A.R. Møller (Ed.)
Progress in Brain Research, Vol. 157
ISSN 0079-6123

CHAPTER 5

Cortical reorganization in the aging brain

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Abstract: Aging exerts major reorganization and remodeling at all levels of brain structure and function. Studies in aged animals and in human elderly individuals demonstrate that sensorimotor cortical representational maps undergo significant alterations. Because cortical reorganization is paralleled by a decline in perceptual and behavioral performance, this type of cortical remodeling differs from the plastic reorganization observed during learning processes in young individuals where map changes are associated with a gain in performance. It is now clear that brain plasticity is operational into old age; therefore, protocols for interventions such as training, exercising, practicing, and stimulation, which make use of neuroplasticity principles, are effective to ameliorate some forms of cortical and behavioral age-related changes, indicating that aging effects are not irreversible but treatable. However, old individuals cannot be rejuvenated, but restoration of function is possible through the emergence of new processing strategies. This implies that cortical reorganization in the aging brain occurs twice: during aging, and during treatment of age-related changes.

Keywords: aging; plasticity; cortical maps; cortical processing; perception; behavior; enriched environment; amelioration of aging effects; intervention

Introduction

Aging societies

From the very beginning of human civilization, the process of aging appeared to exert a peculiar attraction and fascination. The fear of aging and the associated inevitable vanishing of life quality find their expression in a desire for measures that provide longevity, a yearning frequently captured in fine arts. However, it is only for a few decades that we experience a dramatic increase of life span. Although aging is an old problem, the emergence of such longevity for a substantial portion of the population is a fairly new phenomenon.

In fact, we witness a unique restructuring of the aging pattern in the societies of the industrial nations, characterized by an increasing probability to reach old age (Fig. 1). Concomitantly, the probability to suffer from age-related disorders has increased dramatically, indicating an urgent need for a more comprehensive understanding of the different facets of aging. Therefore, the investigation of the aging brain is not only fascinating from the standpoint of how aging affects neural structures, but also vital with respect to the many implications of aging on social disciplines, such as psychology, sociology, health care, and politics in general. However, surprisingly little research efforts are devoted to unravel the diverse aspects of the aging brain.

Given the restructuring in the industrial civilizations, the preservation of every-day life competence of aged populations becomes increasingly important. In particular, the maintenance of cognitive

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DOI: 10.1016/S0079-6123(06)57005-0

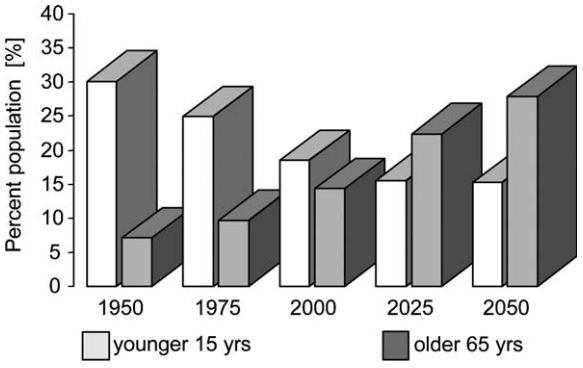


Fig. 1. Development of the aging structure of the industrialized countries USA, Europe, and Japan (adopted from world population prospects. The 2002 Revision, UN, New York).

and sensorimotor abilities is crucial for maintaining an independent life style at old age. In this context it is of far-reaching consequences to understand whether age-related changes are due to the accumulation of degenerative processes and thus largely irreversible, or whether age-related changes can be understood in the framework of neuroplasticity and subsequent compensatory mechanisms, for which there are possibilities of effective treatment.

Few other medical disciplines have to contest similar misconceptions and anecdotal and erroneous knowledge as gerontology. For example, when young and adult people were questioned about their expectancies about the social and psychological conditions at old age, their response pattern revealed a significant underestimation of the quality of life at older age, exemplifying the misconception of aging in the public opinion (Palmore, 1988). According to the "Berlin study," there exists a clear negative correlation between age and measures of intelligence (Linderberger and Baltes, 1992). However, in spite of this overall correlation, the interindividual variability in the population of people aged between 70 and 103 years is enormous. As a result, despite the negative correlation, the highest rating in intelligence performance is reached by a woman aged 87.

Aging theories

In the search of understanding of aging processes, many "aging theories" have been developed. Some of these theories are stochastic in nature and describe aging processes by a probabilistic accumulation of factors that progressively exert deteriorating effects onto the organism. Other theories are deterministic in nature and assume that aging is the consequence of endogenous and/or genetically programmed processes. Among the stochastic theories are "tear and wear" (Pearl, 1924), "free radicals" (Harman and Piette, 1966), "collagen/cross linkage" (Verzar, 1963), "error and fidelity theory" (Orgel, 1963) and the "immune theory" (Walford, 1967). Deterministic theories are known as the "absolute metabolic scope theory" (Rubner, 1908) and the "cell doubling theory" (Hayflick, 1968). While each of these theories can account for only some aspects observed during aging, there is now agreement that aging cannot be explained by a single theory, but instead, must almost be regarded as caused by a multitude of factors.

Further evidence that aging must not automatically imply a general decline comes from studies of the so-called "oldest old," i.e., participants 100 years and older, who characteristically display considerable mental and physical fitness. With few exceptions these individuals report a high degree of subjective wellness that include active participation in social and cultural life. Interestingly, no correlations have so far been established between specific events in their individual life-span history and the amount of vitality at very old age (Perls, 1995).

It has been a main desire to be able to interfere with aging processes in order to delay or to ameliorate the impact of age-related changes. In rodents, it is well established that diet and caloric restrictions have significant life-extending effects. It has been discussed whether comparable effects exist in primates and humans (cf. Walford, 1985; Sohal and Weindruch, 1996). A longitudinal study at the University of Wisconsin of the effects of caloric restrictions on longevity and diseases in rhesus monkeys is expected to show results at or about year 2020 (Wanagat et al., 1999). Other evidence suggests that maintained physical and mental exercise are prerequisites for what has been called "successful aging," although definite answers might not be revealed until the next decades

(Rowe and Kahn, 1987; Elward and Larson, 1992; Kramer et al., 1999). New approaches that are based on neuroplasticity and use specific training and stimulation protocols are currently being tested. These approaches provide new intervention techniques with the overall goal of ameliorating age-related decline in neural function (Dinse et al., 2005, 2006). The goal of these techniques is not to extend life expectancy, but to achieve healthy aging for as long as possible.

Myths and facts

An editorial with the title ''How old is old?'' addressed a most crucial question in aging research (Coleman, 1989) and discussed a survey of articles published in the journal Neurobiology of Aging in which rodents had been defined as ''aged'' or ''old'' at ages that varied from 18 to 53 months. One article describes changes at 7 months of age as an ''early manifestation of aging.'' Without further comments, this highlights the imperative need for multiple time points in aging studies (Coleman et al., 1990), not only in respect to rodents, but in all types of aging studies.

The acknowledgment of a large heterogeneity and interindividual variability in brain structure was an important step in the development of gerontology. This variability seems to be a general characteristic and has been observed not only in elderly humans, but also in aged primates and rodents. A large degree of variability has been shown to be present at any possible level of description and for any possible variable and parameter, making studies of aging complex (Rapp and Amaral, 1992; Gallagher and Rapp, 1997).

''The concept that cortical neurons are lost with age and that this is the basis for cognitive decline is so embedded in our culture that when someone elderly is a little forgetful it is often said that 'He/she is losing his/her neurons.'' (cited from Peters et al., 1998a). In fact, the hypothesis that there is a significant loss of neurons during normal aging dates back to Brody (1955). However, recent studies revealed a remarkable degree of constancy of the number of neurons in the brain (Flood and Coleman, 1988; Morrison and Hof, 1997; Peters et al., 1998a). Estimations of the number of neurons in the brain are hampered by technical problems and by the large individual variations in the number of neurons in the brain. For example, the size of area 17 in the human or primate brain can vary by a factor of three among individuals (Stensaas et al., 1974; Peters et al., 1998a, b). This enormous variability raises doubt about the significance of a loss of up to 10% of neurons, when individual variations can be more than 100%. Rapp and Gallagher (1996), in a study of neuron counts in representative samples of the entire hippocampus of behaviorally tested rats, showed no age-related loss of neurons, even in the animals that had the greatest age-related behavioral impairments. The question regarding the presence of detectable structural counterpart to the behavioral impairments that occurs during aging thus remains.

Cellular and molecular changes during aging

It had been suggested that only certain subpopulations of neurons might undergo losses and that there may be reductions of specific sets of dendritic spines demonstrated to occur in the prefrontal cortex during aging (Peters et al., 1998b). Molecular shifts in morphologically intact circuits have been described in the dentate gyrus in old monkeys (Gazzaley et al., 1996). Old rats with spatial learning deficits displayed significant reductions in synaptophysin immunoreactivity in CA3 of the hippocampus relative to either young controls or age-matched animals with preserved learning (Smith et al., 2000). More recently it was shown that behavioral performance correlates with *N*-methyl-D-aspartate (NMDA) receptor-dependent long-term depression (LTD) (NMDAR-LTD) in young animals and with non-NMDAR-LTD in old animals. NMDAR-LTD is reduced in old rats with learning deficits, but age-matched unimpaired animals show increased non-NMDAR-LTD. This suggests that high-functioning old rats maintain the ability to generate LTD, but do so by different mechanisms than those used by young adults (Lee et al., 2005). Thus, while hippocampal information processing can deteriorate during normal aging without detectable significant neuronal loss, these findings imply that a

circuit-specific pattern of variability in the molecular organization of the hippocampus is coupled to individual differences in cognitive function during normal aging.

