Review

Experience-dependent structural plasticity in the adult human brain

Arne May

Department of Systems Neuroscience, University Clinic Hamburg Eppendorf (UKE), D-20246 Hamburg, Germany

Contrary to assumptions that changes in brain networks are possible only during crucial periods of development, research in the past decade has supported the idea of a permanently plastic brain. Novel experience, altered afferent input due to environmental changes and learning new skills are now recognized as modulators of brain function and underlying neuroanatomic circuitry. Given findings in experiments with animals and the recent discovery of increases in gray and white matter in the adult human brain as a result of learning, the old concept of cognitive reserve, that is the ability to reinforce brain volume in crucial areas and thus provide a greater threshold for age-dependent deficits, has been reinforced. The challenge we face is to unravel the exact nature of the dynamic structural alterations and, ultimately, to be able to use this knowledge for disease management. Understanding normative changes in brain structure that occur as a result of environmental changes and demands is pivotal to understanding the characteristic ability of the brain to adapt.

Structural and functional plasticity in the brain

An intrinsic property of the human central nervous system is the lifelong ability for structural and functional brain reorganization [1]. The term 'plasticity' refers to functional or structural changes (which may trigger each other) that occur in the adult brain to adjust to changes in the external environment or internal milieu [2,3]. The extent of plastic reorganization is conditional on the relevance of the alterations for the individual and can have either beneficial or maladaptive behavioral consequences [1].

An excellent recent review focused on evidence that interindividual variability in a wide range of human behaviors could perhaps be predicted from the structure of gray and white matter tracts of the human brain measured with structural imaging [4]. However, to take one example, the apparent fact that individual differences in distractibility (or the tendency to lose focus of attention) are reflected in the structure and function of the human parietal cortex [5] does not tell us what the cause is and what the effect: do differences in structure and function of the parietal cortex give rise to differences in distractibility or vice versa? Intuitively we tend to see brain structure as hardwired and interpret a structural peculiarity (e.g. the microstructural integrity of the corpus callosum as assessed by diffusion tensor imaging (DTI; see Glossary) in healthy volunteers) as the reason for interindividual differences (in this case, in interhemispheric transmission time) [6]. However, it may well be the other way around: nearly all studies investigating brain morphology on an individual basis over time, that is not comparing cohorts, have found a strong direct correlation between learning and brain changes [7–13]. For instance, posterior hippocampal gray matter volume has been shown to correlate positively with spatial representation skills [14]. This is probably not innate but depends on the extent of detail and/or duration of use of spatial representations [15].

There is no doubt that genetic factors significantly influence cortical structure [16] and that differences in subjective experiences and skills can be attributed to regionally specific morphological differences in the brain [4]. It is by all means reasonable to assume that plasticity

Glossary

Adult neurogenesis: a specific case of cell-based brain plasticity where new neurons (and not only neurites and synapses) are added to the brain network in an activity-dependent way. In humans, new neurons are generated throughout life in the hippocampal region, which is thought to provide the functional backbone for learning and memory. Recent animal and human studies have proposed the hippocampus and neurogenesis a prime target in a number of diseases, most notably dementias as well as major depression.

Angiogenesis: the physiological process of growing new blood vessels.

Cross-sectional versus longitudinal studies: in morphometric studies investigating brain plasticity, two approaches are currently used. In cross-sectional studies the brain morphology of two cohorts of participants is compared, in longitudinal studies, the same participants are investigated twice: before and after an intervention (such as learning). Longitudinal studies are elaborate and time consuming but allow the detection of subtle changes that cannot be detected in cross-sectional studies because of anatomical differences between brains.

Diffusion tensor imaging (DTI): DTI and fiber tractography are new methods that can demonstrate the orientation and integrity of white matter fibers in the brain *in vivo*. This is done by measuring the microscopic molecular motion of water using specific MRI-sequences, taking advantage of the fact that large white matter tracts constrain random molecular motion by densely packed axonal membranes and myelin sheaths. Thus water will preferentially diffuse along the direction of the axon bundle rather than perpendicular to it. The measurement of this anisotropic diffusion of water forms the basis for diffusion imaging and allows investigation of white matter microstructure. Using this method, recent findings suggested that the observed improvement of working memory capacity is correlated to an increased myelination after training.

Enriched environment: the classical model to study the impact of 'experience' on the brain in animals is to compare the behavior, morphological changes and so on, of animals living in an enriched environment with animals living under the usual rather plain conditions of laboratory housing. This simple manipulation has far-reaching effects on the brain and its function. It was mentioned first, anecdotally, by Hebb, who reported that rats that he took home as pets showed behavioral improvements over their litter mates kept at the laboratory.

Synaptogenesis: the physiological process of increasing synapse number and dendritic complexity. This process may happen in a matter of days and is exercise dependent even in older age on the level of synaptic bulk and neurites.

Corresponding author: May, A. (a.may@uke.de)

1364-6613/$ – see front matter doi:10.1016/j.tics.2011.08.002 Trends in Cognitive Sciences, October 2011, Vol. 15, No. 10

is a characteristic of the nervous system that evolved for coping with changes in the environment [9]. Because some elegant studies could demonstrate a reorganization of cortical representation fields due to changes in environmental demands [17–20], the term brain plasticity very often refers to functional changes of brain activity. Understanding changes in brain structure also as a crucial result of learning and adaptation is pivotal in understanding the characteristic flexibility of our brain to adapt. Not everything is hardwired.

To date the strongest evidence for learning/training-induced structural reorganization in the adult brain comes from primate and nonprimate animal studies [21–24]. The crucial limitation however, is the invasive character of these studies and the fact that they can detect only very localized structural changes due to the nature of the techniques used. Imaging techniques such as magnetic resonance imaging (MRI), positron emission tomography and magnetoencephalography offer the opportunity to investigate human brain organization *in vivo* noninvasively. Due to its noninvasiveness and high spatial resolution, MRI has become the preferred imaging technique for the detection of structure–function relations characteristic for plasticity-driven processes. Cross-sectional and prospective studies demonstrated clear correlation between learning abilities and structural properties of the brain shedding light on plasticity phenomena in the healthy brain [8,25,14,26]. The same holds true for morphometric studies correlating external features such as years of practice or disease, skill level and so on with anatomical brain measures [10,27]. Furthermore, subsequent lesion studies confirmed the notion that neuroimaging techniques adopting cross-sectional or prospective experimental design can even provide a biomarker of outcome after brain injury [28,29] and disease prediction [30,31].

