidated by incorporation of behavioral data, but a wealth of such studies are expected in the future.

Similar to the investigation of structural (network-) changes, exercise induced brain plasticity may affect functional activities of the brain. Functional neuroimaging methods such as electroencephalography (EEG), magnetoencephalography (MEG), functional MRI (fMRI) and others offer non-invasive tools to investigate plasticity on functional levels. Functional networks may be activated extrinsically (by an external stimulus) or intrinsically (resting state). Especially the latter ones ›

have gained interest and attention over the past years, not only in conjunction with physical exercise and sports, but also with (neurological) diseases. Especially the Default Mode Network (DMN), an assembly of highly connected neurons of the medial pre-frontal, medial parietal and lateral temporal brain regions, seems to play a major role in operating the resting brain (22). It consummates most of the brain's energy and controls as a superior hierarchical network other intrinsic and extrinsic networks (for example visual or auditory integration) by issuing timing signals and cues to other brain areas. Its function and structure is altered in brain diseases such as Alzheimer's Disease (3) or temporal lobe epilepsy (24), but its integrity can be improved by physical exercise: Functional connectivity in some parts of the DMN can for example be increased in an elderly cohort by aerobic walking exercise (36). Applying a seeding technique, in which the time course of the signal in a known network hub is used as a reference for correlations with signal time courses of other brain regions, it was shown that (among others) connectivity of medial temporal areas to bilateral parahippocampal gyri, the lateral occipital cortex and the prefrontal cortex are increased by aerobic walking (36). These changes have further been shown to correlate with an increase of neurotrophic factors like BDNF, IGF-1 and VEGF (35). Could this be a mechanism that may not only account for basic neuroplastic effects of sports and exercise, but also a potentially disease modifying and preventive effect of exercise for neurodegenerative disease? What role do other (fronto-parietal, executive) networks play in this context? Many brain regions that become atrophic following ultra-marathon running indeed belong to the DMN (11), so does the brain try to conserve energy by reducing DMN activity? On the other hand, functional activity of parts of the DMN may play a role in visuo-spatial working memory strategies that may distinguish beginners from experienced athletes in coordination demanding sports like archery (25). Furthermore, functional activity of the DMN may be sensitive to (central) fatigue, so one could also hypothesize that the DMN is a crucial part for sensorimotor control and therefore coordinative performance in sports and its energy demands should be maintained as much as possible (9). More (specific) data is clearly needed to confirm or refute this promising hypothesis that may have to potential to lead to a biomarker to investigate (disease) specific effects of interventions containing a variable type, volume and intensity of exercise.

Conclusion – from bench to bedside?

Human sports and exercise is certainly more complex than wheel running in a rodent model. It will be most interesting and challenging to further elucidate, whether and how types (cardiovascular, coordination or strength), volume and intensity of exercise affect and stimulate human adult neurogenesis (and which property thereof). Based on the current basic science literature it may well be possible that Hollmann's five forms of motor demands (coordination, flexibility, strength, speed and endurance) have a distinct impact on adult neurogenesis and brain plasticity (12) . With this knowledge it would be possible to regard and utilize sports and exercise rather like a pharmacy than a single medication by designing disease specific exercise and sports specific training programs that may most effectively restore and/or enhance brain function, one of the great challenges of sports medicine in the years to come.

References

(1) **ALTMAN J, DAS GD.** Post-natal origin of microneurones in the rat brain. Nature. 1965;207(5000):953-956. doi:10.1038/207953a0

(2) **BEAUQUIS J, ROIG P, DE NICOLA AF, SARAVIA F.** Short-term environmental enrichment enhances adult neurogenesis, vascular network and dendritic complexity in the hippocampus of type 1 diabetic mice. PLoS ONE. 2010;5(11):e13993. doi:10.1371/journal.pone.0013993

(3) **BUCKNER RL, SNYDER AZ, SHANNON BJ, LAROSSA G, SACHS R, FOTENOS AF, SHELINE YI, KLUNK WE, MATHIS CA, MORRIS JC, AND MINTUN MA.** Molecular, structural, and functional characterization of Alzheimer's disease: evidence for a relationship between default activity, amyloid, and memory. J Neurosci. 2005;25(34):7709-7717. doi:10.1523/JNEUROSCI.2177-05.2005

(4) **CARONI P, DONATO F, MULLER D.** Structural plasticity upon learning: regulation and functions. Nat Rev Neurosci. 2012;13(7):478-490. doi:10.1038/nrn3258

(5) **DERY N, PILGRIM M, GIBALA M, GILLEN J, WOJTOWICZ JM, MACQUEEN G, AND BECKER S.** Adult hippocampal neurogenesis reduces memory interference in humans: opposing effects of aerobic exercise and depression. Front Neurosci. 2013;7:66. doi:10.3389/fnins.2013.00066

(6) **DESALVO MN, DOUW L, TANAKA N, REINSBERGER C, STUFFLEBEAM SM.** Altered structural connectome in temporal lobe epilepsy. Radiology. 2014;270(3):842-848. doi:10.1148/radiol.13131044