Aging of sensorimotor behavior and cortical map plasticity

Decline of cognitive and sensorimotor abilities is clearly associated with aging but the magnitude and the time of onset of age-related changes differ considerably between individual animals. While there is a growing body of information about age-related changes at the cellular and molecular levels, little is known about how aging affects the way in which neurons process and integrate sensory information, and therefore little is known about how aging affects the functional representation of sensory information in human cerebral cortices. While human aging processes influence all stages of sensorimotor processing, it is not known how cortical representations of somatosensory input are affected by normal, nonpathological aging, and how cortical changes affect tactile perception and sensorimotor functions.

It is well documented that both the human and nonhuman somatosensory systems contains highly ordered maps of the body surface. These maps are not fixed, but subject to modification through expression of neural plasticity. Imaging studies have shown that continuous and long-lasting practice of specific sensorimotor functions resulted in expansions of the respective cortical areas, as described for blind Braille readers and musicians (Pascual-Leone et al., 1993; Elbert et al., 1995; Pantev et al., 1998; Sterr et al., 1998). These studies corroborated earlier animal studies, which demonstrated that training-induced enlargement of cortical maps as a result of expression of cortical plasticity (Recanzone et al., 1992, 1993; Dinse and Merzenich, 2002). There is often a direct proportionality between the amount of cortical reorganization and the individual improvement of performance and skills (Recanzone et al., 1992; Pascual-Leone et al., 1993; Xerri et al., 1994; Elbert et al., 1995; Buonomano and Merzenich, 1998; Dinse and Merzenich, 2002). The opposite effect has been demonstrated to occur from disuse such as after immobilization through cast wearing (Liepert et al., 1995; Ragert et al., 2003). After days to weeks of wearing a cast the respective cortical representations shrink and that has been associated with decreased perceptual abilities. After removal of the cast these changes reversed and functions returned to the baseline conditions. These data thus demonstrate use-dependent neural plasticity applies to situations of severely reduced use.

These findings regarding different forms of neural plasticity suggest that at least some forms of age-related changes of somatosensory processing and behavior can be explained in the framework of use-dependent plasticity.

Taking advantage of new technologies such as magnetic resonance imaging (MRI) makes it possible to analyze gray matter density in healthy human individuals. In participants in an MRI study with age from 7 to 87 years, the density of gray matter decreased significantly with age. The decrease in dorsal frontal and parietal association cortices occurred in a nonlinear way, most rapidly between the age of 7 and 60 years (Sowell et al., 2003). The age effects were inverted in the left posterior temporal region, where the increase of the density of gray matter continued up to age 30 and then rapidly declined. Visual, auditory and limbic cortices where fibers are known to become myelinated early, showed a more linear pattern of aging. Similarly, data from longitudinal measures of five-year change in the regional brain volumes in healthy adults revealed substantial shrinkage of the caudate, the cerebellum, the hippocampus, and the association cortices, with minimal change in the entorhinal and none in the primary visual cortex (Raz et al., 2005). Both studies showed that age-related brain volume changes are very localized with large difference in time course and time of onset.

Cortical reorganization in the aging brain occurs twice: during aging, and during treatment of age-related changes

In the following we provide a summary of results obtained from studies of a commonly used animal model of aging. The aim of the research was to explore the nature of age-related changes of tactile

perception and cortical reorganization in healthy elderly and the possibilities for ameliorating the age-related changes. It emerges from these studies that aging causes major restructuring of the brain and reorganization of its function. Moreover, it was demonstrated that intervention protocols using the principles of neural plasticity can ameliorate many forms of age-related deteriorations. These positive effects are based upon cortical remodeling, which leads to the emergence of what may be called the third brain: A reorganized aged brain that in many aspects differs from an untreated old brain (see p. 75).

Rat aging

Cortical reorganization in rats during normal aging

Rats are convenient for studies of aging because they age within 2–3 years. We used male hybrid Fischer 344 × Brown Norway (FBNF1) rats to study age-related changes of sensorimotor cortical representation (maps) and information processing using single- or multiunit recordings.

> The FBNF1-strain is specifically recommended for aging research by the National Institute of Aging (http://www.nia.nih.gov/ResearchInformation/ScientificResources). Animals were kept in standard housing environments to study age-related changes of somatosensory cortex. The 50% probability of survival in an aging colony is approximately 34.5 months for male FBNF1 (Sprott, 1997). If not otherwise stated, the FBNF1 animals were 29 months of age or older. A particular advantage of the FBNF1 animals is that they age in a rather healthy way, and that the gain in body weight during aging is small with 400–450 g in young vs. 500–530 g in old rats.

Age-related changes of rat sensorimotor behavior
Deterioration of walking, particularly of the hindlimbs are the characteristic impairment of the sensorimotor state in old rats, which typically slide and drag their limbs due to insufficient elevation of the feet (Ingram, 1988; Schuurman and Traber, 1989a, b; Stoll et al., 1990; Spengler et al., 1995). Old rats use the more distal parts of the heels in addition to the digits and pads for locomotion used by younger rats. This leads to reduced sensory stimulation of the hindpaw (cf. Fig. 2). This sensorimotor impairment is mainly restricted to the hind-limb. We hypothesized that the use of the forelimbs is intact because they are engaged in cleaning, feeding, and looming behavior throughout life. However, despite the behavioral intactness of the forelimb, walking in old rats is slowed down and displays many compensatory changes such as increased step frequency and increased duty cycle (Schulze and Dinse, unpublished).

Age-related changes of rat sensorimotor cortex organization
The cortical receptive fields (RFs) in young adult animals (3–6 months of age) to cutaneous stimulation of the hindpaw usually are small comprising only single or neighboring digits and pads, while RFs on the proximal part of the paw represent larger skin areas. In contrast, cutaneous RFs of the hindpaw in old rats were significantly enlarged compared to adults (about 200% on average). RFs in old animals represented multiple digits and pads, and the RFs of the proximal parts of the paw were much larger than in younger adults (Fig. 3). Since the skin surface is about the same in young and old rats, the enlargement of the RF means that RFs overlap to a greater extent in old than in younger adult rats (Spengler et al., 1995).

Mapping the hindpaw representation on the surface of the SI cortex of old rats revealed several differences from younger rats: First, because the size of the RFs increased, so did the cortical point-spread function (Fig. 4). The average cortical area excited by tactile stimulation in old rats was $0.051\,mm^2 +/- 0.018$ (s.d.) compared to $0.016\,mm^2 +/- 0.011$ (s.d.) in young control rats (two-sided unpaired Student's t-test, $p < 0.001$). Secondly, the overlap between zones of activity evoked by stimuli to different skin sites increased as well contributing to an overall loss of fine grained topography and the topographic order of the hindpaw map was severely deteriorated.

Fig. 2. Comparison of sensorimotor performance of young and of old rats. Footprints of the hindpaw as shown on the left are typically found in young rats serving as control group. This walking pattern is correlated with distinct and selective sensory inputs where single digits and pads are placed on the ground. Prints depicted in the middle and on the right are typical for old rats. The footprints shown in the middle are correlated with an intermediate state of sensorimotor performance; those on the right are correlated with multiple and diffuse inputs, sometimes even from the dorsal side of the paw; when the foot is twisted and dragged behind the body (reprinted from Spengler et al. (1995) with permission from Lippincott Williams & Wilkins).

To visualize the effects of aging on the topography of the underlying cortical representations, we reconstructed somatosensory maps using a computer interpolation algorithm based on a linear least square approximation of sampling coordinates of penetration sites and corresponding receptive field centers. (Reconstructions of a cortical hindpaw representation are shown in Fig. 3 for a young and for an old rat where cortical topographies are represented as a regular lattice within somatosensory cortex.)

Thirdly, the total amount of cortical territory devoted to the representation of the hindpaw was reduced by approximately 30% (Spengler et al., 1995;

Jürgens and Dinse, 1997) in old rats. The changes in walking behavior of the hind-limbs in old rats occurred in parallel with a large decline of the functional organization of the somatosensory cortex.

Studies of age-related maps of the motor cortex representing hind-limb muscles using intracortical microstimulation revealed profound age-related changes consisting of large reductions of the size of the maps, a loss in muscle topology, an increase in thresholds for evoking movements, and prolonged latencies of the electromyogram (EMG) responses (Dinse et al., 2001). The results indicate that the motor system of the hind-leg is affected by age in a similar way, as are sensory cortices.

Small age-related peripheral changes

It is important to consider whether central changes are a mere consequence of age-related alterations developing in the periphery, and whether age-related changes of cortical sensory processing are a simple reflection of changes occurring already at the level of mechanoreceptors. We therefore investigated the effects of aging on rapidly (RA) and slowly adapting (SA) cutaneous mechanoreceptors by means of single fiber recordings and evoked sensory nerve action potentials (NAPs) of the hindpaw of the N. plantaris in adult and old rats. Recordings of NAPs revealed similar shapes and amplitudes in all animals of all age groups. In old rats, conduction velocities were reduced by approximately 15%, (differences were significant, $p = 0.001$) and the number of SA units was reduced. However, there were no differences in RF size and in threshold between old and adult animals (Reinke and Dinse, 1996).

Evidence for a similar lack of age-related effects at peripheral levels comes from studies of the monkey retina. Stereological procedures used to compare the densities, numbers, and soma sizes of retinal ganglion cells in young adult and old rhesus monkeys revealed no noticeable changes with age (Kim et al., 1996). Studies of the electroretinograms showed only modest age-related prolongation of the latencies of the retinal response and decrease of the amplitude of the electroretinogram (Trick et al., 1986; Porciatti et al., 1992).

Lack of comparable age-related changes in the rat forepaw system — evidence against global breakdown of function

If age-related changes in cortical maps are due to degeneration, it would be expected that concomitant changes would occur in the representation of fore- and hindpaws. If the age-related cortical changes of the hindpaw system are in any way related to the behavioral state, the cortical forepaw system would be expected to have less age-related deterioration than that of the hindpaw.