The neuroanatomical basis of structural brain plasticity

During the past decade, a steadily growing number of studies in primate and nonprimate animals confirm the notion that experience, learning new skills but also damage of the nervous system, can cause functional and structural reorganization of the brain. At the functional level it has been convincingly demonstrated that even loss of sensory input due to peripheral nerve lesion can induce reorganization of cortical representation fields [17–20]. At the structural level, these studies confirm the presence of reorganization due to expansion of remaining afferents into deprived areas in subcortical areas. This is followed by a large-scale cortical reorganization mainly due to transneuronal degeneration [19,32]. These examples raise the question whether it is adequate to distinguish between functional and structural plasticity, or whether this distinction is rather artificial.

The concept of an enriched environment, described anecdotally already by Hebb [33], is one of the most widely used experimental paradigms for studying learning-induced plasticity. Whether this model is specific for learning is not undisputed [34]. At the behavioral level enrichment is associated with increased learning and memory and reduction in age-related memory decline [35,36]. At the cellular level, enrichment results in hippocampal cell proliferation, angiogenesis and microglia activation [37]. These effects are probably, among others, mediated through increased expression of brain-derived neurotrophic factor, nerve growth factor, as well as N-methyl D-aspartate and α-amino-3hydroxy-5methyl-4isoxazole propionic acid modulation [38,39]. Furthermore, an enriched environment can interact with genotype previously described in animal models of neurodegenerative diseases like Huntington's disease, Parkinson's disease and brain injury [40–42].

Learning-induced structural changes can also affect the anatomical connectivity in the adult brain. Recent work has identified axonal remodeling, growth of new dendritic spines and synapse turnover as important structural mechanisms for experience-dependent plasticity in mature cortex [43]. A tracer study demonstrated that primates trained to use a rake to reach food showed stronger and denser temporoparietal junction connections within the intraparietal sulcus compared with untrained animals [44].

A very recent study provided compelling evidence that a specific environmental challenge during childhood shapes the macroscopic structure of the human basal ganglia [45]. Considering the impact of the environment on the function and structure of the brain [16], we face the challenge of modeling all genetic and environmental effects and interactions that influence brain morphology to understand the true potency of brain plasticity.

Cross-sectional differences: the hen or the egg?

A vast number of cross-sectional morphometric studies (Box 1) have demonstrated neuroanatomical correlates of learning and experience in different cognitive domains. For example, navigational experience has been reported to be correlated with posterior hippocampus size [14] and musical proficiency to be associated with volume enlargement of motor and auditory areas and their anatomical connections [10,26,46]. More recent studies discussed morphological enlargement in the cerebellar vermian lobules VI–VII in basketball players [47], changes in the motor system in professional female ballet dancers [48], gray and white matter changes in a frontoparietal network in golfers [11], increased gray matter in the left inferior frontal and bilateral inferior parietal lobules in academic mathematicians [49], and white matter changes in long-term trained Baduk players [50], a game that, like chess, requires higher-order cognitive capacities, such as learning, spatial imagination and abstract reasoning. Visual memory performance and visuospatial attention is reported to be correlated with fractional anisotropy (FA; a measure of axonal integrity and coherence) [51,52]. Parietal gray matter volume and underlying white matter fibers have been highlighted for their pivotal role in acquisition of novel sounds and knowledge of vocabulary [25,53,54]. Morphometric properties of predefined anatomical structures have even been used to predict learning abilities of novel speech sounds.

However, all of the above studies used cross-sectional analysis: that is, compared a specific professional skill or competence with sex- and age-matched controls at a single time point [15]. The question arises whether in some humans a (possibly genetic) structural difference in specific

Box 1. Morphometry: methodological issues

With the advent of modern *in vivo* imaging methods, in particular MR imaging, studies of brain morphology were no longer exclusively dependent on autopsy material. Although early neuroimaging studies provided a qualitative description of normal brain morphology and its deviations in disease (i.e. tumors), more recently developed MR-based methods allow a semi-quantitative (e.g. approximation of the amount of different brain tissues) evaluation between cohorts but also longitudinally, capturing brain changes over time. All quantitative MR-based methods are subsumed under the heading of MR morphometry of the brain and are based on the idea of using a common coordinate system or atlas. Normally, three-dimensional, high-resolution, T1-weighted MRI images acquired with conventional 1.5 T MR scanners and 1 mm^3 voxels provide sufficient detail and contrast whereas scanners with higher field strength (3 to 7 Tesla) allow for greater spatial resolution. Currently, the number of surface-, shape- or volume-based methods that capture different and complementary morphological characteristics of the brain is steadily growing. One of the widely used and best validated morphometric techniques used to capture structural alterations in the brain is VBM. VBM is a whole-brain method for the analysis of automatically preprocessed structural high resolution MRI data that treats images as continuous scalar measurements. The automated preprocessing of T1-weighted scans involves image intensity bias correction, segmentation into different tissue classes: gray matter, white matter and nonbrain voxels (CSF, skull), and normalization to the same stereotactic space. In summary, VBM represents an established straightforward technique, which became widely used due to the unbiased way of analyzing anatomical data. One of the main advantages of VBM is the intrasubject analysis of different time points in a linear way to explore local differences that cannot be detected in cross-sectional studies. This approach is very effective for shedding light on temporal and spatial patterns of learning/training-induced structural plasticity in the adult human brain.

parts of the brain might act as a precondition for the differences found, or whether these differences are the consequence of physical or cognitive exercise and learning. This question could only be answered by investigating the temporal characteristics of experience/lesion-induced plasticity changes: that is, using a longitudinal design. MR-based morphometry (Box 1), especially in conjunction with longitudinal designs, will add a completely new facet to our understanding of brain plasticity, in that it provides *in vivo* evidence of the capacity of the human brain not only to achieve functional reorganization [55] but to also adapt structurally with an unexpected amount of plasticity.

