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Effects of ageing on topographic organization of somatosensory cortex

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Deficits in limb coordination and decreased motor activity have been described in old rats older than 24 months, an approved animal model in ageing research. We investigated the implications of age-related decline of sensorimotor performance by studying the functional cortical organization of aged rats. The cutaneous receptive fields of the hindpaw representations in somatosensory cortex and the cortical areas excited by tactile point-stimulation were enlarged and highly overlapping in old rats when compared with young rats. This gives rise to a complete loss of topographic detail. These functional changes were correlated with the rat's individual walking patterns, indicating that age-related deficits in sensorimotor performance are paralleled by degradation of the functional representations in the ageing nervous system.

Key words: Somatosensory cortex; Receptive fields; Representational maps; Sensorimotor performance; Ageing; Topography; Input selection; Use-dependent plasticity; Information processing; Post-ontogenetic plasticity

Introduction

The process of ageing can be characterized by a great number of physiological modifications, including structural changes such as neuronal degeneration and cell loss due to changes in cellular protein synthesis and metabolic capacity, and biochemical changes such as alterations in Ca^{2+} or cholinergic dysfunction.[1–3] Age-related changes in neuronal systems are often, but not inevitably, accompanied by cognitive decline and memory impairment. While there is a growing body of information about age-related changes at a cellular and biochemical level, almost nothing is known about effects of ageing on the way in which neurones process and integrate complex information from the external environment, i.e. about functional changes at higher, cortical levels.[4] Consequently, little is known about the relationship between changes in neuronal functions, neural structure and behaviour during ageing.

On the other hand, recent studies of cortical plasticity have revealed that the cortical organization of adults can undergo dramatic changes, even after the end of the critical developmental period. Considerable plastic adaptive capacities were observed in the cortex after circumscribed damage to peripheral receptor arrays leading to complete reorganization of the input-deprived cortical areas after weeks and months of recovery.[5–7] More interestingly, remodelling of sensory representations following behavioural training, classical conditioning and prolonged natural sensory stimulation suggests that cortical maps and receptive fields are also subject to modification by use.[8–12]

Rats > 24 months of age are an approved model in research focusing on various age-dependent modifications. For example, deficits in limb coordination and decreased motor activity have been described in old rats.[13,14] These factors can be assumed to modify the sensory inputs from muscles and skin. According to our hypothesis that experience and use are crucial factors influencing the idiosyncratic layout of cortical representations, we used 'old' rats as a model to study the impact of age-related decline of sensorimotor performance on cortical organization by analysing receptive fields and representational maps of the hindpaw of primary somatosensory cortex.

Materials and Methods

A total of 30 old male Wistar rats (24–36 months) and 40 control Wistar and Sprague–Dawley rats of both sexes (3–13 months) were anaesthetized with urethane (20% in Ringer solution, 1.5 g kg^{-1}, i.p.) and held under urethane anaesthesia during the entire course of the experiments. Single units or small clusters of units were extracellularly recorded in layer IV in the primary somatosensory cortex using glass microelectrodes filled with 3 M NaCl. Treatment of all animals was within the regulations of the National Institution of Health Guide and Care for Use of Laboratory Animals (Rev. 1987). For experimental details see Refs 15 and 16. For mapping, cells that responded to just visible skin indentations were classified as cutaneous. Cells responding either to high threshold stimuli, joint movements or deep inputs were classified as non-cutaneous. Penetrations were usually placed 100–200 μm apart, which allowed a precise definition of the spatial extent and topography of the hindpaw representation and its borders. The size of receptive fields and the 25, 50, 75 and 100% overlap with a reference receptive field (skin field on digit 2) was determined by measurements from computer drawings.

The spatial activity distribution in cortical layer IV evoked by tactile stimulation on the digits and the pads

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of the hindpaw was recorded as local field potential (LFP) maps by multiple penetrations in seven old and in five young control rats. The spatial distribution of activity was computed at the 40%, 60% and 80% level of the LFP amplitudes.

To evaluate the nature and organizational degree of topographic maps, we used an interpolation algorithm based on a linear least square approximation, which can be solved by minimizing a local weight error term.[17] The local weighting depends on the RF sizes and the local distribution of their centres, determining the sigma in the weighting function, which is modelled by a modified Gaussian. The resulting matrices are solved by singular value decomposition.

Two weeks before the electrophysiological recording experiments, free behaving old and control rats, kept under normal light/dark cycles, were videotaped during a daily session (60 min) in observation cages (50 × 80 × 30 cm) in order to determine the mean diurnal activity. Footprints were reproduced from walked-over photographic paper to quantify the individual walking patterns.[18] Rearing rates were determined from the number of erected and biped postures lasting >5 s.