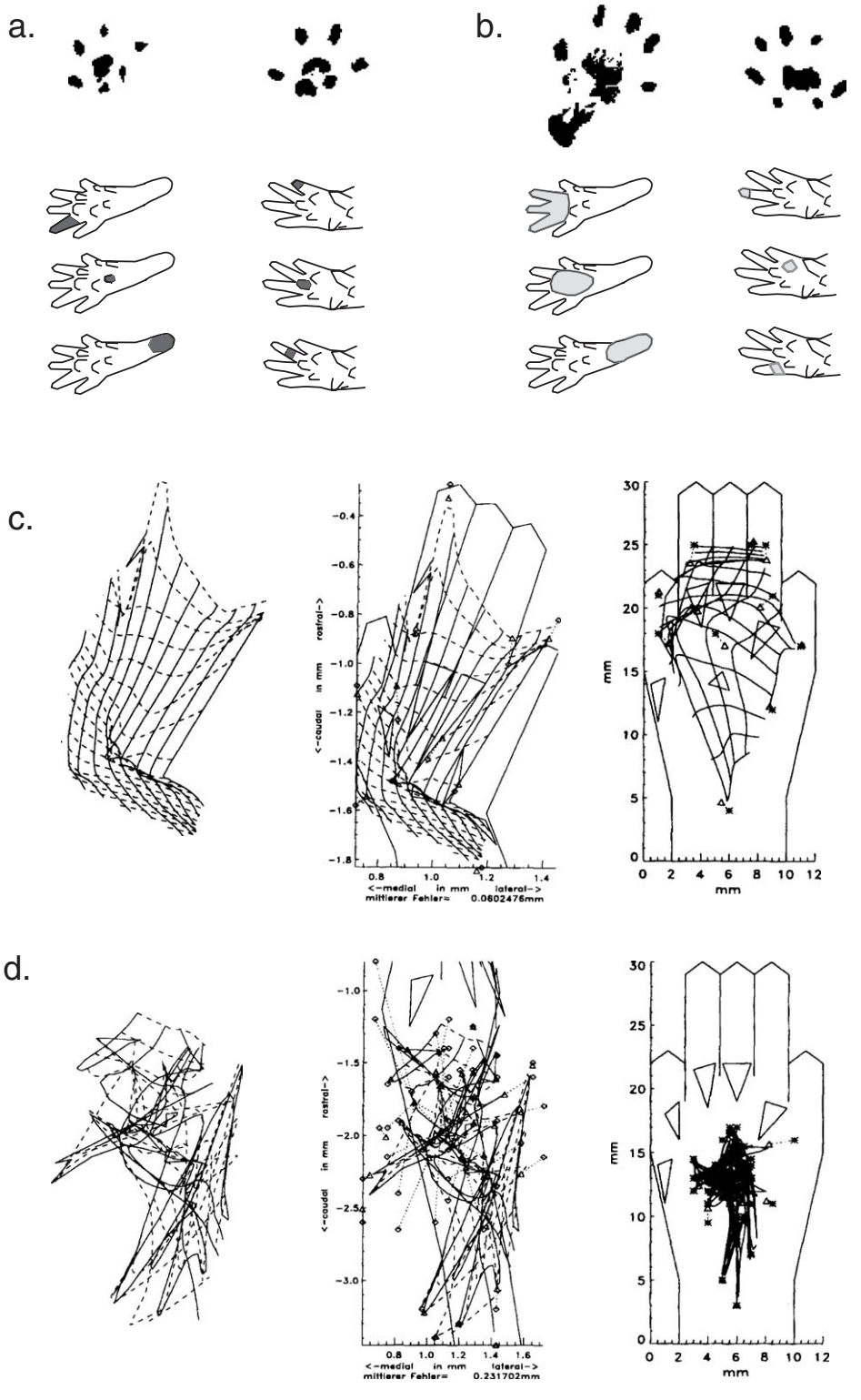
Studies have shown no similar increase in RF size in the cortical representation of the forepaw in old animals as seen for RF of the hindpaw (Fig. 3). Even in the oldest animal tested (43 months) there were no indications of changes in the size of the RF of the forepaw. The lack of changes in the RF for the forepaw indicates that there is no global breakdown of function at old age.

Age-related prolongation of neuronal response latencies — evidence for global degeneration

The conduction velocity in fiber tracts decreases during aging mainly due to demyelinization (Verdu et al., 2000; Peters, 2002). Given the robustness of the cortical forepaw representation in terms of RFs and map size during aging, it was therefore of interest to investigate whether latencies of cortical forepaw neurons remained similarly unaffected. Compared to adult controls, the latency of the response from neurons in the somatosensory cortex to stimulation of both the fore- and the hindpaw in old animals were significantly prolonged in the range of 30% ($p < 0.001$ for neurons recorded in the fore- and the hindpaw representation) (Jürgens and Dinse, 1995, 1997).

Degenerative vs. plastic-adaptive changes

If the observed age-related changes were caused by degeneration, it might be expected that similar changes occurred in the cortical representation of both the fore- and hindpaws. However, the RFs of the cortical forepaw representation of old animals were not noticeably different from that of younger animals (Jürgens and Dinse, 1997; Godde et al., 2002) nor were cutaneous RFs of the forepaw of rats 24–28 months of age different from those of younger adults (6.5–8 months) (Coq and Xerri,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2000, 2001). The sensorimotor behavior of the forelimbs were largely unaffected by age, presumably because the forepaws are used in feeding and cleaning behavior. These results imply that age-related changes can be regionally specific, and the results implicate a link between age-related neural changes and specific behavioral alterations that occur during aging, extending the concept of use-dependent plasticity to old age.

Age-related changes in other cortical systems and modalities

While reorganization of sensorimotor cortices during aging has been clearly demonstrated, the nature of age-related cortical alterations in other sensory modalities are less clear. For example, little age effects were reported in a series of papers for primary visual cortex of monkeys 24 years of age and older, neither in terms of cell loss, nor functionally (Kim et al., 1997; Peters et al., 1997, see also Spear, 1993). More recently, evidence for a significant degradation of orientation and direction selectivity in old macaque monkeys was described (Schmolesky et al., 2000). According to this study, the decreased direction selectivity of cells in old animals was accompanied by increased responsiveness to all orientations and directions as well as an increase in spontaneous activity (Schmolesky et al., 2000). The authors suggested that the decreased selectivity and increased excitability of cells in old animals might be attributable to an age-related degeneration of intracortical inhibition. In contrast, the percentage of neurons in the auditory cortex of old rats that showed direction preference of FM sweep was not different from young animals (Mendelson and Ricketts, 2001).

Age-related changes beyond cortical maps — temporal processing

Repetition of stimuli can alter the behavior of cortical neurons as compared to presentation of a single stimulus isolated in time (Gardner and Costanzo, 1980; Lee and Whitsel, 1992; Tommerdahl et al., 1996, 1998; Buonomano, 1999). This means that response properties to repetitive stimulation are different from the response to solitary stimulation. This phenomenon is often referred to as short-term plasticity (Zucker, 1989; Varela et al., 1997; Buonomano, 1999) or paired-pulse suppression (Castro-Alamancos and Connors, 1996).

Following repetitive stimulation with trains of tactile stimuli of variable interstimulus intervals (ISIs – 30–1000 ms) of the hindpaw (10 stimuli, intertrial pause of 5 s) large impairment of coding of such stimuli were observed in old rats as compared to young controls (Jürgens and Dinse, 1995). While SI neurons of both young and aged animals can follow trains of tactile stimuli of ISIs of 200 ms, the response to stimuli of shorter ISIs decreased more in old than in young animals. The neurons of old animals could barely follow stimuli with ISIs of 30 ms (Fig. 5).

Fig. 3. Specific effects of age on receptive fields of the hindpaw recorded in somatosensory cortex of aged rats. In addition, representative examples of behavioral changes of walking pattern derived from footprint analysis are shown: (a) young, control animal; (b) old animal. On the left: hindpaw; on the right: forepaw. Note selectivity of walking impairment restricted to hind-leg. At bottom of (a) and (b) are examples of receptive fields recorded in the hindpaw representation ((a) and (b), left) and in the forepaw representation ((a) and (b), right) in a young (a) and an old animal (b). Age-related changes are limited to the behaviorally impaired extremity. To visualize the effects of aging on the topography of the underlying cortical maps, we reconstructed somatosensory maps using a computer-based interpolation-algorithm based on a linear least square approximation of sampling coordinates of penetration sites and corresponding receptive field centers. Reconstructions of a cortical hindpaw representation are shown for a control (c) and for an old rat (d). Left: examples of cortical topographies represented as a regular lattice within somatosensory cortex. Middle: the extrapolated cortical representation of a schematic and standardized drawing of the hindpaw. Dashed lines indicate horizontal, solid lines the vertical components of the lattice. One square of the lattice represents 1 mm^2 skin area. Diamonds indicate penetration sites; squares give the interpolated RF centers. Dotted lines give the deviation between them. Right: back projection of the regular lattice of the cortical map onto the hindpaw. Squares give the interpolated, asterisks the measured RF centers. One square of the lattice represents the skin portion that is represented by 0.01 mm^2 cortical areas. According to these reconstructions, maps of the hindpaw representation recorded in old animals, which are characterized by a selective impairment of the hind-limbs, show a dramatic distortion of their representational maps and a loss of topographic order (modified from Spengler et al., 1995; Jürgens and Dinse, 1997b). See Plate 5.3 in Colour Plate Section.

