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Age-related changes in primary somatosensory cortex of rats: evidence for parallel degenerative and plastic-adaptive processes

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Abstract

Aged rats show a characteristic decline of the sensorimotor state, most strikingly expressed in an impairment of the hindlimbs leading to significantly reduced sensory stimulation on the hindpaw. We review recent studies using optical imaging and electrophysiological recordings to investigate the effects of aging on somatosensory cortex and to identify age-related changes in terms of degeneration or plastic adaptation. For the cortical hindpaw representation, reduction of map size, receptive field enlargement and reduced response strength were described. None of these changes were reported in the forepaw representation in the same individual, however, in both the fore-and hindpaw representations response latencies and cerebral blood flow were affected. Changes of latencies and blood flow are best explained by degeneration, but the regional and specific changes of maps, receptive fields and response strength by plastic phenomena arising from the reduced sensory inputs. While the degenerative changes are not modifiable by enriched environmental conditions or application of Ca^{2+} blocker, the plastic changes were fully reversible under these conditions. We discuss the implications of these findings for cognitive functions at old age and possible treatments of age-related changes in human subjects.
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1. Introduction

Aging comprises a number of physiological modifications, including structural and metabolic changes. Possibly due to the overwhelming impression evoked by the negative implications of aging, it is almost exclusively associated with aspects of degeneration. While there is a growing body of information about age-related changes at cellular and biochemical levels and a decline of higher cognitive processes such as memory functions, little is known about how aging affects intermediate levels of sensory cortical processing, i.e. the way in which neurons process and integrate complex information from the external environments.

Higher mammals contain complete and ordered topographic maps of the skin of the body surface, giving rise to a so-called 'homunculus', where the extent of cortical territory reflects the behavioral importance of the respective sensory input zones (Fig. 1). Adjacent locations on the skin are represented at adjacent locations in the cortex. However, there is now compelling evidence from both animal and human studies that cortical maps and cortical response properties are in a permanent state of use-dependent fluctuations suggesting that small alterations in behavior due to special demands imposed in everyday life alters early cortical representations rapidly and reversibly.

The framework of 'modified use' as a determinant of cortical reorganization can be applied for the investigation of age-related modifications of cortical representational maps. In the following, experiments are summarized that characterize the effects of aging at a level of early sensorimotor processing. In the first part, the nature of age-related changes of rat somatosensory cortical neurons is

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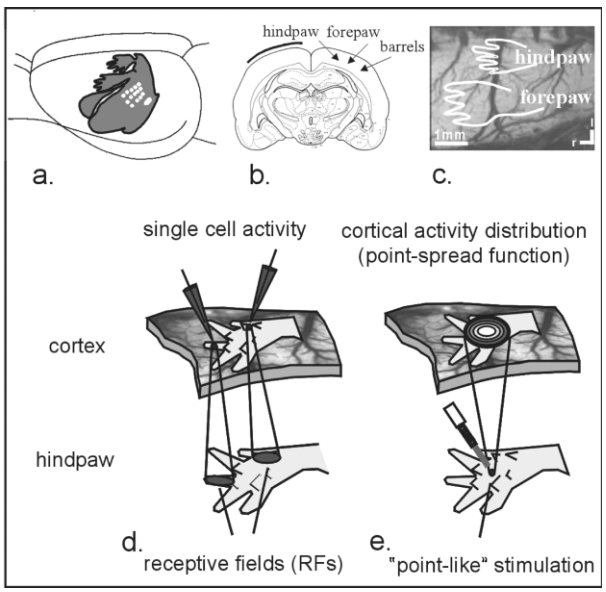