Dynamic changes in human brain structure

Longitudinal studies in which imaging data are acquired at multiple time points during experimental intervention have the potential to unveil dynamic properties of learning-related plastic changes. The first longitudinal studies investigated a specific learning paradigm, namely 3-ball cascade juggling [7]. Juggling represents a complex visuomotor task, where perception and anticipation of moving targets determine the planning of subsequent motor action. Daily training for three months assured the ability to perform the required minimum of 60 seconds three-ball cascade juggling. Volunteers were scanned at three time points: before starting to learn how to juggle, three months later when their juggling proficiency was tested and another three months later after a period of juggling restriction. At the second time point, a transient gray matter increase was observed in the extrastriate motion specific area hMT/V5 bilaterally and in the left inferior parietal sulcus (Figure 1). Interestingly, these regional gray matter changes degraded nearly to baseline with declining juggling performance after training had been stopped. Indeed, juggling performance at the third time point was much worse than at the peak of skilled performance at the second time point.

A follow-up study using the same design focused on the temporal aspects of the structural changes [13] and investigated whether these changes are performance or physical exercise dependent. A third study investigated whether and to what extent the elderly brain is still able to exhibit such structural plasticity [12]. The data confirmed the earlier observation and in addition showed that learning to juggle can alter gray matter in the occipitotemporal cortex as early as after 7 days of training and that, at least in principle, the human brain even in older age maintains its capacity to change its structure according

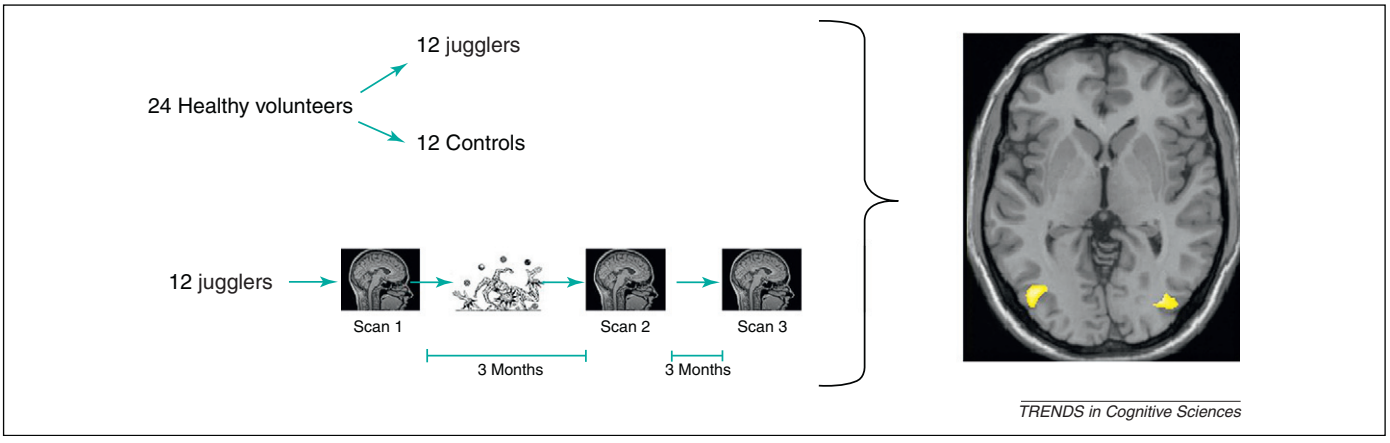

Figure 1. Methods and results of the first study demonstrating exercise dependant structural changes in the adult human brain. Diagram displaying the methods (left side of the Figure) and the results (right side of the Figure) of [7]. In this study, a homogeneous group of volunteers (21 female, 3 male; mean age 22 years) was matched by sex and age into two groups: 'jugglers' and 'nonjugglers'. Both groups were inexperienced in terms of juggling at the time point of the first scan. The volunteers from the 'jugglers' group were given 3 months to learn classic three-ball cascade juggling. The second scan was performed at the time of skilled performance (at least 60 seconds of endurance juggling). A third scan was carried out 3 months later. The group comparison at baseline showed no significant regional differences in gray matter between 'jugglers' and 'nonjugglers'. The longitudinal analysis demonstrated transient structural changes in the 'jugglers' group opposed to the 'nonjugglers'. A significant gray matter expansion between the first and the second scan was found in the midtemporal area (hMT/V5) bilaterally, which decreased towards the third scan.

to learning or physical exercise demands. Neither performance nor exercise alone could explain these changes. The qualitative change (i.e. learning of a new task) seems to be more crucial for the brain to change its structure than continued training of an already-learned task [12,13].

Using the same study design and diffusion imaging, a very recent study extended these findings and detected a localized increase in fractional anisotropy, a measure of microstructure, in white matter following training of a complex visuomotor skill [56]. Since then a large number of cross-sectional morphometric studies have demonstrated neuroanatomic correlates of learning and experience in different cognitive domains. Navigational experience has been reported to be correlated with posterior hippocampus size [14] and musical proficiency to be associated with volume enlargement of motor and auditory areas and their anatomical connections [10,26,46]. Learning a new language will prompt structural changes in the left inferior frontal gyrus, which are correlated with increase in second language proficiency [57]. Parietal gray matter volume and underlying white matter fibers have been highlighted for their pivotal role in the acquisition of novel sounds and knowledge of vocabulary [25,53]. Taken together, these studies have shown that not only experience-dependent functional but also structural remodeling of specific neocortical circuits underlies the acquisition of new skills.