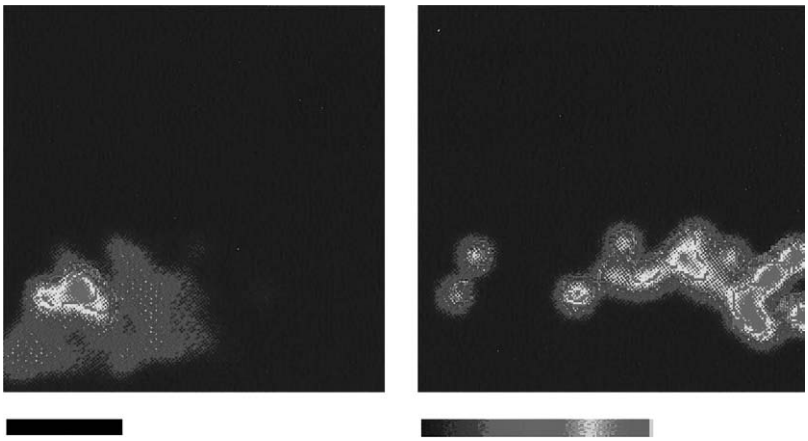

Fig. 4. Local field potential (LFP) maps constructed on the basis of LFP recorded by multiple penetrations showing the spatial activity distributions evoked by tactile stimulation in the hindpaw representation of the primary somatosensory cortex of a young (left) and an old rat (right). Shown are activity distributions following stimulation of a digit. Normalized LFP-amplitudes are color-coded and projected onto the cortical area of the hindpaw representation reconstructed from [*x*, *y*] coordinates of penetration sites. Scale bar: 1 mm; each plot is oriented with rostral left and lateral up (reprinted from Spengler et al. (1995) with permission from Lippincott Williams & Wilkins). See Plate 5.4 in Colour Plate Section.

Studies of the responses from single cells in the auditory cortex of young and old rats in response to frequency-modulated (FM) sweeps showed that the majority of cells in young rats responded most vigorously to fast and medium rates of changes in frequency of the sounds while most units in old animals responded best to sounds the frequency of which was changed slowly (Mendelson and Ricketts, 2001). These results demonstrate that aging has a pronounced effect on not only cortical maps and receptive fields but also processing temporal information.

Treatability of age-related changes in the rat

Assuming that at least certain aspects of age-related cortical reorganizations are caused by expression of neural plasticity, it should be possible to reverse these changes by treatment using protocols activating appropriate forms of neuroplasticity. Housing animals in an enriched environment that exert behavioral challenges have beneficial effects on a wide range of morphological, molecular, and physiologic features of the brain. Enriched environments that target sensorimotor modalities (Dinse, 2004) have been shown to improve cognitive function (Rosenzweig and Bennett, 1996), facilitate recovery from injury or stroke (Johansson, 2000), and prevent age-related decrease in synaptic density in the aged brain (Saito et al., 1994). Such enriched environments have also been shown to increase brain weight (Cummins et al., 1973), cortical thickness (Diamond and Connor, 1982), dendritic arborization (Connor et al., 1982), and neurotrophic factors (Mohammed et al., 1993). It is noteworthy that housing animals under enriched conditions can induce neurogenesis (Kempermann et al., 1997). More recently, beneficial effects have been described for the auditory system from housing rats in an acoustically enriched environment (Engineer et al., 2004).

Effects of enriched environment on aging rats — behavior and cortical organization

Beneficial effects on cortical forepaw neurons had been reported for animals that were kept in enriched conditions for their entire life (Coq and Xerri, 2001). We have addressed the question whether age-related changes can be affected through enriched housing even after they developed. Rats at an age of 26–29 months needed only to be exposed to enriched environments for a few months to regain nearly normal walking and

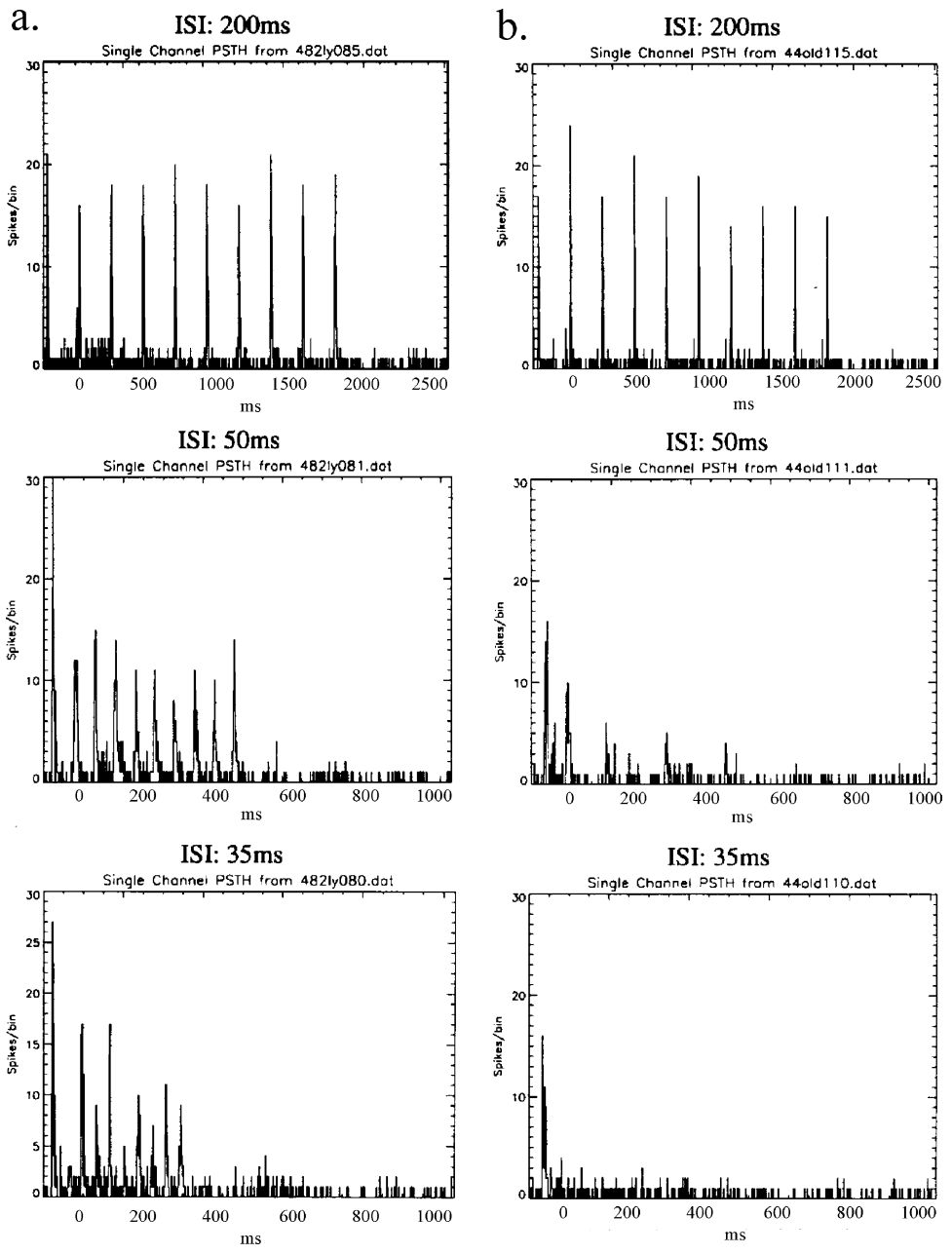

Fig. 5. The effect of aging on temporal sequence representation was investigated using trains of 10 tactile stimuli of variable interstimulus intervals (ISIs). Shown are examples of poststimulus time histograms (PSTHs) recorded in a young rat (a) and an old rat (b). ISIs used were 200, 50 and 35 ms. Bin size is 1 ms, time on abscissa as indicated, and neural activity in spikes per bin on ordinate. Each PSTH gives the response accumulated over 32 trials; pause between each single trial was 5 s. For a slow repetition rate of tactile stimuli, neurons recorded in young and old rats follow truthfully each stimulus as indicated by about the same peak activity evoked by each stimulus. While neurons recorded in young animals are still able to represent the sequence of stimuli delivered at an ISI of 50 ms, there is a significant deterioration in the ability to follow this sequence in the neuron recorded in an old rat. This failure to represent fast sequences becomes even more dramatic at an ISI of 35 ms. In addition to massive changes of topography developing during aging (cf. Fig. 2), there is also a significant deterioration of temporal processing abilities, which are also correlated to the behavioral status of the hind-limb as the temporal deficits can be ameliorated by housing the animals in an enriched environment that ameliorates the hind-limb impairment (modified from Jürgens and Dinse, 1995; Churs et al., 1996).

sensorimotor behavior of the hind-limbs. The typical age-related enlargement of RFs of the hind-paw was almost eliminated, and input sequence representation largely restored (Churs et al., 1996). Old rats exposed to enriched environment under the same schedule showed nearly complete recovery from age-related functional shrinkage of cortical motor territory typically found in animals housed under standard conditions (Dinse et al., 2001). The age-related prolongation of the latencies of cortical responses and of EMG responses remained unaffected. The decrease in the thresholds of the responses from motor cortex neurons, which normally occur with age, was unaffected by the enriched housing (see also p. 76).