Fig. 1. Higher mammals contain complete and ordered topographic maps of the skin of the body surface, giving rise to a so-called 'homunculus'. Adjacent locations on the skin are represented at adjacent locations in the cortex. Exceptions such as the face–hand border arise from the problem to map a three-dimensional object onto a two-dimensional surface. Example of a rat 'homunculus' is shown (a). In rats the primary somatosensory cortex is mapped along the dorsolateral aspect of the cortex, see locations of hindpaw, forepaw and barrel system (b). An video-image of the dorsal surface of the brain as indicated by the thick dark line in (b) is shown (c). With the locations of the hind-and forepaws marked in white one can distinguish two different and complimentary ways to assess cortical maps, activity distributions and receptive fields (RFs) (d). RFs are mapped by inserting microelectrodes, usually into the middle layers, of the cortex to record action potentials from single cells or small clusters of neurons. The RF is defined as that region on the skin surface where light touches evoke changes in the neuron's activity. This procedure maps activity recorded in the cortex into the stimulus space. When moving the electrode to an adjacent location in the cortex, a systematic shift in the corresponding receptive field location will be encountered. A complete topographic map can be obtained when a large number of electrode penetrations are combined in such a way, that the penetration coordinates are related to the corresponding receptive field coordinates (e). The inverse approach is taken when cortical activity distributions are measured. In contrast to (d), a fixed stimulus, ideally a small, 'point-like' stimulus, is applied, and the entire activity in the cortex evoked by that stimulus is measured. This type of activity distribution is often referred to as 'point spread function—PSF'. Technologies often employed for this kind of analysis are optical imaging and fMRI. However, it should be noted that the PSF could be obtained using microelectrodes. In this case, single or multiple neuron activity evoked by the 'point-like' stimulus is recorded and its spatial distribution is derived from a systematic mapping at different locations. In theory, receptive fields and PSFs are the corresponding counterparts of a mapping rule that describes how input is represented in a topographic map. In practice, however, due to differences in threshold and due to particularities in methodological constraints, both descriptors of cortical representations may yield different results.

described using the method of optical imaging of intrinsic signals and multi-unit electrophysiological recordings. The question is addressed whether age-related changes are a consequence of degeneration, or alternatively, develop due to plastic reorganization. In the second part, the findings are discussed in relation to alterations in cognitive competence. Finally, possible attempts are described to ameliorate age-related alterations.

2. Walking behavior in old rats

Compared to elderly humans, old rats show significantly reduced agility and mobility. The characteristic impairment of the sensorimotor state is most strikingly expressed in a deterioration of walking, particularly of the hindlimbs. Animals of high age typically display sliding and dragging of the limbs due to insufficient elevation [1–3]. In contrast to normal adult animals, aged rats not only use digits and pads for locomotion, but also the more distal parts of the heels, which leads to reduced sensory stimulation of the hindpaw (Fig. 2). The described sensorimotor impairment is restricted to the hindlimb with only little or no effects on the forelimb. In fact, the forelimbs are engaged in cleaning, feeding and looming behavior throughout life. However, despite the behavioral intactness of the forelimb, walking in aged rats is slowed down and displays a number of compensatory changes such as increased step frequency and increased duty cycle (Schulz et al. in preparation).

Fig. 2. We recorded footprints (DeMedicanelli et al. 1982) of the hindpaws to visualize the characteristic impairment of the sensorimotor state as most strikingly expressed in a deterioration of walking. Young adult rats only use digits and pads for locomotion. Their walking pattern produces distinct and selective sensory inputs, when single digits and pads are placed on the ground (left). In contrast, aged rats also use the more distal parts of the heels. Animals of high age display typically sliding and dragging of one leg due to an insufficient elevation (middle and right). This pattern gives rise to multiple and diffuse inputs, sometimes even from the dorsal side of the paw. As a consequence, rats of high age show reduced agility and mobility, which in turn leads to severely restricted sensory stimulation of the hindpaw as compared to normal adults. The foreleg of aged rats does not develop comparable changes (modified and reprinted with permission from Ref. [6]).

3. Age-related changes of rat somatosensory cortex: comparison of fore- and hindpaw representations

Dinse and colleagues used male hybrid Fischer 344 x Brown Norway (FBNF1) and male Wistar rats kept in standard housing environments to study age-related changes of rat somatosensory cortex. The 50% probability of survival in an aging colony is about 34.5 months for male FBNF1, and 31 months for male Wistar rats [4,5]. As a rule, the FBNF1 animals were 29 months of age and older, while the Wistar rats used were 24 months and older. For the age groups studied, gain in body weight during aging was small for both strains: 400–450 g in young vs. 500–530 g in old FBNF1 rats, and 360–400 g in young vs. 380–430 g in old Wistar rats.