Learning and experience shaping the brain

Several studies have built on and extended the findings in procedural learning [45,58–61] by studying longitudinally morphometric changes related to memory and learning. The first study of this type investigated a 'real-life' situation: the German basic medical exam, called 'Physikum' [8], which includes both oral and written tests in biology, chemistry, biochemistry, physics, social sciences, psychology, human anatomy and physiology demanding a high level of encoding, retrieval and content recall. This study observed differential effects of learning regarding dynamic temporal characteristics on cortical structures such as the hippocampal and parahippocampal gray matter and the posterior parietal cortex (PPC). The reported learning-related structural changes in PPC confirm its role in memory retrieval and memory success next to its previously assigned key function as part of space-based attention and motor intention circuitry [62]. The authors also tested for any decreases in gray matter as well as white matter changes and found a 'decrease' of gray matter between the first and second time point exclusively in the occipital parietal lobe. These changes were however directly adjacent to a highly significant 'increase' of white matter in this region which is in accordance with the literature [25]. An increase in white matter volume (i.e. a change of the classification of individual voxels from gray to white matter) will prompt an inverse effect (i.e. regional loss in gray matter volume) in adjacent gray matter. Using cortical thickness measurements across the cortical mantle, another study showed that memory training in the elderly improved source memory performance as well as regional increases in cortical thickness in the right fusiform and lateral orbitofrontal cortex, which correlated positively with improvement in source memory performance [63]. A combined longitudinal functional and morphometric MRI study on healthy volunteers who learned to decipher Morse code found an increase in task-specific neural activity in brain regions known to be crucially involved in language perception and memory, such as the inferior parietal cortex bilaterally and the medial parietal cortex and occipitotemporal region [64].

As in procedural learning [56], the changes in brain morphometry following training are not restricted to gray matter. A recent study showed that in declarative learning the amount of working memory training correlated with increased FA measures of fiber tracts in specific white matter regions, prompting the suggestion that a possible mechanism for the observed improvement in working memory capacity is increased myelination after training [65].

Physical exercise: shaping the brain or the mind or both?

Physical activity and an enriched environment have been shown to improve the rate of adult neurogenesis and maintenance of these new neurons [37,66]. A recent study demonstrating *in vivo* correlates of physical exercise-induced changes in the hippocampus confirms the theoretical possibility of angiogenesis/neurogenesis underlying plasticity processes [67]. Interestingly, these findings have been replicated in older and aged animals [68], suggesting that age is not *per se* a limiting factor for structural plasticity.

Regarding humans, several studies now suggest that, at least in principle, the human brain even in older age maintains its capacity to change its structure according to learning and physical or cognitive exercise demands [12,63]. Moreover, a large cohort study (more than a million participants) showed that cardiovascular fitness, as measured by ergometer cycling, positively associated with intelligence after adjusting for relevant confounders [69]. Consequently, it was proposed that mental stimulation might serve as a reserve mechanism in brain aging, given that macrostructural brain changes in response to cognitive training have been demonstrated in younger as well as older participants [63]. The idea of reserve against physiological brain atrophy and decline in higher cognitive functions stems from the repeated observation that there does not seem to be a direct relation between the degree of brain atrophy or brain damage and the clinical manifestation of that damage [70]. Aerobic activity improves cardiovascular fitness but it is not known whether this sort of fitness is necessary for improved cognitive function. Recently, Colcombe *et al*. demonstrated that aerobic fitness training of older humans can increase brain volume in that population [71]. A recent Cochrane review, however, came to the conclusion that the published data are insufficient to show that the improvements in cognitive function, which can be attributed to physical exercise, are due to improvements in cardiovascular fitness alone [72]. Nevertheless, the data published so far support conclusions about the potential value of exercise for elderly people (and children). A brain plasticity-based training program would potentially promise an improvement of the operational capabilities of aging adults. It is clear that as people age, they should not do less but more to keep and maintain their abilities [12].

Maladaptive plasticity: the flip side of the coin

Maladaptive plasticity can be defined as behavioral loss or even the development of disease symptoms resulting from plasticity changes in the adult human brain. Recent studies provide sufficient evidence that faulty practice or excessive demand could pose a risk of maladaptive plasticity depending on individual predisposition [73]. Animal models demonstrate that repetitive somatosensory stimulation of the fingers in primates results in abnormal hand postures similar to the clinical picture of dystonic writer's cramp in humans [74]. Voxel-based morphometry (VBM) studies demonstrated invariably gray matter increase in the neural circuitry involved in the pathophysiology of different focal forms of dystonia [75]. The inadequate changes in sensorimotor coupling and loss of somatotopy are considered to play a pivotal role in creating a pathological pattern of cortical activation leading to behavioral consequences in dystonia [76]. This theory is supported by the beneficial effect of sensorimotor retuning achieved by constraining excessive motor activity [77], sensorimotor discrimination training [78] and transient improvement of dystonic symptoms after slow-frequency repetitive transcranial magnetic stimulation to the contralateral motor cortex [79].

It is not understood why only a relatively small proportion of humans develop a chronic pain syndrome, considering that pain is a universal experience. Recently, local morphologic alterations of the brain in areas responsible for the transmission of pain were detected in patients suffering from phantom pain, chronic back pain, neuropathic pain, irritable bowel syndrome, fibromyalgia and two types of frequent headaches [80,81]. These alterations were different for each pain syndrome but overlapped in the cingulate cortex, the orbitofrontal cortex, the insula and dorsal pons. Additional affected structures bilaterally comprised the thalamus, basal ganglia and parahippocampus. These regions function as multi-integrative structures during the experience and anticipation of pain. Most of these data are discussed as representing damage or loss of brain gray matter, reinforcing the idea of chronic pain as a progressive disease. However, any data of an increase or decrease in gray matter in pain syndromes need to be considered in the light of all the observations which have been gathered in the past 10 years and probably do not justify a discussion of brain damage or consideration of whether or not the disease is progressive. It is probable that these changes are the consequence and not the cause of the respective pain syndromes because they may reverse, once the pain is adequately treated [82]. Moreover, structural changes of the brain may not be specific to a particular pain syndrome and for the moment only mirror the magnitude or duration of pain suffered. The topographical distributions of gray matter changes may well be the consequence of cortical regions having varying susceptibilities. It is interesting that 7 of the nearly 30 studies on chronic pain found gray matter changes in motor areas (M1 or SMA) between patients and controls, given that chronic pain often hinders physical exercise. One could reason that the qualitative change (i.e. pain or no pain) is more crucial for the brain to change its structure than a quantitative change of day-to-day activity (e.g. more or less exercise). Furthermore, one would expect changes following the physiotherapy regimen at least in osteoarthritis patients with hip-replacement therapy but both available studies did not describe such findings [82,83]. Further studies with more patients and using perhaps an even longer follow-up frame are certainly warranted. Nevertheless, chronic nociceptive input leads to intracortical remodeling, which highlights the remarkable potential of the adult brain to undergo anatomical changes. Improving our understanding of experience-dependent changes in cortical plasticity will have vast clinical implications for the treatment of chronic pain.