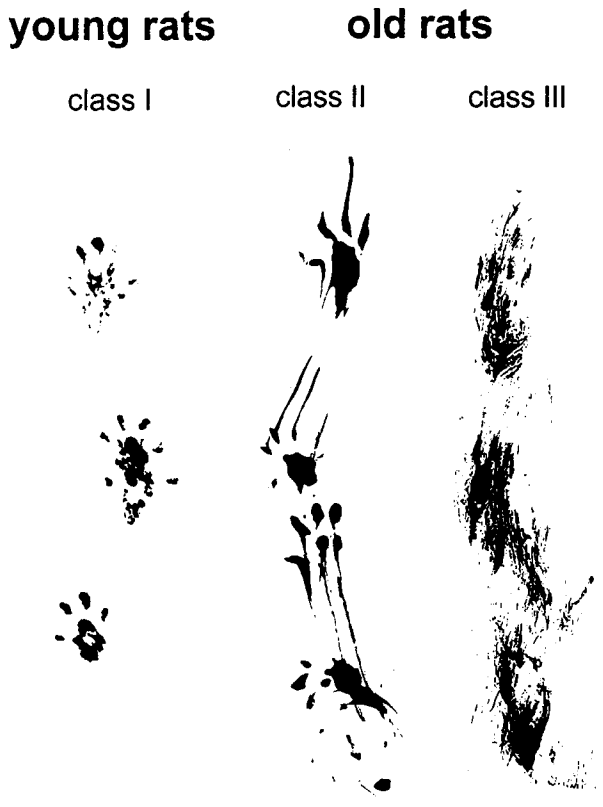

FIG. 1. Comparison of sensorimotor performance of young and of old rats. Class I footprints of the hindpaw are usually found in young rats serving as control group. This walking pattern is correlated with distinct and selective sensory inputs where single digits and pads are placed on the ground. Class II and III are typical for old rats. Class II is correlated with an intermediate state of sensorimotor performance; Class III is 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. Forepaw performance displays retardation in feeding and cleaning behaviour, but remains otherwise relatively unchanged.

Results

We compared age-related representational changes in the primary somatosensory cortex (SI) in old rats (>24 months) and control rats (3–13 months). In order to assess quantitatively deficits of sensorimotor performance, we determined the activity levels in old and in control rats (3–13 months). The rate of rearing was about 77% less in old rats than in young controls. Characteristics of walking patterns were determined from reconstructions of individual footprints. Walking patterns of old rats revealed dramatic changes: temporally distinct inputs from digits, toes and pads were replaced by multiple and dynamically diffuse inputs from skin surfaces all over the paw (Fig. 1). It is conceivable that the impaired walking patterns give rise to abnormal sensory inputs that may affect receptive field representations. We tested this hypothesis of use- and disuse-dependent adaptational mechanisms that are involved in the process of ageing first by analysing the receptive field size and overlap of neurones in the somatosensory cortex of old rats (>24 months) and second by correlating the cortical representations with the age and state of sensorimotor performance for each animal. We found highly enlarged receptive fields in the hindpaw representations in old rats compared with control rats 3–13 months old. The mean receptive field size of the hindpaw increased several-fold (Fig. 2, Table 1). In control rats, the mean size of receptive fields ($n = 306$) on the hindpaw was 32 ± 24 mm² skin surface (± s.d.); in old rats receptive fields were an average of 104 ± 46 mm² (unpaired Student's t-test: $p < 0.0001$). As a consequence of this receptive field enlargement, the receptive field overlap between single receptive fields also increased. This was quantitatively assessed by measuring the mean skin area represented by completely overlapping receptive fields of the hindpaw which was expanded from 32 ± 24 mm² in control rats ($n = 108$) to 185 ± 82 mm² in old rats ($n = 78$; $p < 0.001$, t-test, Table 1).

In order to measure the spatial dimensions of the cortical representational area evoked by point-like tactile stimulation and to assess the degree of overlap between zones of activity evoked by stimuli successively applied to different skin sites of the digits and pads, we constructed local field potential (LFP) maps on the basis of LFP recorded by multiple penetrations. As a rule, the total cortical area of excitation evoked by tactile stimulation was increased in old rats (Fig. 3 and Table 1). The most striking feature was the emergence of a high degree of overlap between zones of activity evoked by stimuli to different skin sites. As the cortical representational area is limited by the surrounding representations of other body parts, such an increase in the representation of restricted skin fields must inevitably