In normal, young adult animals (3–6 months of age, denoted 'young' or 'adult' in the following), cutaneous RFs on the hindpaw usually comprise only single or neighboring digits and pads, while RFs on the proximal part of the paw normally represent larger skin areas (Fig. 3, top row). In contrast, in aged rats cutaneous RFs on the hindpaw were significantly enlarged compared to adults (about 200%, on average). RFs in these animals were characterized by representations of multiple digits and pads and by substantially enlarged RFs in the proximal parts of the paw (Fig. 3, bottom row). As a consequence, because the overall skin surface is about the same, the RF enlargement is paralleled by a substantial increase of RF overlap [6]. Mapping the hindpaw representation in old rats with electrophysiological multi-unit recordings revealed that at the cortical level, the topographic order of the hindpaw map was severely deteriorated, and that the total amount of cortical territory devoted to the representation of the hindpaw was reduced by about 30% [6,7]. Accordingly, the changes in walking behavior of the hindlimbs in aged rats are paralleled by a dramatic decline of the functional organization of the somatosensory cortex.

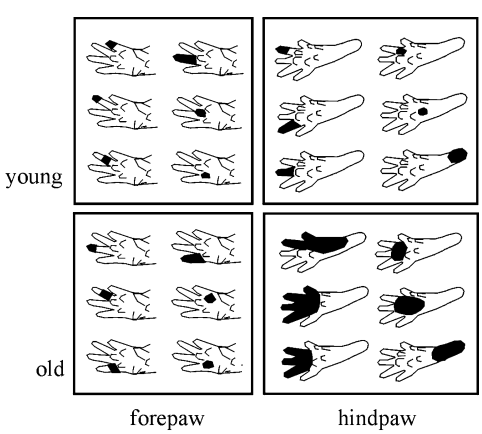

Fig. 3. Typical examples of cutaneous receptive fields (RF) of the fore-and hindpaw representations for a young adult (top, sensorimotor performance according to the left track in Fig. 2) and an aged rat (bottom, right track in Fig. 2). RF mapping was performed using handplotting as described in Fig. 1. RF size on the forepaw was about the same in young adult and aged rats (13.3 and 16.1 mm^2; respectively, $p = 0.8$), but hindpaw RFs in aged rats were about twice as large than in young adults (58.7 vs. 29.6 mm^2; $p < 0.001$).

As described earlier, the sensorimotor impairment is restricted to the hindlimb. Accordingly, each individual can serve as its own control, when comparing age-related changes of cortical topography and RF size on the fore-and the hindpaws. In case of degeneration one would expect comparable changes to occur in both the fore-and the hindpaw representation. In contrast, no comparable increase in RF size could be detected in the forepaw area of the same aged animals in which significant enlargement of the hindpaw RFs were found (Fig. 3). Even in the oldest animal tested (43 months), there were no indications for changes of forepaw RF size. Similarly, at the level of cortical maps, no changes in the areal extent of the cortical representations of the forepaw could be detected.

To assess complete maps of the paw representations, optical imaging of intrinsic signals was used to map the functional organization in rat primary somatosensory cortex after tactile paw stimulation [8,9]. Optical imaging is based on reflectance changes of the cortical tissue related to the concentration of oxygenated and de-oxygenated hemoglobin and has been proven to show high-resolution maps of neuronal activity [10,11]. Therefore, maps of reflectance changes can be regarded as a form of neural activity distribution. Young rats showed cortical activation patterns similar in layout and extent for both the hind-and forepaw representations (Fig. 4(a)–(c)). Typically, homogenous and compact zones of high activity (shown in red) were surrounded by regions of lower, probably subthreshold activity (yellow to green).

In aged rats optical imaging revealed drastic changes. While the forepaw representations were about the same shape and size as described for the adult controls (Figs. 4(d) and 5(a)), the hindpaw representations were significantly reduced in size. In addition, they had a more patchy appearance consisting of separated zones of high activity surrounded by regions with no activity, giving rise to separated islands of activity (Figs. 4(b) and 5(a)). Interestingly, the size of the hindpaw representations in aged rats determined optically using a 50% threshold criterion was about the same size as those determined by electrophysiological mapping of RFs, or by local field potential mapping [9].