Cellular events underlying experience-dependent structural plasticity

The first study describing subtle anatomical changes using morphometry (in this case VBM) in patients was published in 1999 [84] and despite several hundred studies published since then, the nature of the underlying cellular events is still essentially unknown. In some respects, this situation resembles that in the functional MRI-field some years ago, when its use for our understanding of brain function was unquestioned, yet the long-supposed physiological correlate of the blood oxygen level-dependent signal was not yet proven.

For such changes in brain structure in response to exercise and learning, animal studies suggest that the increase in cortical gray matter is the result of a complex array of morphological changes including local synaptic events, such as the formation of new connections by dendritic spine growth and change in the strength of existing connections [21,23,85–87] (see also Figure 2).

Processes involving larger scale cortical reorganization might also involve mechanisms such as axonal remodeling, possibly in response to fundamental shifts in the environment. It is probable that the signal changes detected with morphometric techniques represent structural rearrangements at the cellular level rather than true volumetric expansion. However, a host of changes, including increase in the size of the soma and nucleus of neurons, glia and capillary dimensions, have also been demonstrated to

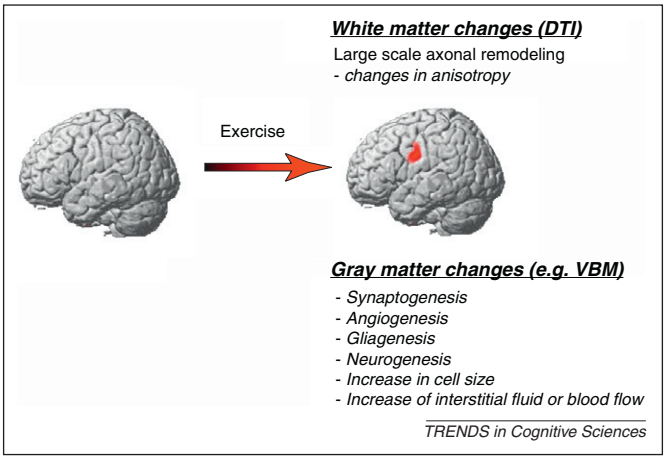

Figure 2. Possible causes for structural brain changes. Structural brain changes as a result of exercise or learning may have several causes at the macroscopic level. It is probable that the signal changes detected with morphometric techniques represent structural rearrangements at the cellular level rather than true volumetric expansion. In general, an increase in gray matter could be due to an increase in cell size, neural or glial cell genesis, spine and synaptic densities as well as changes in blood flow or interstitial fluid.

influence cortical morphology in animals exposed to enriched environments (for a review see [88]).

There is some direct *post mortem* evidence that similar processes occur in humans. Early VBM studies even described regional correlates of intelligence quotient (IQ). Despite the abovementioned caveats regarding cross-sectional studies, it is interesting that individuals with a high IQ demonstrated a greater number of dendrites on neurons in cortical regions important for language processing, whereas individuals with very low IQs seem to have less dendritic branching [89]. Potential correlates of these morphometric changes include a simple change in cell size, growth or atrophy of neurons or glia, as well as changes in the intracortical axonal architecture (i.e. synaptogenesis) [90]. In general, an increase in gray matter could be due to an increase in cell size, neural or glial cell genesis, spine and synaptic densities as well as changes in blood flow or interstitial fluid [9,37,91]. Changes in the synaptic contacts known to be the morphological substrate of long-term potentiation and long-term depression, or the cellular properties, are one component of the increasingly sophisticated explanations of brain plasticity. Further mechanisms reported to be linked to behavioral training-related plasticity are changes in gene expression [92], protein synthesis [93] and dendritic density [94]. Recent reports claim to have observed learning-related astrocytic proliferation, supporting the intriguing idea of glial involvement in learning-induced plasticity [95]. The time-course of some studies describing exercise-dependent gray matter increase [13,91] suggest rather fast adjusting neuronal systems, such as spine and synapse turnover [23], rather than such slow evolving mechanisms as neuronal or glial cell genesis [66]. Of note, a recent study demonstrating *in vivo* correlates of exercise-induced neurogenesis in the hippocampus confirms the theoretical possibility of angiogenesis underlying plasticity processes. The two most intuitively promising possibilities have been described in seasonally breeding songbirds, where the neural plasticity in the song-control system accompanies seasonal changes in singing behavior. One would be a simple increase in cell size [96] and the other spine and synapse turnover [97]. Although cellular structures such as neurons or glial cells themselves may be highly stable and nonplastic, they are integrated into highly dynamic and plastic neural networks that adapt to environmental and intrinsic changes.

Concluding remarks

Technical advances in live imaging studies and molecular approaches have contributed significantly to our current understanding of developmental plasticity and also focused our attention on plasticity exhibited by the mature brain. Neuroplasticity can be understood as the environmentally driven constant rearrangement of network homeostasis balancing the integration of neuronal activity, neurotransmitter release, neuronal (and perhaps glial) morphogenesis and changes in network formation including formation and elimination of synaptic structures. However, considering the lack of knowledge regarding the precise nature of the underlying events and their potential impact on the MRI signal, all of the abovementioned studies face the dilemma of choosing the optimal time span between the scans. It is indisputable that we are still missing crucial information regarding the kinetics of training-induced neuroplastic changes: how quickly, how enduring and simply how do these changes in white and gray matter come about? Moreover, assuming the inevitable impact of environmental influences outside the experimental condition systematic biases cannot be excluded. Future research (see Box 2) faces the challenge of understanding the principles of neural network reorganization at a structural level because this knowledge is relevant for a deeper understanding of long-term memory formation as well as for the treatment of neurological diseases such as stroke and dementia.