(7) **DRAGANSKI B, GASER C, BUSCH V, SCHUIERER G, BOGDAHN U, MAY A.** Neuroplasticity: changes in grey matter induced by training. Nature. 2004;427(6972):311-312. doi:10.1038/427311a

(8) **ERIKSSON PS, PERFILIEVA E, BJORK-ERIKSSON T, ALBORN AM, NORDBORG C, PETERSON DA, AND GAGE FH.** Neurogenesis in the adult human hippocampus. Nat Med. 1998;4(11):1313-1317. doi:10.1038/3305

(9) **ESPOSITO F, OTTO T, ZIJLSTRA FR, GOEBEL R.** Spatially distributed effects of mental exhaustion on resting-state FMRI networks. PLoS ONE. 2014;9(4):e94222. doi:10.1371/journal.pone.0094222

(10) **FABEL K, WOLF SA, EHNINGER D, BABU H, LEAL-GALICIA P, KEMPERMANN G.** Additive effects of physical exercise and environmental enrichment on adult hippocampal neurogenesis in mice. Front Neurosci. 2009;3:50.

(11) **FREUND W, FAUST S, GASER C, GRON G, BIRKLEIN F, WUNDERLICH AP, MULLER M, BILLICH C, AND SCHUTZ UH.** Regionally accentuated reversible brain grey matter reduction in ultra marathon runners detected by voxel-based morphometry. BMC Sports Sci Med Rehabil. 2014;6(1):4. doi:10.1186/2052-1847-6-4

(12) **HOLLMANN W.** Zur Trainingslehre: Muskuläre Beanspruchungsformen und ihre leistungsbegrenzenden Faktoren. Sportarzt Sportmed. 1967;11:443.

(13) **KAZANIS I, LATHIA JD, VADAKKAN TJ, RABORN E, WAN R, MUGHAL MR, ECKLEY DM, SASAKI T, PATTON B, MATTSON MP, HIRSCHI KK, DICKINSON ME, AND FFRENCH-CONSTANT C.** Quiescence and activation of stem and precursor cell populations in the subependymal zone of the mammalian brain are associated with distinct cellular and extracellular matrix signals. J Neurosci. 2010;30(29):9771-9781. doi:10.1523/JNEUROSCI.0700-10.2010

(14) **KEMPERMANN G, FABEL K, EHNINGER D, BABU H, LEAL-GALICIA P, GARTHE A, AND WOLF SA.** Why and how physical activity promotes experience-induced brain plasticity. Front Neurosci. 2010;4:189. doi:10.3389/fnins.2010.00189

(15) **KEMPERMANN G, KUHN HG, GAGE FH.** More hippocampal neurons in adult mice living in an enriched environment. Nature. 1997;386(6624):493-495. doi:10.1038/386493a0

(16) **KOBILO T, LIU QR, GANDHI K, MUGHAL M, SHAHAM Y, VAN PRAAG H.** Running is the neurogenic and neurotrophic stimulus in environmental enrichment. Learn Mem. 2011;18(9):605-609. doi:10.1101/lm.2283011

(17) **KRONENBERG G, BICK-SANDER A, BUNK E, WOLF C, EHNINGER D, KEMPERMANN G.** Physical exercise prevents age-related decline in precursor cell activity in the mouse dentate gyrus. Neurobiol Aging. 2006;27(10):1505-1513. doi:10.1016/j.neurobiolaging.2005.09.016

(18) **KUHN HG, DICKINSON-ANSON H, GAGE FH.** Neurogenesis in the dentate gyrus of the adult rat: age-related decrease of neuronal progenitor proliferation. J Neurosci. 1996;16(6):2027-2033.

(19) **MARR D.** Simple memory: a theory for archicortex. Philos Trans R Soc Lond B Biol Sci. 1971;262(841):23-81. doi:10.1098/rstb.1971.0078

(20) **NEEPER SA, GOMEZ-PINILLA F, CHOI J, COTMAN C.** Exercise and brain neurotrophins. Nature. 1995;373(6510):109. doi:10.1038/373109a0

(21) **NOTTEBOHM F.** A brain for all seasons: cyclical anatomical changes in song control nuclei of the canary brain. Science. 1981;214(4527):1368-1370. doi:10.1126/science.7313697

(22) **RAICHLE ME, MACLEOD AM, SNYDER AZ, POWERS WJ, GUSNARD DA, SHULMAN GL.** A default mode of brain function. Proc Natl Acad Sci USA. 2001;98(2):676-682. doi:10.1073/pnas.98.2.676

(23) **REDILA VA, CHRISTIE BR.** Exercise-induced changes in dendritic structure and complexity in the adult hippocampal dentate gyrus. Neuroscience. 2006;137(4):1299-1307. doi:10.1016/j.neuroscience.2005.10.050