4. Cortical map changes at high age are not related to age-related changes in cerebral blood flow

It is well documented that the functional metabolism of the brain and the cerebral blood flow decline with aging [12,13]. On the other hand, optical imaging of intrinsic signals is based upon the changes of local cerebral blood flow [10]. To obtain information about the size of activated

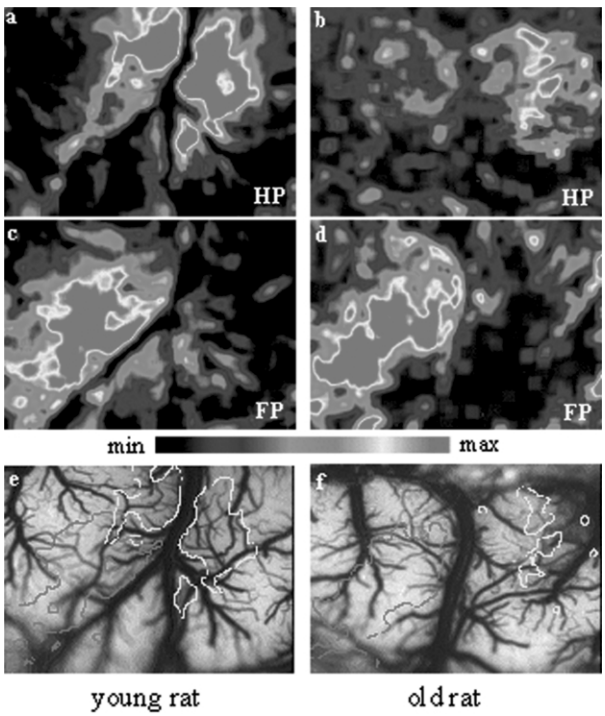

Fig. 4. Examples of optically measured activity distributions in young adult (a,c) and old (b,d) rats after tactile stimulation of the hindpaw (a,b) and forepaw (c,d) using a specifically designed cushion that allowed simultaneous stimulation of the entire paws. For optical imaging of intrinsic signals, we used a slow scan 12 bit CCD-camera. The cortex was illuminated with a 546 nm cold light source. 90 consecutive images of 80 ms duration each were recorded and accumulated over six stimulus repetitions. Always five consecutive frames were summed resulting in a sequence of 18 images of 400 ms duration each for a given stimulus. Maps of reflectance changes were computed by dividing each single image by a pre stimulation control image (blank). The frame with highest reflectance changes, generally between 2000 and 2400 ms after stimulus onset, was used for further analysis. After low-pass filtering, the spatial distributions of reflectance changes were color-coded with maximal activity in red and no activity in black (see colorbar). Maps were quantitatively analyzed by computing the cortical area for which 50% of the maximal reflectance change was achieved (Fig. 5(a)). For better comparison of hind-and forepaw representations within animals, outlines of activity distributions from a to d are superimposed onto images of the cortical surface (red forepaw, yellow hindpaw, e,f). Young adult rats (a,c) show cortical activation patterns characterized by homogenous and compact zones of maximal activity (shown in red) surrounded by regions of lower, probably subthreshold activity (yellow to green) that are disrupted by shadows arising from blood vessels In contrast, in old rats, the hindpaw representations were significantly smaller and had a patchy appearance with separated zones of maximal activity and regions of no activity within the paw representation (b).

areas from optical imaging experiments, the number of pixels reaching a certain threshold of reflectance changes relative to the maximum changes in the recording are calculated. It is therefore possible that the effects on representational area size found in the hindpaw representation of aged rats might simply reflect a decrease of cortical perfusion rather than changes in neuronal activity.

This possibility was ruled out by comparison of the maximal reflectance changes from the optical recordings after stimulation of the hind-and forepaw in young and aged rats. Berkefeld et al. found a reduction of reflectance changes by about the same amount was found for both hindpaw and forepaw stimulation (Fig. 5(c)), while the size of the forepaw representational area remained unaffected (Fig. 5(a)). Within the experimental groups (aged vs. young controls) there was no significant difference between reflectance changes observed for the fore- and hindpaws [9]. Based on these findings it was concluded that the global decrease in reflectance changes reflect a decrease in cerebral blood flow. Computing the Pearsson correlation coefficient between reflectance changes and representational areas for the hind-and the forepaw, revealed no relationship between these two measures ($r^2 = 0.323$, $p = 0.177$, hindpaw and $r^2 = 0.009$, $p = 0.975$, forepaw). Therefore, the decline in optically measured cortical activation area in the hindpaw representations of aged rats is most probably independent of the global decrease of cerebral metabolism due to age.