Box 2. Questions for future research

To date it is generally accepted that cognitive and physical exercise will trigger structural, that is morphological, as well as functional changes of brain networks. Considering the impact of the environment on the function and structure of the brain, we face several questions for future research:

- **The cellular bases of structural MRI signal changes**. Although the changes in gray matter that have been observed to date may reflect alterations in cell genesis, the time-course of our data suggest fast adjusting neuronal systems, such as spine and synapse turnover, rather than such slow evolving mechanisms as neuronal or glial cell genesis. Further work is needed to clarify whether vascular changes due to increased cerebral blood volume and/or cerebral blood flow may have additional effects to the observed changes.
- **The kinetics of structural MRI signal changes**. Important contributions to the exact causes of the structural changes will come from studies that look at the time parameters of these changes and include independent factors (i.e. electrophysiology or genetics).
- In addition, **animal studies** (allowing direct comparison of imaging and histological data) are a crucial and indispensable step towards a greater understanding of the structural changes found with modern morphometric techniques.
- **Characterizing the interplay between exercise-dependent changes in structure and function of the brain and performance**. Exercise-dependent brain changes are bidirectional: they can trigger each other. We need to better understand this interaction and answer the question whether it is reasonable to distinguish between functional and structural plasticity.
- **Neuroanatomical structures may be affected by age and disease but also by genetic and even environmental factors**. Future studies should attempt to model all genetic and environmental effects and interactions that influence brain morphology to understand the true potency of brain plasticity.
- **Computerized morphometric methods have the potential to detect early stages in the progression of neuroanatomical changes with the consequent ability to use these methods for diagnosis and (monitoring) treatment.** At the moment, however, the comparison of MR morphometry studies done at different research centers is almost impossible due to scanner and site-specific properties. One of the great challenges in the future is the validation of morphometric methods as well as the development of reliable means that allow the pooling of data from several scanners and centers. With the application of these methods, MR-based morphometry will become an extremely powerful tool for multicenter and therapeutic trials of several brain diseases.

Acknowledgments

The author wishes to thank Gerd Kempermann, Christian Gaser and Bogdan Draganski for valuable discussion and input.