Effects of enriched environment on aging rats — cellular changes

Lipofuscin and gliosis increase with progressing age (12–36 months) in functionally characterized cortical areas, and area-specific loss of perineuronal nets occurs in the somatosensory cortical representation of the hind-limbs (Fig. 6). The accumulation of lipofuscin and increased gliosis, the loss of perineuronal nets, and the reduction of nonphosphorylated neurofilament H, which normally occur with age, were reduced or prevented by housing the animals under enriched environmental conditions between 33 and 36 months of age. Reduction of astrocytosis (by 20%) coincided with a reduction in the loss of extracellular matrix

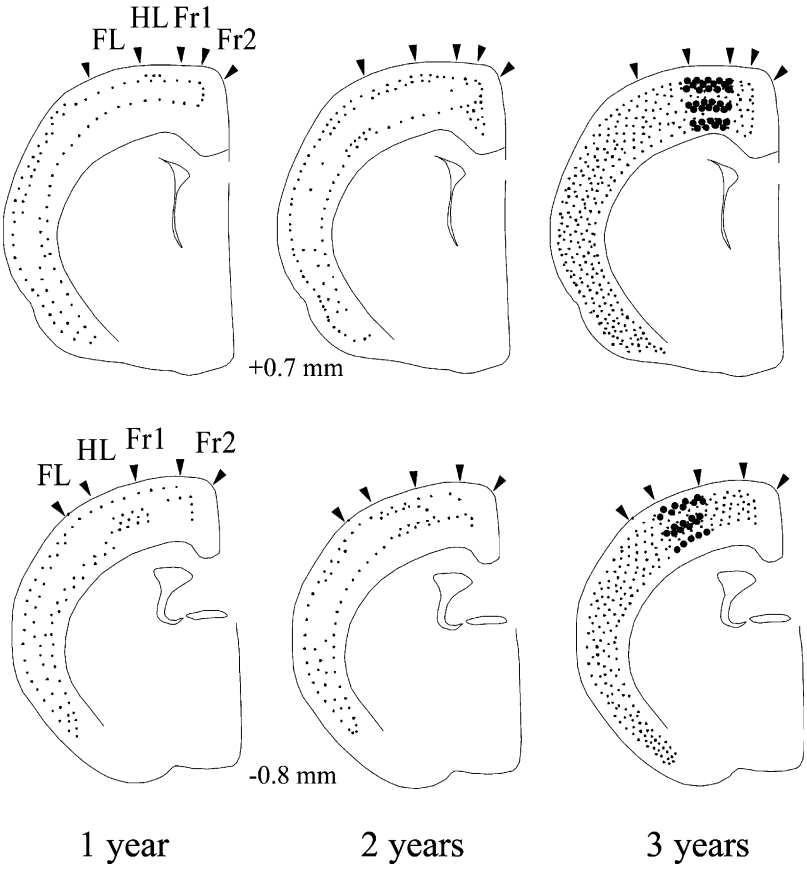

Fig. 6. Schematic drawings of cortical sections +0.7 and −0.8 mm relative to Bregma illustrating the lipofuscin accumulation for animals of different age groups. FL, forelimb area; HL, hind-limb area; Fr1, Fr2 motor cortex according to Zilles (1985). Note the dramatic increase of lipofuscin accumulation with increasing age, particularly in the hind-limb area (modified according to Hilbig et al., 2002a).

components involved in forming the glia-neuron-interface demonstrates. These results indicate that the aging cortex can retain its potential for functional plasticity (Hilbig et al., 2002a), but the sensitivity to aging processes between the fore- and hind-limb is different regarding their SI representation.

Changes in the expression of the nitric oxide synthase (NOS) isoforms have been implicated in age-related neurodegeneration. Immunohistochemical examination of the age-dependent NOS-I and NOS-II expression in rats at 3, 12, 24, and 36 months of age as well as in 36-month-old rats, which were housed in an enriched environment for their last 3 months of life, revealed a significant decrease in NOS-I expression with aging while NOS-II was increased in rats of 36 months of age. NOS-II expression in old rats that were kept under enriched environmental conditions was much reduced. These results indicate that both NOS-I and II may contribute to age-related degenerative processes, but in contrast to NOS-I, the age-dependent changes of NOS-II are reduced or even reversed by environmental stimulation (Hilbig et al., 2002b).

Effects of pharmacological intervention on aging rats

During aging, the cellular Ca^{2+} homeostasis is impaired due to an elevated influx through voltage-gated Ca^{2+} channels, which leads to severe cytotoxic effects. Nimodipine blocks selectively the L-type voltage-dependent Ca^{2+} channels (Godfraind and Govoni, 1995), which are important for maintenance of the neuronal Ca^{2+} homeostasis (Miller, 1987). Schuurman and Traber demonstrated that a long-term treatment with nimodipine can delay the typical deterioration of walking behavior in old rats. Animals that displayed an impairment of walking at 24 months of age had significant reduction of their sensorimotor deficits after receiving 6 weeks of nimodipine treatment (Schuurman et al., 1987; Schuurman and Traber, 1989a, b).

We studied the effects of long-term administration of nimodipine on RFs in the fore- and hind-paw representations of primary somatosensory neurons of aged Wistar rats 23–31 months of age, starting the nimodipine treatment at 19 months of age. These studies confirmed the beneficial effects of nimodipine on the overall state and walking pattern of the hind-limbs, and in addition, optical imaging revealed a normal layout of cortical hind-paw maps and reversal of the age-related increase of RF size to the size found in normal adult animals. This reversal was restricted to a period of 5.5–9 months of treatment corresponding to an age of 24.5–28 months. The RFs of the forepaw were not affected by administration of nimodipine.

These results thus demonstrate that nimodipine can delay typical age-related changes of the hind-paw representation in a similar way as it affects the sensorimotor state of the hind-limbs. Nimodipine did not affect the age-related prolongation of the latencies of the responses from cortical cells representing the hindpaw or those representing the forepaw. These findings indicate a specific mode of action of nimodipine and an overall effectiveness of this kind of intervention in terms of decreasing age-related cortical changes (Berkefeldt et al., 1996; Jürgens and Dinse, 1997).

Recently, de Rivera et al. (2005) studied the effect of dietary supplements that were rich in antioxidants (blueberry phytochemicals) on temporal processing in primary auditory (AI) cortical neurons in old rats that had been placed on either a blueberry-supplemented or control diet 2 months prior to the physiological recordings. The results showed that most cells from the blueberry-fed rats responded vigorously to fast FM sweeps, similar to that of cells in young rats, but most cells recorded from the control rats showed a preference for slow FM sweep rates as described above (p. 66). These results indicate that age-related changes in temporal processing in AI may be reversed by dietary supplementation of blueberry phytochemicals (de Rivera et al., 2005), offering alternative options for slowing age-related changes.

Hypothesis on rat aging

Experimental data support the hypothesis that the primary cause of motor decline in old rats is mechanical in nature and consists of muscle atrophy resulting from reduced use. The beneficial effects of administration of nimodipine may be caused by unspecific factors, such as an elevation of the level of arousal, which in turn enhance motor activity.

This hypothesis is compatible with the concept of use-dependent plasticity whereby increased motor activity increases sensory stimulation that modifies cortical representations. The difference in the age-related impairment of sensorimotor performance of the fore and hindpaws could be attributed to maintained intensive use. An alternative hypothesis may be that synaptic efficiency, and hence cortical information processing capacities, are progressively impaired during aging and that failure in maintaining Ca^{2+} homeostasis affects cellular and network properties such as inhibitory mechanisms that regulate RF size. In the case of nimodipine treatment, the Ca^{2+} overload developing during aging is prevented. This could explain why RFs of the hindpaw are not enlarged after nimodipine. Maintained use of the forepaws may counteract a Ca^{2+} overload, and therefore RF size of the forepaw remains unaffected by age.

Combined, the results from the studies of the effect of an enriched environment and of administration of nimodipine show that age-related changes may be treatable. The results of these studies clearly imply that age-related changes can be reversed even if they have developed. This may also be taken as a sign that the properties of these changes are not degenerative by nature (Godde et al., 2002; Dinse, 2005).

Human aging

Cortical reorganization in healthy humans during normal aging

The studies in the rat data discussed above have inspired studies in humans. In these investigations, psychophysical studies were combined with non-invasive imaging studies (in cooperation with Dr. Martin Tegenthoff, Department of Neurology at the Ruhr-University). Assuming that age-related changes in humans develop in a similar way as in the rat, we wanted to study the implications of impaired cortical sensorimotor organization for tactile perception. Naturally, the different lifespan of rats and humans must be taken into account in such studies.

Earlier studies have found that the functional organization of the somatosensory cortex in humans is linearly related to tactile discrimination abilities (Pleger et al., 2001). We therefore assumed that ''normal'' cortical processing of sensory information is required for ''normal'' perceptual and motor performance, and that large changes in the cortical organization occurring in elderly humans lead to severe perceptual impairments. Studies on spatial (2-point) discrimination in elderly individuals revealed significantly impaired discrimination (Stevens, 1992; Woodward, 1993; Wohlert, 1996; Dinse et al., 2006). The impairment on the toe was much greater than that on the fingertip (400% deterioration of acuity on the foot as compared to 130% on the finger) (Stevens and Choo, 1996). These results are thus in agreement with results from the rat, and also in humans these differences may be caused by difference in the use of the foot and the hand.

Analysis of sensorimotor and cognitive functions in healthy elderly

We have accumulated a large database on 2-point discrimination performance in young individuals in the context of tactile learning (Pleger et al., 2001, 2003; Dinse et al., 2003, 2005; Ragert et al.; 2004; Tegenthoff et al., 2005).

> Using that database as a reference we studied sensorimotor and cognitive functions in healthy elderly individuals including absolute touch threshold, localization performance, 2-point discrimination, and tactile object recognition. We also assessed cognitive performance using the Raven Progressive Matrices test, a nonreading, nonlanguage-based measure of fluid intelligence.
>
> Aged individuals were recruited by poster announcements in senior residences. All participants in the study were right-handed and underwent neurological examination, and were without neurological symptoms and in good physical condition. The participants were divided into three age groups (group 50: 45 55 years, group 70: 65–75 years, and group 80: 75–85 years). Young adults served as control (20–30 years). Eligibility criteria for participating in the study group were

lucidity, independence in activities of daily living, and absence of motor and sensory handicaps and of any impairment due to arthritis or other causes of joint immobility. Individuals with visual or hearing loss, former or actual diseases of the central or peripheral nervous system or individuals who took central nervous acting medication were excluded. Cognitive abilities were assessed using the "Mini Mental State Examination." Only individuals scoring 27–30 out of 30 indicative of "no dementia" were included in the study.