5. Effect of aging on neuronal response latencies and spike rate

So far we considered representational aspects of cortical organization such as RFs and cortical maps. We showed that age-related changes could display a substantial degree of regional selectivity. The lack of changes for the forepaw argues against a global breakdown of function. Are there then no degenerational changes in the aging brain? Therefore, Jürgens and Dinse extended their studies to response latencies as an additional parameter that describes properties of conduction, synaptic transmission and synaptic integration [7]. The rationale for examining latencies was that conduction velocity is slowed down during aging mainly due to demyelinization [14,15]. Accordingly, conduction is a parameter well-known for being subject to degenerational processes. 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, neurons in the fore-and the hindpaw representation of somatosensory cortex of aged animals showed a significant lengthening of response latencies [7]. As summarized in Fig. 5(d), a similar amount of increase of latencies was found in aged rats as compared to young controls for the hindpaw as well as for the forepaw representation.

In contrast, inspection of response magnitude in terms of spike rate evoked by tactile stimulation of the RF revealed a similar pattern as that described for RFs. In young animals, spike rate was comparable for stimulation of RFs on the fore- or hindpaw. However, in aged rats, response magnitude for hindpaw stimulation was significantly reduced, while spike rate for forepaw stimulation remained unaltered (Fig. 5(c)).

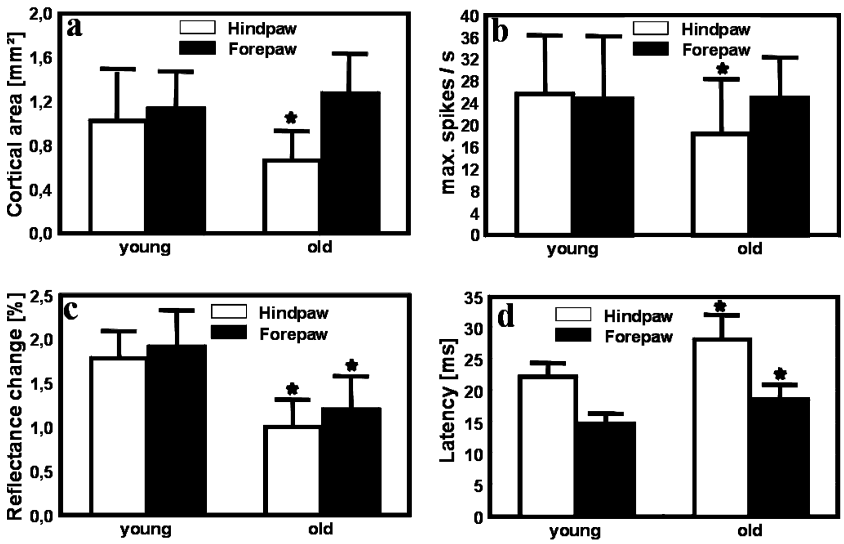

Fig. 5. Summary diagrams illustrating age-related changes for representational area (a), stimulus evoked spike rate (b), magnitude of reflectance changes (c), and neuronal response latencies (d). Mean values and standard deviations, stars indicate significance levels of $p < 0.01$. In young adults, the mean size of the representations was 1.02 mm^2 for the hindpaw and 1.13 mm^2 for the forepaw. In aged rats, the forepaw representations were about the same shape and size (1.27 mm^2) as described for young adults. However, the size of the hindpaw representations was significantly smaller (0.66 mm^2) as compared to the forepaw representations in the same animals ($p < 0.01$) as well as to the hindpaw representations in young controls ($p < 0.03$). Similar effects were found for the spike rate after tactile stimulation. On the forepaw spike rate was about the same for young and old rats (24.8 vs. 25.0 spikes/s), but reduced after hindpaw stimulation from 25.6 in young to 18.3 in aged rats ($p < 0.01$). Response latencies were lengthened from 14.8 to 18.6 ms on the forepaw ($p < 0.001$) and from 22.2 to 28.2 ms on the hindpaw ($p < 0.001$). The reduction in optically measured reflectance changes was from 1.91 to 1.20% for the forepaw ($p < 0.001$) and from 1.78 to 1.00% for the hindpaw representation ($p < 0.001$).

6. Identification and separation of degenerative vs. plastic changes observed in old rats

In the following, we compare primary somatosensory cortical paw representations in young and aged rats to get insight into the nature of age-related changes at the level of early cortical sensorimotor processing. In this approach, the comparison between aging-effects on the fore-and the hindpaws plays a crucial role, as the typical sensorimotor impairment is largely limited to the hindlimb. In view of the apparent correlation between cortical and behavioral alterations, it has been suggested that some aspects of age-related changes might reflect plastic reorganization as a consequence of prolonged disuse or reduced use of the hindlimbs rather than cortical degeneration as a consequence of aging. In fact, the results showed that changes of RFs and cortical maps occurring during aging are limited to the hindpaw representations (for a summary of differential aging-effects for the fore-and hindpaw, see Table 1). This is consistent with recent findings who reported no age-related changes of cutaneous RFs on the forepaw of rats 24–28 months of age as compared to adults (6.5–8 months) [16,17]. These results imply that age-related changes can be regionally very specific, and implicate a link between neural changes and specific behavioral alterations emerging during aging.