References

1 Pascual-Leone, A. *et al.* (2005) The plastic human brain cortex. *Annu. Rev. Neurosci.* 28, 377–401

2 Zilles, K. (1992) Neuronal plasticity as an adaptive property of the central nervous system. *Ann. Anat.* 174, 383–391
3 Kempermann, G. (2006) Adult neurogenesis. In *Lifespan Development and the Brain* (Baltes, P.B. *et al.*, eds), pp. 82–107, Cambridge University Press
4 Kanai, R. and Rees, G. (2011) The structural basis of inter-individual differences in human behaviour and cognition. *Nat. Rev. Neurosci.* 12, 231–242
5 Kanai, R. *et al.* (2011) Distractibility in daily life is reflected in the structure and function of human parietal cortex. *J. Neurosci.* 31, 6620–6626
6 Westerhausen, R. *et al.* (2006) Interhemispheric transfer time and structural properties of the corpus callosum. *Neurosci. Lett.* 409, 140–145
7 Draganski, B. *et al.* (2004) Neuroplasticity: changes in grey matter induced by training. *Nature* 427, 311–312
8 Draganski, B. *et al.* (2006) Temporal and spatial dynamics of brain structure changes during extensive learning. *J. Neurosci.* 26, 6314–6317
9 Draganski, B. and May, A. (2008) Training-induced structural changes in the adult human brain. *Behav. Brain Res.* 192, 137–142
10 Gaser, C. and Schlaug, G. (2003) Brain structures differ between musicians and non-musicians. *J. Neurosci.* 23, 9240–9245
11 Jancke, L. *et al.* (2009) The architecture of the golfer's brain. *PLoS ONE* 4, e4785
12 Boyke, J. *et al.* (2008) Training-induced brain structure changes in the elderly. *J. Neurosci.* 28, 7031–7035
13 Driemeyer, J. *et al.* (2008) Changes in gray matter induced by learning–revisited. *PLoS ONE* 3, e2669
14 Maguire, E.A. *et al.* (2000) Navigation-related structural change in the hippocampi of taxi drivers. *Proc. Natl. Acad. Sci. U.S.A.* 97, 4398–4403
15 Maguire, E.A. *et al.* (2003) Navigation expertise and the human hippocampus: a structural brain imaging analysis. *Hippocampus* 13, 250–259
16 Thompson, P.M. *et al.* (2001) Genetic influences on brain structure. *Nat. Neurosci.* 4, 1253–1258
17 Jenkins, W.M. and Merzenich, M.M. (1987) Reorganization of neocortical representations after brain injury: a neurophysiological model of the bases of recovery from stroke. *Prog. Brain Res.* 71, 249–266
18 Pons, T.P. *et al.* (1991) Massive cortical reorganization after sensory deafferentation in adult macaques. *Science* 252, 1857–1860
19 Jain, N. *et al.* (2000) Growth of new brainstem connections in adult monkeys with massive sensory loss. *Proc. Natl. Acad. Sci. U.S.A.* 97, 5546–5550
20 Henderson, L.A. *et al.* (2011) Functional reorganization of the brain in humans following spinal cord injury: evidence for underlying changes in cortical anatomy. *J. Neurosci.* 31, 2630–2637
21 Holtmaat, A. *et al.* (2006) Experience-dependent and cell-type-specific spine growth in the neocortex. *Nature* 441, 979–983
22 Knott, G.W. *et al.* (2006) Spine growth precedes synapse formation in the adult neocortex *in vivo*. *Nat. Neurosci.* 9, 1117–1124
23 Trachtenberg, J.T. *et al.* (2002) Long-term *in vivo* imaging of experience-dependent synaptic plasticity in adult cortex. *Nature* 420, 788–794
24 Dancause, N. *et al.* (2005) Extensive cortical rewiring after brain injury. *J. Neurosci.* 25, 10167–10179
25 Golestani, N. *et al.* (2002) Anatomical correlates of learning novel speech sounds. *Neuron* 35, 997–1010
26 Sluming, V. *et al.* (2002) Voxel-based morphometry reveals increased gray matter density in Broca's area in male symphony orchestra musicians. *Neuroimage* 17, 1613–1622
27 Jancke, L. (2009) The plastic human brain. *Restor. Neurol. Neurosci.* 27, 521–538
28 Bates, E. *et al.* (2003) Voxel-based lesion-symptom mapping. *Nat. Neurosci.* 6, 448–450
29 Crinion, J.T. and Leff, A.P. (2007) Recovery and treatment of aphasia after stroke: functional imaging studies. *Curr. Opin. Neurol.* 20, 667–673
30 Reetz, K. *et al.* (2009) Structural findings in the basal ganglia in genetically determined and idiopathic Parkinson's disease. *Mov. Disord.* 24, 99–103
31 Turner, M.R. *et al.* (2011) Towards a neuroimaging biomarker for amyotrophic lateral sclerosis. *Lancet Neurol.* 10, 400–403
32 Kaas, J.H. *et al.* (1999) Subcortical contributions to massive cortical reorganizations. *Neuron* 22, 657–660
33 Hebb, D. (1947) The effects of early experience on problem-solving at maturity. *Am. Psychol.* 2, 306–307
34 Kempermann, G. *et al.* (2010) Why and how physical activity promotes experience-induced brain plasticity. *Front. Neurosci.* 4, 189
35 Rampon, C. *et al.* (2000) Effects of environmental enrichment on gene expression in the brain. *Proc. Natl. Acad. Sci. U.S.A.* 97, 12880–12884
36 van Praag, H. *et al.* (2000) Neural consequences of environmental enrichment. *Nat. Rev. Neurosci.* 1, 191–198
37 Gage, F.H. (2002) Neurogenesis in the adult brain. *J. Neurosci.* 22, 612–613
38 Pham, T.A. *et al.* (1999) CRE-mediated gene transcription in neocortical neuronal plasticity during the developmental critical period. *Neuron* 22, 63–72
39 Ickes, B.R. *et al.* (2000) Long-term environmental enrichment leads to regional increases in neurotrophin levels in rat brain. *Exp. Neurol.* 164, 45–52
40 Spires, T.L. *et al.* (2004) Environmental enrichment rescues protein deficits in a mouse model of Huntington's disease, indicating a possible disease mechanism. *J. Neurosci.* 24, 2270–2276
41 Bezard, E. *et al.* (2003) Enriched environment confers resistance to 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine and cocaine: involvement of dopamine transporter and trophic factors. *J. Neurosci.* 23, 10999–11007
42 Wagner, A.K. *et al.* (2002) Intervention with environmental enrichment after experimental brain trauma enhances cognitive recovery in male but not female rats. *Neurosci. Lett.* 334, 165–168
43 Barnes, S.J. and Finnerty, G.T. (2010) Sensory experience and cortical rewiring. *Neuroscientist* 16, 186–198
44 Hihara, S. *et al.* (2006) Extension of corticocortical afferents into the anterior bank of the intraparietal sulcus by tool-use training in adult monkeys. *Neuropsychologia* 44, 2636–2646
45 Kloppel, S. *et al.* (2010) Nurture versus nature: long-term impact of forced right-handedness on structure of pericentral cortex and basal ganglia. *J. Neurosci.* 30, 3271–3275
46 Bengtsson, S.L. *et al.* (2005) Extensive piano practicing has regionally specific effects on white matter development. *Nat. Neurosci.* 8, 1148–1150
47 Park, I.S. *et al.* (2009) Experience-dependent plasticity of cerebellar vermis in basketball players. *Cerebellum* 8, 334–339
48 Hanggi, J. *et al.* (2010) Structural neuroplasticity in the sensorimotor network of professional female ballet dancers. *Hum. Brain Mapp.* 31, 1196–1206
49 Aydin, K. *et al.* (2007) Increased gray matter density in the parietal cortex of mathematicians: a voxel-based morphometry study. *AJNR Am. J. Neuroradiol.* 28, 1859–1864
50 Lee, B. *et al.* (2010) White matter neuroplastic changes in long-term trained players of the game of 'Baduk' (GO): a voxel-based diffusion-tensor imaging study. *Neuroimage* 52, 9–19
51 Tuch, D.S. *et al.* (2005) Choice reaction time performance correlates with diffusion anisotropy in white matter pathways supporting visuospatial attention. *Proc. Natl. Acad. Sci. U.S.A.* 102, 12212–12217
52 Begre, S. *et al.* (2007) Relation of white matter anisotropy to visual memory in 17 healthy subjects. *Brain Res.* 1168, 60–66
53 Mechelli, A. *et al.* (2004) Neurolinguistics: structural plasticity in the bilingual brain. *Nature* 431, 757
54 Lee, H. *et al.* (2007) Anatomical traces of vocabulary acquisition in the adolescent brain. *J. Neurosci.* 27, 1184–1189
55 Flor, H. *et al.* (1995) Phantom-limb pain as a perceptual correlate of cortical reorganization following arm amputation. *Nature* 375, 482–484
56 Scholz, J. *et al.* (2009) Training induces changes in white-matter architecture. *Nat. Neurosci.* 12, 1370–1371
57 Stein, M. *et al.* (2010) Structural plasticity in the language system related to increased second language proficiency. *Cortex*, doi:10.1016/j.cortex.2010.10.007
58 Taubert, M. *et al.* (2010) Dynamic properties of human brain structure: learning-related changes in cortical areas and associated fiber connections. *J. Neurosci.* 30, 11670–11677
59 Herdener, M. *et al.* (2010) Musical training induces functional plasticity in human hippocampus. *J. Neurosci.* 30, 1377–1384