(24) **REINSBERGER C, TANAKA N, COLE AJ, LEE JW, DWORETZKY BA, BROMFIELD EB, HAMIWKA L, BOURGEOIS BF, GOLBY AJ, MADSEN JR, AND STUFFLEBEAM SM.** Current dipole orientation and distribution of epileptiform activity correlates with cortical thinning in left mesiotemporal epilepsy. Neuroimage. 2010;52(4):1238-1242. doi:10.1016/j.neuroimage.2010.04.264

(25) **SEO J, KIM YT, SONG HJ, LEE HJ, LEE J, JUNG TD, LEE G, KWON E, KIM JG, AND CHANG Y.** Stronger activation and deactivation in archery experts for differential cognitive strategy in visuospatial working memory processing. Behav Brain Res. 2012;229(1):185-193. doi:10.1016/j.bbr.2012.01.019

(26) **SPALDING KL, BERGMANN O, ALKASS K, BERNARD S, SALEHPOUR M, HUTTNER HB, BOSTROM E, WESTERLUND I, VIAL C, BUCHHOLZ BA, POSSNERT G, MASH DC, DRUID H, AND FRISEN J.** Dynamics of hippocampal neurogenesis in adult humans. Cell. 2013;153(6):1219-1227. doi:10.1016/j.cell.2013.05.002

(27) **SPALDING KL, BHARDWAJ RD, BUCHHOLZ BA, DRUID H, FRISEN J.** Retrospective birth dating of cells in humans. Cell. 2005;122(1):133-143. doi:10.1016/j.cell.2005.04.028

(28) **STAM CJ.** Modern network science of neurological disorders. Nat Rev Neurosci. 2014;15(10):683-695. doi:10.1038/nrn3801

(29) **STRANAHAN AM, KHALIL D, GOULD E.** Running induces widespread structural alterations in the hippocampus and entorhinal cortex. Hippocampus. 2007;17(11):1017-1022. doi:10.1002/hipo.20348

(30) **THOMAS C, BAKER CI.** Teaching an adult brain new tricks: a critical review of evidence for training-dependent structural plasticity in humans. Neuroimage. 2013;73:225-236. doi:10.1016/j.neuroimage.2012.03.069

(31) **VAN PRAAG H, CHRISTIE BR, SEJNOWSKI TJ, GAGE FH.** Running enhances neurogenesis, learning, and long-term potentiation in mice. Proc Natl Acad Sci USA. 1999;96(23):13427-13431. doi:10.1073/pnas.96.23.13427

(32) **VAN PRAAG H, KEMPERMANN G, GAGE FH.** Running increases cell proliferation and neurogenesis in the adult mouse dentate gyrus. Nat Neurosci. 1999;2(3):266-270. doi:10.1038/6368

(33) **VAN PRAAG H, KEMPERMANN G, GAGE FH,** NEURAL CONSEQUENCES OF ENVIRONMENTAL ENRICHMENT. NAT REV NEUROSCI. 2000 DEC;1(3):191-8

(34) **VIVAR C, POTTER MC, VAN PRAAG H.** All about running: synaptic plasticity, growth factors and adult hippocampal neurogenesis. In: C Belzung and P Wigmore editors. Neurogenesis and Neural Plasticity. Berlin, Heidelberg: Springer-Verlag; 2013, pp. 189 - 210.

(35) **VOSS MW, ERICKSON KI, PRAKASH RS, CHADDOCK L, KIM JS, ALVES H, SZABO A, PHILLIPS SM, WOJCICKI TR, MAILEY EL, OLSON EA, GOTHE N, VIEIRA-POTTER VJ, MARTIN SA, PENCE BD, COOK MD, WOODS JA, MCAULEY E, AND KRAMER AF.** Neurobiological markers of exercise-related brain plasticity in older adults. Brain Behav Immun. 2013;28:90-99. doi:10.1016/j.bbi.2012.10.021

(36) **VOSS MW, PRAKASH RS, ERICKSON KI, BASAK C, CHADDOCK L, KIM JS, ALVES H, HEO S, SZABO AN, WHITE SM, WOJCICKI TR, MAILEY EL, GOTHE N, OLSON EA, MCAULEY E, AND KRAMER AF.** Plasticity of brain networks in a randomized intervention trial of exercise training in older adults. Front Aging Neurosci. 2010;2.

(37) **WANG Z, VAN PRAAG H.** Exercise and the brain: neurogenesis, synaptic plasticity, spine density, and angiogenesis. In: H Boecker, CH Hillman, L Scheef and HK Strueder editors. Functional Neuroimaging in Exercise and Sport Sciences. New York: Springer Science+Business Media; 2012, pp. 3-24.

(38) **WINKLER AM, KOCHUNOV P, BLANGERO J, ALMASY L, ZILLES K, FOX PT, DUGGIRALA R, AND GLAHN DC.** Cortical thickness or grey matter volume? The importance of selecting the phenotype for imaging genetics studies. Neuroimage. 2010;53(3):1135-1146. doi:10.1016/j.neuroimage.2009.12.028

(39) **ZHAO C, DENG W, AND GAGE FH.** Mechanisms and functional implications of adult neurogenesis. Cell. 2008;132(4):645-660. doi:10.1016/j.cell.2008.01.033