Mapping studies of the same type have been performed in the ventral posterior lateral (VPL) nucleus of the thalamus of aged rats. According to these findings, thalamic cutaneous RFs showed a similar aging pattern, with profound enlargement of RFs on the hindpaw, and a lack of changes for RFs on the forepaw [18].

Mapping the hindpaw motor cortex by means of intracortical microstimulation also revealed profound age-related changes consisting of a dramatic reduction in the areal size, a loss in muscle topology, an increase in thresholds for evoking movements and lengthening of EMG latencies [19,20] indicating that the motor system of the

Table 1
Summary of the differential effects of aging for the fore-and hindpaw

	OI signal strength	Response latency	RF size	Cortical area	Topographic order	Response strength
Forepaw	↘	↗	→	→	→	→
Hindpaw	↘	↗	↘	↘	↘	↘

Arrows indicate increase (↗), decrease (↘) or no change (→) of respective parameters.

hindleg is also severely affected by age (but see effects of enriched environment on motor cortex below).

Interestingly, no age effects were found for primary visual cortex of monkeys 24 years of age and older, neither in terms of cell loss, nor functionally [21–23]. These findings corroborate our hypotheses that there are very little degenerative changes of cortical processing, given its sensory modality is engaged in normal use.

7. Relation of age-related changes to use-dependent plasticity

From a more general point of view, these findings extend the framework of use-dependent plasticity to high age. In animals and humans intensified sensory stimulation accompanied by extensive use or training has been shown to result in enlarged cortical representations of the respective body parts [24–27]. For example, the seasonal nursing behavior of lactating rats results in extended representations of the ventral trunk [28]. On the other hand, besides deafferentiation or amputation studies, there are only few studies dealing with the role of decreased sensory input or disuse in cortical reorganization. Cutting a tendon of the hindlimb of rats leading to reduced walking and slight changes in the locomotion behavior results in an increase of RF size and a shrinkage of the cortical map within a few days. Both behavioral effects and cortical changes are reversible within weeks [26]. Complete prevention from use was accomplished in adult rats under space flight conditions or hindlimb suspension [29]. Both approaches resulted in modified posture and gait which returned to normal after about 2 weeks. Behavioral adaptations were paralled by a reduction in the number of GABA-immunoreactive cells [30] indicating that changes in the activity of GABAergic cells are involved in regaining effective movement control following alterations in the afferent information. For the human motor system, similar fast adaptational regulations have been reported using transcranial magnetic stimulation (TMS) mapping. In subjects who had unilateral immobilization of the ankle joint without peripheral nerve lesions the area of motor cortex representing the tibial anterior muscle was significantly reduced compared to the unaffected leg [31]. The amount of areal reduction was correlated with the duration of immobilization, an effect rapidly reversed by voluntary muscle contractions. These studies suggest that small alterations in behavior due to special demands imposed in everyday life alters early cortical representations rapidly and reversibly.

8. Cortical age-related changes are not a reflection of peripheral changes

To show that the described age-related changes of cortical sensory processing are not a simple reflection of changes occurring already at the periphery, Reinke and Dinse 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 (EAPs) of the hindpaw of the N. plantaris in adult and old rats. EAPs revealed comparable shapes and amplitudes in all animals of all age groups. In aged rats, conduction velocities were significantly lengthened by about 15% and mechanoreceptor composition was different from adults, resulting in a lower number of SA units. However, there were no differences in RF size and in threshold between old and adult animals [32].

For 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 changes with age [33]. In addition, there appears to be no massive cell losses in the LGN or striate cortex [21,22,34]. Physiological results in the monkey LGN suggest that the functional properties of LGN neurons are also not significantly affected by aging [35]. For a general discussion of aging-effects on cell number see Ref. [36], and this issue.