60 Granert, O. *et al.* (2011) Manual activity shapes structure and function in contralateral human motor hand area. *Neuroimage* 54, 32–41
61 Hyde, K.L. *et al.* (2009) The effects of musical training on structural brain development: a longitudinal study. *Ann. N. Y. Acad. Sci.* 1169, 182–186
62 Buchel, C. *et al.* (1999) The predictive value of changes in effective connectivity for human learning. *Science* 283, 1538–1541
63 Engvig, A. *et al.* (2010) Effects of memory training on cortical thickness in the elderly. *Neuroimage* 52, 1667–1676
64 Schmidt-Wilcke, T. *et al.* (2010) Distinct patterns of functional and structural neuroplasticity associated with learning Morse code. *Neuroimage* 51, 1234–1241
65 Takeuchi, H. *et al.* (2010) Training of working memory impacts structural connectivity. *J. Neurosci.* 30, 3297–3303
66 Kempermann, G. *et al.* (1997) More hippocampal neurons in adult mice living in an enriched environment. *Nature* 386, 493–495
67 Pereira, A.C. *et al.* (2007) An *in vivo* correlate of exercise-induced neurogenesis in the adult dentate gyrus. *Proc. Natl. Acad. Sci. U.S.A.* 104, 5638–5643
68 Kempermann, G. *et al.* (2002) Neuroplasticity in old age: sustained fivefold induction of hippocampal neurogenesis by long-term environmental enrichment. *Ann. Neurol.* 52, 135–143
69 Aberg, M.A. *et al.* (2009) Cardiovascular fitness is associated with cognition in young adulthood. *Proc. Natl. Acad. Sci. U.S.A.* 106, 20906–20911
70 Stern, Y. (2003) The concept of cognitive reserve: a catalyst for research. *J. Clin. Exp. Neuropsychol.* 25, 589–593
71 Colcombe, S.J. *et al.* (2006) Aerobic exercise training increases brain volume in aging humans. *J. Gerontol. A: Biol. Sci. Med. Sci.* 61, 1166–1170
72 Angevaren, M. *et al.* (2008) Physical activity and enhanced fitness to improve cognitive function in older people without known cognitive impairment. *Cochrane Database Syst. Rev.* CD005381
73 Rosenkranz, K. *et al.* (2005) Pathophysiological differences between musician's dystonia and writer's cramp. *Brain* 128, 918–931
74 Wang, X. *et al.* (1995) Remodelling of hand representation in adult cortex determined by timing of tactile stimulation. *Nature* 378, 71–75
75 Draganski, B. *et al.* (2003) 'Motor circuit' gray matter changes in idiopathic cervical dystonia. *Neurology* 61, 1228–1231
76 Hummel, F. *et al.* (2002) Inhibitory control of acquired motor programmes in the human brain. *Brain* 125, 404–420
77 Candia, V. *et al.* (2003) Effective behavioral treatment of focal hand dystonia in musicians alters somatosensory cortical organization. *Proc. Natl. Acad. Sci. U.S.A.* 100, 7942–7946
78 Byl, N.N. *et al.* (2003) Effect of sensory discrimination training on structure and function in patients with focal hand dystonia: a case series. *Arch. Phys. Med. Rehabil.* 84, 1505–1514
79 Siebner, H.R. *et al.* (2003) Patients with focal arm dystonia have increased sensitivity to slow-frequency repetitive TMS of the dorsal premotor cortex. *Brain* 126, 2710–2725
80 May, A. (2008) Chronic pain may change the structure of the brain. *Pain* 137, 7–15
81 May, A. (2011) Structural brain imaging: a window into chronic pain. *Neuroscientist* 17, 209–220
82 Rodriguez-Raecke, R. *et al.* (2009) Brain gray matter decrease in chronic pain is the consequence and not the cause of pain. *J. Neurosci.* 29, 13746–13750
83 Gwilym, S.E. *et al.* (2010) Thalamic atrophy associated with painful osteoarthritis of the hip is reversible after arthroplasty: a longitudinal voxel-based-morphometric study. *Arthritis Rheum.* 62, 2930–2940
84 May, A. *et al.* (1999) Correlation between structural and functional changes in brain in an idiopathic headache syndrome. *Nat. Med.* 5, 836–838
85 Chklovskii, D.B. (2004) Synaptic connectivity and neuronal morphology: two sides of the same coin. *Neuron* 43, 609–617
86 Chklovskii, D.B. *et al.* (2004) Cortical rewiring and information storage. *Nature* 431, 782–788
87 Sur, M. and Rubenstein, J.L. (2005) Patterning and plasticity of the cerebral cortex. *Science* 310, 805–810
88 Muotri, A.R. and Gage, F.H. (2006) Generation of neuronal variability and complexity. *Nature* 441, 1087–1093
89 Huttenlocher, P.R. (1991) Dendritic and synaptic pathology in mental retardation. *Pediatr. Neurol.* 7, 79–85
90 Aimone, J.B. *et al.* (2006) Potential role for adult neurogenesis in the encoding of time in new memories. *Nat. Neurosci.* 9, 723–727
91 May, A. *et al.* (2007) Structural brain alterations following 5 days of intervention: dynamic aspects of neuroplasticity. *Cereb. Cortex* 17, 205–210
92 Kleim, J.A. *et al.* (1996) Synaptogenesis and Fos expression in the motor cortex of the adult rat after motor skill learning. *J. Neurosci.* 16, 4529–4535
93 McAllister, A.K. *et al.* (1995) Neurotrophins regulate dendritic growth in developing visual cortex. *Neuron* 15, 791–803
94 Kolb, B. *et al.* (1994) Dissociation of the medial prefrontal, posterior parietal and posterior temporal cortex for spatial navigation and recognition memory in the rat. *Cereb. Cortex* 4, 664–680
95 Kleim, J.A. *et al.* (2007) Systematic assessment of training-induced changes in corticospinal output to hand using frameless stereotaxic transcranial magnetic stimulation. *Nat. Protoc.* 2, 1675–1684
96 Thompson, C.K. and Brenowitz, E.A. (2005) Seasonal change in neuron size and spacing but not neuronal recruitment in a basal ganglia nucleus in the avian song control system. *J. Comp. Neurol.* 481, 276–283
97 De Groof, G. *et al.* (2009) Structural changes between seasons in the songbird auditory forebrain. *J. Neurosci.* 29, 13557–13565