Touch thresholds increased from $0.25 \pm 0{,}013$ mN in young adults to $1.16 \pm 1{,}71$ mN in the intermediate age group, to 2.82 ± 2.65 mN in the group-70 and 2.05 ± 1.66 mN in the group 80 (Kleibel, Kalisch, Tegenthoff, Dinse, unpublished data). The results of 2-point discrimination tests confirmed previous findings showing a significant deterioration of performance with increasing age, beginning at the age of 50 years (Fig. 7). No significant correlation (Pearson) between the individual touch threshold and 2-point discrimination scores was present, indicating that both parameters change independently, and that touch threshold is not a predictor for tactile acuity.

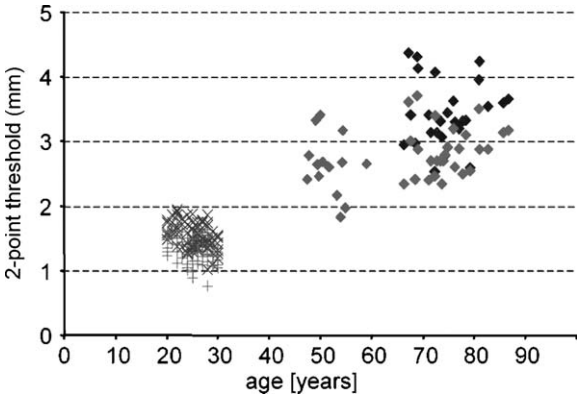

Fig. 7. Tactile 2-point discrimination thresholds of the tip of the right index finger as a function of age (total of 120 participants). According to univariate ANOVA (with age $F(2,118) = 347.785$; $p < 0.001$) the differences across the three age groups were significant. After coactivation (pink symbols), thresholds of the coactivated participants (young control group and group of elderly) were significantly reduced. Coactivation-induced improvement in the group aged 66–86 was several fold stronger in magnitude as compared to the young subject. As a result, after coactivation thresholds of the elderly resembled those found in the participants 47–55-years old (reprinted from Dinse et al. (2006) with permission from Wiley-Liss, Inc.). See Plate 5.7 in Colour Plate Section.

The effect of aging on tactile object recognition was studied by having the participants identify small cubic objects without visual support using a method modified from Newell et al. (2001). The results showed large effect of aging on object recognition. The number of errors and the time to fulfill the object-classification task increased significantly with age. Interestingly, the decline in object recognition was highly gender specific: Female participants had a much greater impairment than age-matched male participants. No gender specific trends were present within the young individuals (Kalisch and Dinse, submitted).

Age-related changes of human SI cortical maps

The studies discussed above showed that the representation of the hindpaw on the SI cortex undergoes considerable age-related changes. In humans the representation of the hands on the primary somatosensory cortex undergoes continuous adaptation through expression of neural plasticity arising from environmental input, with altered use or injury leading to substantial reorganization of body surface representation with regards to the size, extent, and position.

Using SEP mapping in combination with electric source localization, we investigated the influence of healthy aging on the human cortical hand representation in relation to tactile performance. The results showed that the hand representations within S1 on both hemispheres in elderly between 60 and 85 years of age were substantially enlarged as indicated by an increase of the distance between the dipole of the index and the little finger by approximately 40%. Correlation analysis revealed a significant positive relation between perceptual performance (2-point discrimination) and cortical map size (difference between dipoles for index and little finger). These results indicate that normal aging affects the cortical organization of the hand representations within SI, and that the enlargement of the cortical hand representation is paralleled by impaired tactile acuity (Kalisch et al., submitted).

These results are of interest for two reasons: First, as discussed above (p. 60) map expansion observed in young individuals during learning is usually associated with a gain in performance. In contrast, the age-related changes in cortical maps and in tactile abilities changed in opposite directions (enlarged maps were associated with impaired performance). These changes may therefore be assumed to reflect different forms of cortical reorganization.

Second, studies in rats showed that the cortical representation of the forepaw had little age-related changes, while the cortical territory representing the hindpaw decreased noticeably with age and the hindpaw motor map became extended. This means that animal and human data for cortical reorganization are contradictory. There are several possibilities explaining these differences such as differences in accumulated years or reorganization to compensate for slowing down of conduction and processing speed.

Treatability of age-related changes in human elderly

Given that aging in the rat is subject to various forms of interventions, it is of interest to explore if similar strategies are also effective in humans. It is well known that extensive training and repeated exercise improves perceptual and motor skills, and it is assumed that these improvements are at least to some extent a result of expression of neural plasticity (Recanzone et al., 1992; Pascual-Leone and Torres, 1993; Elbert et al., 1995; Pantev et al., 1998). Therefore, the typical approach to ameliorate age-related changes is to subject elderly to intense schedules of training and practicing, and there is no doubt about the effectiveness of such intervention even at old age (Bock and Schneider, 2002; Sawaki et al., 2003; Floel et al., 2005; Kornatz et al., 2005; Smith et al., 2005). However, since many elderly suffer from restricted mobility, development of additional and alternative approaches that could supplement, enhance, or even replace conventional training procedures would be advantageous.

In search for enriched environments for elderly

Given the high degree of efficacy of housing old rats under enriched environmental conditions, it is natural to search for equivalent enriched environments for elderly humans. It was recently reported that dancing evokes many beneficial effects (Federici et al., 2005; Jacobson et al., 2005). Nordic walking or other forms of exercising might offer valuable alternatives (cf. Elward and Larson, 1992; Kramer et al., 1999; Jacobson et al., 2005). Both approaches have in common that they emphasize the role of physical exercise. They differ in that dancing involves a much broader scope of factors beyond pure exercising such as social interaction, divided attention capacity, navigation in highly populated spaces, and following musical rhythms. Significant improvement in balance in the dance group was demonstrated at the end of such a program (Federici et al., 2005). Tango dancing improves several balance measures related to moving in confined spaces, and for complex walking tasks (Jacobson et al., 2005). Adherence to tango was higher than for the walking group (1 vs. 4 drop-outs), and out of the 25 individuals who participated in the study, 60% are still participating in tango classes, making this as a feasible alternative to other activity programs.

Amelioration of the effects of aging through passive stimulation protocols

As an alternative approach to training, we have recently introduced tactile coactivation to control and to improve tactile performance in humans on a time scale of only a few hours. Coactivation consists of "passive" and therefore unattended stimulation, which enforces localized activation patterns in the brain. A major advantage of coactivation is that it is applied passively and thus does not require active cooperation of the participants. Coactivation closely follows the principles of Hebbian learning, which states that synchronous neural activity drives plastic changes. The Hebbian nature of coactivation was demonstrated in a control experiment, in which only a very small skin area was stimulated (no coactivation). This protocol caused neither changes of thresholds nor changes in cortical activation, implying that "co"-activation is indeed crucial (Pleger et al., 2003; Ragert et al. submitted)

Coactivation can induce improvement of tactile perceptual performance in parallel to cortical

reorganization in young individuals (Godde et al., 2000; Pleger et al., 2001, 2003; Dinse et al., 2003, 2005, 2006; Ragert et al., 2004). We used tactile coactivation as an alternative intervention to interfere with the aging-related impairment of tactile perception and demonstrated that plastic changes in neural organization are involved in the age-related decline in sensory performance, which is typical for elderly humans, and therefore these changes can be ameliorated through brief periods of this specific form of tactile learning. When the same coactivation protocol as used in previous studies in young individuals is applied to aged participants (Dinse et al., 2006), we found that thresholds were significantly lowered from 3.42 ± 0.50 mm to 2.89 ± 0.40 mm following this coactivation (Figs. 7 and 8).

When all young participants were submitted to similar coactivation their 2-point skin discrimination improved from 1.55 ± 0.19 mm to 1.33 ± 0.19 mm (Figs. 7 and 8). In young individuals the gain in discrimination threshold was 0.22 ± 0.19 mm.The mean improvement in elderly participants was 0.54 ± 0.32 mm.These results demonstrate that the tactile coactivation protocol is also effective at old age improving discrimination thresholds in individuals of up to 89 years. Prior to coactivation there was a clear difference in the discrimination thresholds in the 50-year age group and in groups of older individuals. After coactivation this difference disappeared and the tactile acuity of the aged individuals after coactivation matched the average performance of participants aged 47–59 years. These results demonstrate that age-related decline of perception is not irreversible but can be improved by specific stimulation protocols.

Typical improvement of acuity from coactivation is between 15% and 20%. It is not evident if this magnitude of improvement represents a major advantage for everyday life. Comparing training-induced improvements of tactile acuity for pianists (Ragert et al., 2004) and violinists (unpublished data) to those evoked by coactivation revealed almost identical improvement of tactile discrimination when long-term training and short-time coactivation were compared (Dinse et al., 2005). This indicates that a short time of coactivation is as effective in promoting perceptual improvement as long-term training.