9. Perceptual implications

What are the implications of impaired cortical sensorimotor organization? Here we argue that 'normal' cortical processing of sensory information is required for 'normal' perceptual and motor performance. Pleger et al. could recently demonstrate that in humans the degree of functional organization in somatosensory cortex is linearly related with tactile discrimination abilities [37]. Conceivably, assuming similar drastic changes of cortical organization to occur in elderly human subjects must always certainly lead to severe perceptual impairments. In fact, studies on spatial two-point discrimination in elderly subjects revealed significant higher discrimination thresholds [38–40]. However, there is a controversy whether changes are attributable to peripheral changes [38,40] or those occurring centrally [39], as well as concerning the degree of idiosyncratic changes. Our animal studies as those from others clearly advocate the view that age-related changes in thresholds are highly idiosyncratic. Most interestingly, comparing threshold changes on the toe and fingertip revealed on average a 400% deterioration of acuity on the foot as compared to 130% on the finger [41]. These data are highly compatible with our rat data indicating large regional differences, which might be correlated with the use of the respective body parts. According to preliminary data on two-point discrimination testing in elderly, subjects of high age (>86 years) but with above-average mental and physical fitness showed an increase in thresholds by only 50% implying that idiosyncratic factors might in fact play an important role (Dinse et al. unpublished).

10. Relation to cognition

While we provided evidence that cortical changes can develop during aging that are highly specific and independent of ongoing degenerational processes such as delayed conduction and reduced metabolism, there is the question how modification of sensorimotor processing relates to parallel cognitive age-related alterations. There is a growing evidence from human studies that sensorimotor processing is more closely related to cognition than previously thought [42]. A series of recent behavioral studies showed that aging gives rise to an increasingly strong association between sensory processing and cognitive functioning [43]. In a comparative study of the walking behavior of young and old human subjects, severe locomotion impairments became apparent when subjects were studied under high cognitive loads. These results suggest that sensory and motor aspects of behavior are increasingly in need of cognitive control with advancing age [44].

On the other hand, it is well established that cognitive processing deteriorates in old age as well [45], although there are few studies comparing the parallel decline of both cognitive and sensorimotor functions. In any way, these findings add to the important role of cognitive decay as a contributing factor to age-related sensorimotor impairments. In fact, cognitive decay was found to be a valid predictor of falls [46,47], and of unsafe driving incidents in elderly persons [48]. However, this view implicitly assumes that cognitive functions subserve the preservation of simple sensorimotor behavior. It could well be that alternatively the maintenance of sensorimotor processing is a prerequisite for the maintenance of cognitive functions. In this sense, the argument could be reversed by claiming that high coincidence of falls predict poor cognitive functioning. According to a recent study on short-term fluctuations of sensorimotor performance in elderly subjects, intraindividual variability in walking steps contributed to predicting text and spatial memory performance [49].

11. Ways to ameliorate aging-related alterations

It has always been a main concern to be able to interfere with aging processes in order to delay or to ameliorate the impact of age-related alterations. In rodents, it is well established that diet and caloric restrictions have a significant life-extending effect. There is a lively discussion about comparable effects on primates and humans [50,51]. According to a longitudinal study using rhesus monkeys at the University of Wisconsin, the effects of caloric restrictions on longevity and diseases should be clearly seen by around 2020 [52]. On the other hand, there are many lines of evidence suggesting that maintained physical and mental exercise are prerequisites for what has been called ‘successful aging’, although definite answers might be revealed only in the next decades.

Behavioral challenges through an enriched environment has been shown to increase synaptic density [53], brain weight [54], cortical thickness [55], dendritic arborization [55,56], levels of Ach-esterase [57], and neurotrophic factors [58], and to induce neurogenesis [59].

What about age-related changes of early sensorimotor processing? When old rats at an age of about 26–29 months were exposed to enriched environmental conditions for only a few months, the animals regained nearly normal walking behavior of the hindlimbs, and the typical age-related enlargement of RFs of the hindpaw was nearly abolished [60]. On the other hand, the lengthening of response latencies remained unaffected. For the motor hindpaw representations, old rats exposed to enriched environment under the same schedule showed complete recovery from age-related functional shrinkage of cortical territory typically found in animals housed in standard conditions [19]. Beneficial effects on cortical forepaw neurons have also been reported for animals that were kept in enriched conditions for their entire life [17].

These results indicate that an enriched environment is effective to restore to a large extent mobility and agility of the animals, and counteracts certain parameters of age-related changes that in our view relate to adaptational plasticity and use, but not degeneration. Even more, the beneficial outcome takes effect even in animals of high age.