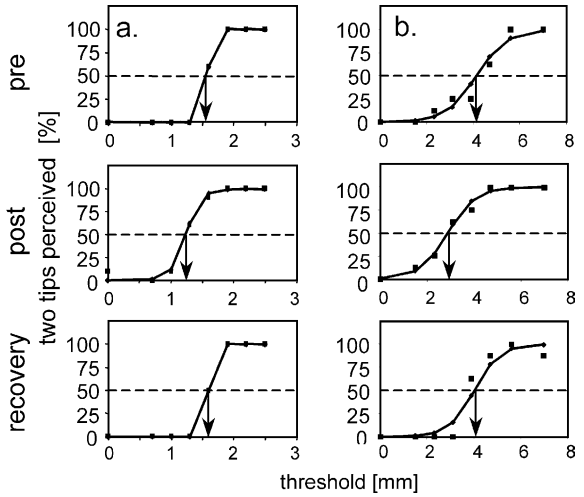

Fig. 8. Effects of coactivation on discrimination thresholds. Psychometric functions illustrating the discrimination performance obtained pre, post, and 24 h after coactivation for a young (a), and an elderly subject (b). Correct responses in percent (squares) are plotted as a function of separation distance together with the results of a logistic regression line (diamonds). 50% level of correct responses is indicated (dashed line) together with resulting thresholds (arrows). (top): precondition before coactivation; (middle): postcondition, immediately after coactivation; (bottom): recovery-condition, 24 h after termination of coactivation. In both the young (26 years) and the elderly subject (81 years), after coactivation there is a distinct shift in the psychometric functions toward lower separation distances, which recover to preconditions 24 h later. In the young subject, thresholds were reduced from 1.56 to 1.23 mm after coactivation, and recovered back to baseline (1.59 mm). In the elderly, thresholds were reduced from 4.2 to 2.8 mm thereby matching prethresholds typically found in a 50-year-old subject (mean threshold of 13 participants aged 47–55 was 2.61 ± 0.48 mm). 24 h later, threshold recovered back to baseline (4.1 mm) (reprinted from Dinse et al. (2006) with permission from Wiley-Liss, Inc.).

While coactivation improves tactile acuity in discrimination-impaired elderly, the lowest thresholds in elderly (2.34 mm) after coactivation were still above the thresholds typically observed in young individuals (approximately 1.5 mm). Linear correlation analysis (Pearson) revealed that the magnitude of coactivation-induced changes in the aged group was systematically dependent on their performance level before subjected to the coactivation treatment: The participants who had the

highest thresholds before the start of the study showed the largest improvement, while participants with low thresholds had only limited improvement, indicating the presence of ceiling effects. The performance observed after coactivation may represent the lowest limit in acuity that can be reached by elderly given the anatomical and morphological changes accumulating over age, or the discrimination thresholds may be further reduced by using different or more refined methods of intervention.

The latter hypothesis is supported by the observation that tactile 2-point discrimination thresholds in elderly are much higher in sighted than in blind people of the same age (Stevens et al., 1996; Heinisch et al., 2006). Especially the members of a group of early blind individuals had significantly lower thresholds as young sighted and blind individuals (Heinisch et al., 2006). These results show that extraordinary discrimination can occur even in elderly individuals, which we take as an argument that physiological, particularly peripheral constraints are unlikely to limit acuity, and they also support the hypothesis that practicing is the major driving force for maintaining high acuity performance even into old age.

Perspectives on passive unattended intervention methods

In a previous study of young participants, it was found that significant improvements of spatial discrimination were present up to 6 h after coactivation (Godde et al., 2000). When coactivation was applied on three consecutive days, the magnitude of changes was not different but the effects lasted longer. Only on day 5 did the thresholds return to preconditions (Godde et al., 2000). Coactivating all fingertips of a hand instead of a single finger resulted in much stronger and longer-lasting effects (Kalisch et al., 2005). Application of high-frequency tactile coactivation mimicking long-term potentiation (LTP)-like stimulation for only 20 min evoked tactile acuity improvements comparable in magnitude to those of the standard coactivation protocol lasting 3 h , which recovered to baseline only after 48 h (Ragert et al., 2005, submitted). Conceivably, combining repeated applications with new forms of coactivation protocols will lead to higher persistence of the evoked improvement.

Alternative attempts to interfere with the age-related decline of sensory capacities have been described (Dhruv et al., 2002; Priplata et al., 2003). Addition of noise to a signal that is to be transmitted can improve the ability to transfer reliably information, a phenomenon known as stochastic resonance (Collins et al., 1996). Electrical noise stimulation applied to the hand of elderly individuals lower touch thresholds (Dhruv et al., 2002), and noise stimulation to the foot can improve postural stability in young and elderly individuals (Priplata et al., 2003). While stochastic resonance affects thresholds by making inputs that would otherwise be subthreshold exceed the threshold, coactivation may alters the modes of neural processing due to specific changes of synaptic efficacy and synaptic connections (cf. Dinse et al., 2003; Pleger et al., 2003).

The unique advantage of coactivation is its passive nature, i.e., it does not require the active cooperation and involvement of the individual person who is being treated. It can be applied even in parallel to other occupations and might therefore be substantially easier to implement. These properties, together with the effectiveness of coactivation to improve tactile discrimination, make coactivation-based principles prime candidates for therapeutic intervention programs that serve as training substitute in individuals with neurological impairments or it may be used in addition to conventional training. Preservation of sufficient tactile acuity to old age is an important prerequisite for the maintenance of independent and autonomous living. We therefore believe that the concept of coactivation might turn out to be beneficial in preserving everyday sensorimotor competence in the elderly through the use of unattended therapeutic interventions.

Treatment of age-related cortical changes

Assessment of tactile discrimination ability, recording of somatosensory evoked potentials and functional magnetic resonance imaging (fMRI) before and after coactivation in young human individuals showed that the coactivation-induced gain of perceptual performance was linearly

correlated with the amount of cortical reorganization of the finger representation in primary somatosensory cortex (Pleger et al., 2001, 2003; Dinse et al., 2003). fMRI studies confirmed that also in the elderly, learning processes localized in somatosensory cortex are likely to be involved in mediating the amelioration of age-related impairment of tactile acuity from coactivation (Pleger et al., unpublished).

The third brain: interventions are no time-travel — insight from intervention studies

At first glance, the old rats from the enriched housing were able to perform nearly as well as young animals. Only closer inspection of these animals revealed that old rats regained their ability by walking in a different way than young animals. Most notable, the behavioral changes were paralleled by significant effects on the cortical maps. In particular, the severe deteriorations of the maps as described above were largely restored. But similar to the behavioral findings, cortical maps in enriched animals were "new" in the sense that they combined features seen in young animals and those never been seen in old animals from standard housing, implying a use-enforced development of new strategies of cortical processing at old age. This observation led us to a more systematic evaluation of the effects of enriched housing (Table 1).

To find out if housing animals in enriched environment restored the cortical organization to a status present earlier in life, we analyzed parameters that describe behavioral performance and cortical organization in animals of intermediate age (29 months) and in animals 34–36 months of age that were kept under enriched conditions (Table 2). The animals were subjected to enriched housing at 29 months of age.

> Behavioral parameters were ground reaction forces as measured during walking, step length/frequency as obtained from video-based analysis of walking, duty factor (defined as the fraction of the stride period that a limb is in contact with the ground), footprints (various parameters such as print length and area), and beam walking (number of droppings, time to cross the beam). Cortical parameters were representational area (size of representational map), muscle complexity (indicates how many different muscles are represented at a single cortical location), muscle topography (topographic order of different muscle representations), location of motor maps (location of cortical map relative to absolute scull coordinates such as bregma), threshold for evoking EMG activity (current needed to evoke movements or EMG activity), and EMG latency (time between current application and onset of EMG activity).

As summarized in Table 1, housing animals under enriched conditions had beneficial effects on

Table 2. Comparison of the 29-month status with that observed in animals aged 34–36 months housed under enriched environmental conditions

Parameter	Compared to 29 months
Representational area	Better
Muscle complexity	Better
EMG threshold	= 29 months
EMG latency	= 29 months
Ground reaction forces	Better
Step length/frequency	= 29 months
Duty factor	Worse
Foot prints	= 29 months

Table 1. Effect of enriched housing on various behavioral and cortical parameters

Restoration	"New" properties	Enhancement of aging	No effect
Representational area	Location of motor maps		EMG thresholds
Muscle complexity			EMG latencies
Muscle topography			
Beam walking		Duty factor	
Ground reaction forces			
Step length/frequency			
Foot prints			

many of the parameters studied, but clearly not every tested parameter was positively affected. Some parameters even showed enhanced aging effects, while others revealed behaviors never seen in young or aged individuals. Comparing the status of a 29-month-old with that of a 33-month-old that was kept under enriched conditions showed that enriched housing does not allow an individual rat to rejuvenate to the status of a younger animal (Table 2). While some parameters became similar to those of younger animals, other parameters improved, and some became worse than those of an untreated aged-matched control from standard housing. Even for that limited range of parameters investigated the results indicate that very complex remodeling of both behavior and cortical processing strategies was behind the observed regaining of sensorimotor abilities.

Major constraints appear to be induced by the observed prolongation of the latencies and by elevation of the thresholds, which both impair control and regulation of walking, causing impaired coordination and stability. The restoration of the size of the cortical maps is a sign of recruitment of processing resources needed for compensation of impaired timing and excitability. Increasing the duty factor is one among other possibilities, which has a significant stabilizing effect and thereby counteracting impairment of walking. Sensory latencies were insensitive to enriched housing or nimodipine-treatment, suggesting that degenerative age changes are not affected by training and stimulation.

Does this conclusion also apply to elderly humans? According to unpublished imaging data from our group (Pleger and coworkers), cortical maps of the fingers in SI cortex of elderly individuals clearly expand (cf. also Kalisch et al., submitted for EEG-based analysis). Coactivating these individuals leads to an improvement of tactile acuity as described above (Dinse et al., 2006), thereby ameliorating the age-related decline in discrimination performance. Similar to what has been observed in young individuals, coactivation in elderly induced a further enlargement of cortical maps indicating the coexistence of two forms of cortical map expansion: Enlargement of cortical representation after coactivation results in perceptual improvement (in elderly in an amelioration of age-related perceptual decline), and the expansion that develops during aging occurs simultaneously with perceptual impairment.