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 is known to block selectively the so called L-type of the voltage-dependent Ca^{2+} channels [61], which play a crucial role in the maintenance of the neuronal Ca^{2+} homeostasis [62]. Schuurman and Traber were able to demonstrate that in aged rats a long-term treatment with nimodipine can delay the typical deterioration of walking behavior when compared to untreated age-matched controls. In addition, in animals that displayed an impairment of walking at 24 months of age, 6 weeks of nimodipine treatment resulted in a significant reduction of the previously acquired sensorimotor deficits [63,64].

Berkefeld et al. and Jürgens and Dinse studied the effects of long-term application of nimodipine on RFs in the fore and hindpaw representations of primary somatosensory neurons of aged Wistar rats 23–31 months of age, starting the nimodipine-treatment at 19 months of age. Parallel to the beneficial effects of nimodipine on the overall state and walking pattern of the hindlegs, they found a significant effect on RF size of the hindpaw representations compared to untreated age-matched controls. In addition, optical imaging revealed that the normal layout of cortical hindpaw maps was preserved. The positive effects resulted in a reversal of the normally observed age-related increase of RF size which came to match the values found in normal adult animals. However, this reversal was restricted to a period of 5.5–9 months of treatment corresponding to an age of 24.5–28 months. In contrast, RFs on the forepaw that did

not show age-related changes in untreated animals, were not affected by the nimodipine treatment. The results demonstrate that nimodipine can delay typical age-related changes of the hindpaw representation in parallel to the sensorimotor state of the hindlimbs. In contrast, nimodipine was not able to affect the age-related lengthening of cortical response latencies as neurons from the hindpaw as well as the forepaw showed the characteristic lengthening with chronological age. Together with the additional lack of effects on RFs of the forepaws these findings suggest a remarkably specific mode of action [7,9].

The primary determinants of motor decline in aged rats are hypothesized to be primarily mechanical in nature, such as muscle atrophy resulting from reduced use.

Given this assumption, one possible explanation for the beneficial effects of nimodipine might be unspecific factors, such as an elevation of the level of arousal, which in turn lead to enhanced motor activity [1,64]. This idea is compatible with the concept of use-dependent plasticity: Increased motor activity intensifies sensory stimulation, thereby modifying cortical representations. In this view, the unimpaired sensorimotor performance of the forepaw in aged animals can be attributed to maintained intensive use. Increase of motor activity induced by nimodipine can be expected to have no further impact on the sensorimotor performance of the forepaw.

Alternatively, the synaptic efficiency and hence, cortical information processing capacities are progressively impaired during aging. Conceivably, dysregulation of the Ca^{2+} homeostasis affects cellular and network properties such as inhibitory mechanisms that regulate RF size. In case of nimodipine-treatment, the Ca^{2+} overload developing during aging is prevented. As a consequence, RFs of the hindpaw are not enlarged. In contrast, the maintained use of the forepaws counteracts a Ca^{2+} overload and RF size of the forepaw remains unaffected by age.

Combined, the results from both the enriched environment and nimodipine medication show the treatability of age-related changes. Most importantly, they clearly imply that age-related changes can be reversed even if they have developed, which we take as a convincing argument for their non-degenerative properties.

12. Outlook and perspectives

We provide experimental evidence at the level of primary somatosensory cortex that changes in aged rats are characterized by a profound regional selectivity. Most strikingly, the often dramatic changes in the size of receptive fields and cortical maps for neurons in the hindpaw representations were completely lacking in the forepaw representation recorded in the same individual. This substantial degree of functional intactness of the cortical forepaw representation correlates with the behaviorally largely unaffected forelimb. On the other hand, response latencies are lengthened in the fore-and the hindpaw representations which might be related to the overall observed slowing down of mobility seen behaviorally. Walking as an integrated behavior displays a number of compensatory measures to allow for preservation of stability, which is highly vulnerable by lengthening in conduction and transmission times. When considered in concert, the accomplishment of maintained behavioral performance in aged animals in spite severe changes of timing must be based upon the emergence of new strategies of sensorimotor cortical information processing. These strategies are speculated to develop from plastic adaptational capacities in response to environmental constraints and age-dependent degenerative processes. Combined, the next logical step consists of identifying mechanisms that allow the considerable compensations, and of searching for signatures of new processing strategies, both perceptually and behaviorally, in both animal models and human subjects.

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