Conclusion

Cognitive impairments during nonpathological aging have been suggested to reflect synaptic alterations in otherwise intact neural circuits rather than loss of neurons, thus an important prerequisite for being able to reverse age-related changes (Morrison and Hof, 1997; Hof and Morrison, 2004). Despite the accumulation of degenerative processes during aging, the findings presented here demonstrate that the typical age-related decline in tactile performance is not inevitable, but it is preventable and if it occurs it is subject to restoration by various forms of intervention. Based on experimental observations aging induces major cortical reorganization, and interventions aiming at ameliorating age-related changes lead to other forms of cortical reorganization, where the outcome is a "new" brain – the third brain – that differs significantly from brains seen in young or in old, but untreated individuals.

Acknowledgments

This research was supported by DFG (DI 334/10-1, 10-2, 10-3, 10-4, 15-1), the International Graduate School of Neuroscience (IGSN) of the Ruhr-University Bochum, a grant of the Schering Stiftung, and a research grant of the Sandoz Foundation for Gerontological Research (EU-94-1-029). We gratefully acknowledge the supply of FBNF1 rats by Bayer, Germany.

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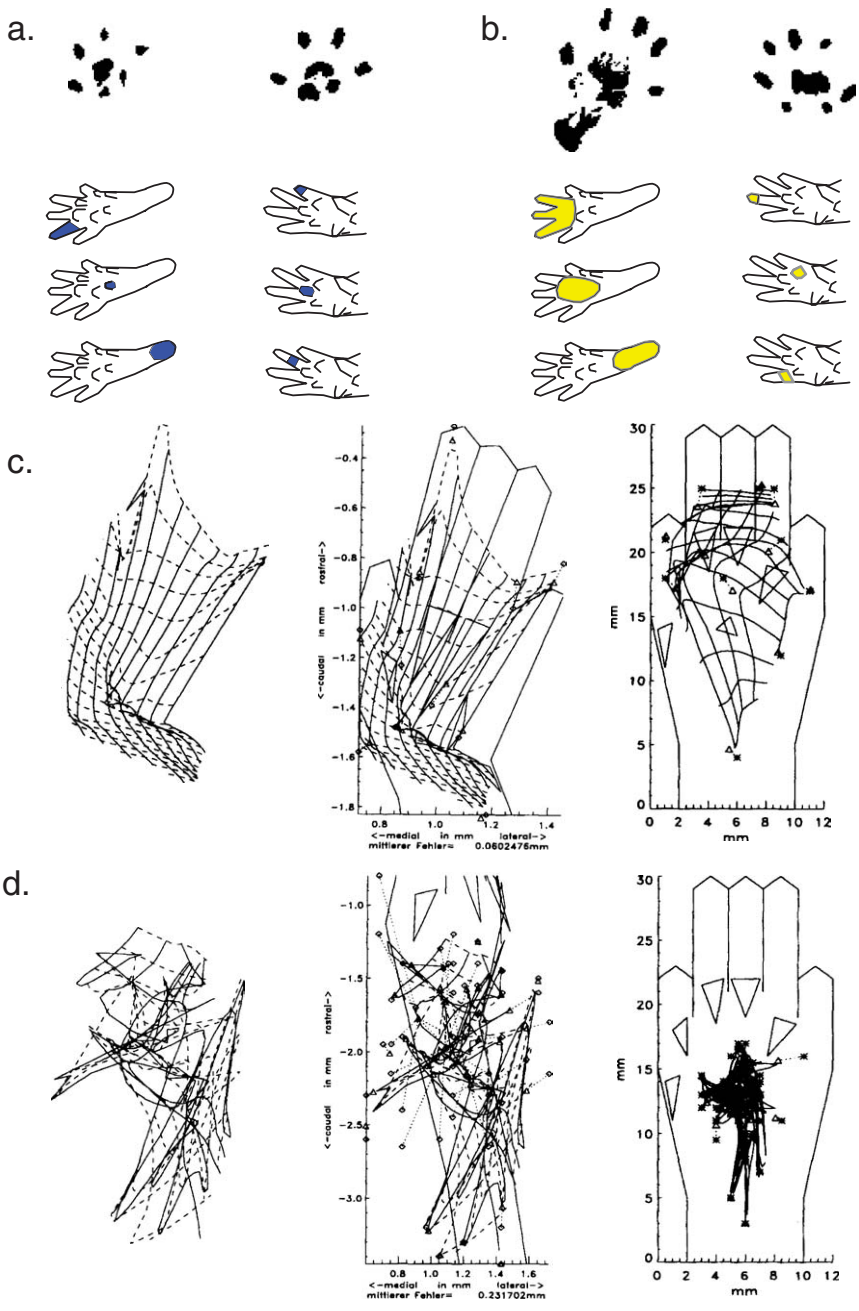

Plate 5.3. Specific effects of age on receptive fields of the hindpaw recorded in somatosensory cortex of aged rats. In addition, representative examples of behavioral changes of walking pattern derived from footprint analysis are shown: (a) young, control animal; (b) old animal. On the left: hindpaw; on the right: forepaw. Note selectivity of walking impairment restricted to hind-leg. At bottom of (a) and (b) are examples of receptive fields recorded in the hindpaw representation ((a) and (b), left) and in the forepaw representation ((a) and (b), right) in a young (a) and an old animal (b). Age-related changes are limited to the behaviorally impaired extremity. To visualize the effects of aging on the topography of the underlying cortical maps, we reconstructed somatosensory maps using a computer-based interpolation-algorithm based on a linear least square approximation of sampling coordinates of penetration sites and corresponding receptive field centers. Reconstructions of a cortical hindpaw representation are shown for a control (c) and for an old rat (d). Left: examples of cortical topographies represented as a regular lattice within somatosensory cortex. Middle: the extrapolated cortical representation of a schematic and standardized drawing of the hindpaw. Dashed lines indicate horizontal, solid lines the vertical components of the lattice. One square of the lattice represents 1 mm^2 skin area. Diamonds indicate penetration sites; squares give the interpolated RF centers. Dotted lines give the deviation between them. Right: back projection of the regular lattice of the cortical map onto the hindpaw. Squares give the interpolated, asterisks the measured RF centers. One square of the lattice represents the skin portion that is represented by 0.01 mm^2 cortical areas. According to these reconstructions, maps of the hindpaw representation recorded in old animals, which are characterized by a selective impairment of the hind-limbs, show a dramatic distortion of their representational maps and a loss of topographic order (modified from Spengler et al., 1995; Jürgens and Dinse, 1997b).

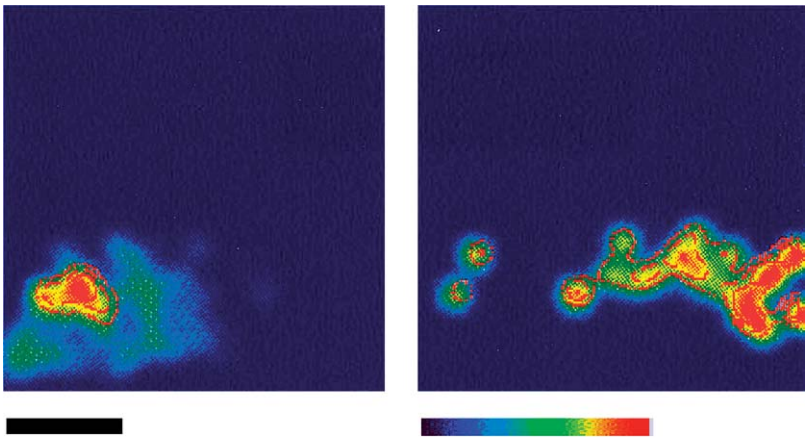

Plate 5.4. Local field potential (LFP) maps constructed on the basis of LFP recorded by multiple penetrations showing the spatial activity distributions evoked by tactile stimulation in the hindpaw representation of the primary somatosensory cortex of a young (left) and an old rat (right). Shown are activity distributions following stimulation of a digit. Normalized LFP-amplitudes are color-coded and projected onto the cortical area of the hindpaw representation reconstructed from [x, y] coordinates of penetration sites. Scale bar: 1 mm; each plot is oriented with rostral left and lateral up (reprinted from Spengler et al. (1995) with permission from Lippincott Williams & Wilkins).

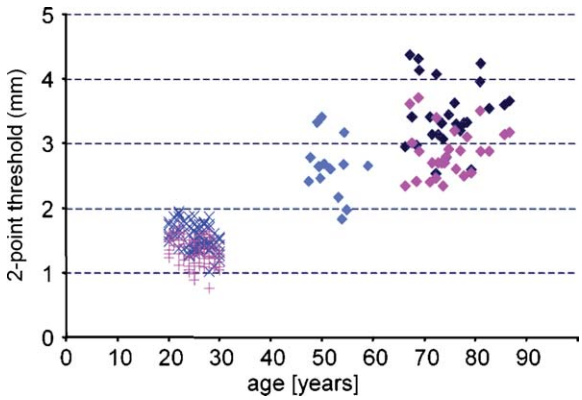

Plate 5.7. Tactile 2-point discrimination thresholds of the tip of the right index finger as a function of age (total of 120 participants). According to univariate ANOVA (with age $F(2,118) = 347.785$; $p < 0.001$) the differences across the three age groups were significant. After coactivation (pink symbols), thresholds of the coactivated participants (young control group and group of elderly) were significantly reduced. Coactivation-induced improvement in the group aged 66–86 was several fold stronger in magnitude as compared to the young subject. As a result, after coactivation thresholds of the elderly resembled those found in the participants 47–55-years old (reprinted from Dinse et al. (2006) with permission from Wiley-Liss, Inc.).