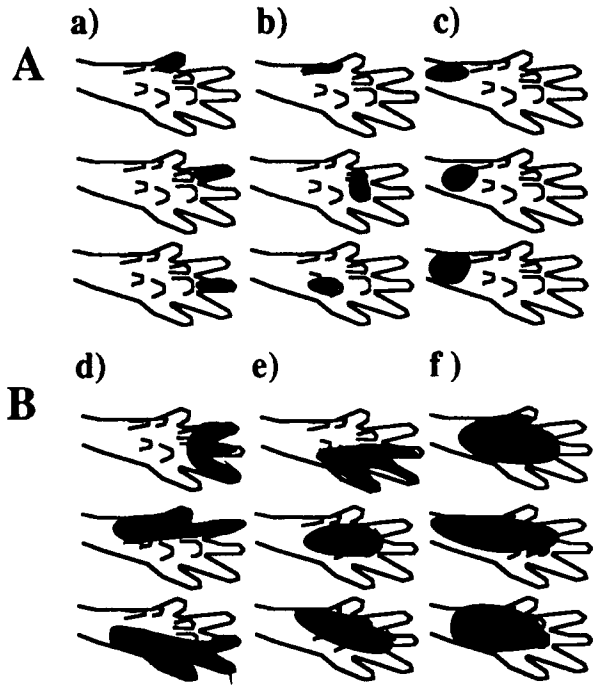

FIG. 2. Examples of receptive fields in a young control rat (6 months, class I sensorimotor performance according to Fig. 1) and in an old rat (24 months, class III, Fig. 1) on the hindpaw [a–f]. In the somatosensory hindpaw representation of young rats (**A**) we observed single receptive fields on the digits, pads and on the heel (columns a–c). In contrast, in old rats (**B**) with a poor sensorimotor performance level (class III), we encountered greatly enlarged receptive fields covering multiple digits, multiple digits and pads and multiple pads and the heel (columns d–f).

Table 1. Comparison of receptive field properties and topographic organization of somatosensory cortex of young and old rats (mean ± s.d.)

	Receptive field size (mm^2)	Receptive field overlap (mm^2)	Cortical area[a] (mm^2)	Relative overlap[b] (%)
Young rats	32 ± 24	32 ± 24	0.016 ± 0.011	1.5 ± 0.8
Old rats	104 ± 46**	185 ± 82*	0.051 ± 0.018*	10.2 ± 4.8**

Unpaired Student's *t*-test; $**p < 0.0001$; $*p < 0.001$.
[a] Average cortical area (LFP mapping) excited by tactile stimulation.
[b] Percentage of overlap of cortical areas (LFP mapping) evoked by three different stimuli.

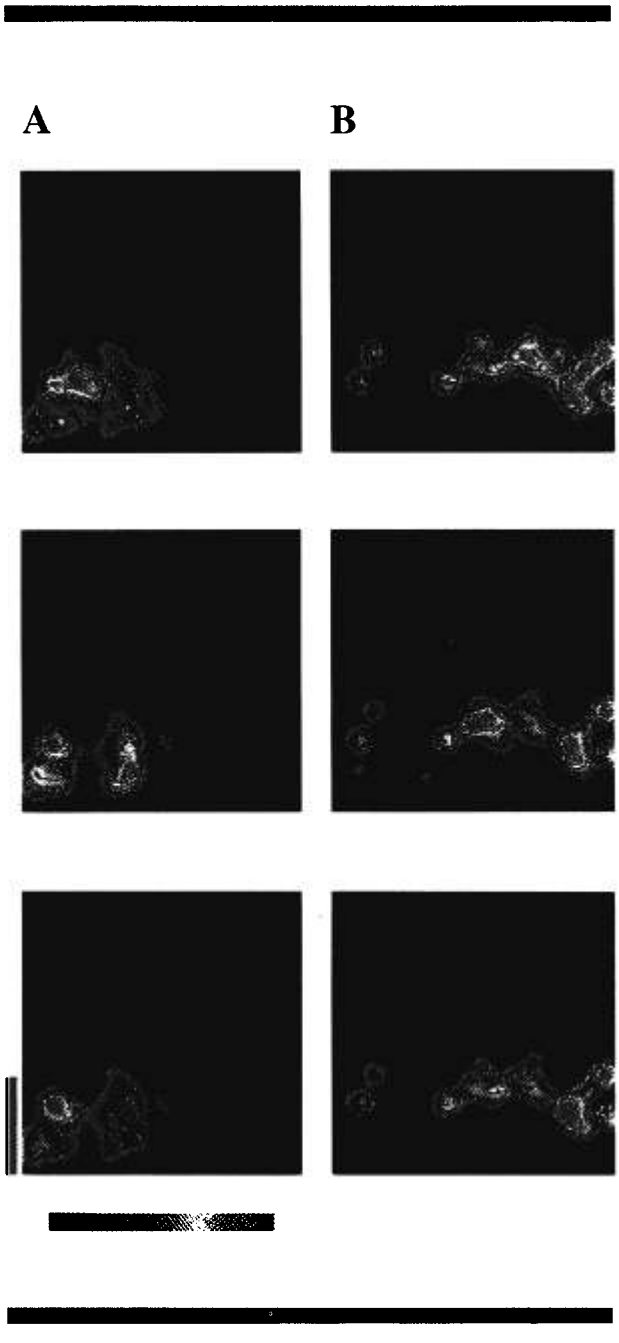

FIG. 3. Local field potential (LFP) maps showing the spatial activity distributions (top and middle row) and the excitational overlaps (bottom row) evoked by tactile stimulation in the hindpaw representation of the primary somatosensory cortex of a control (**A**) and an old rat (**B**). Top row: activity distribution following stimulation of digit, middle row: activity distribution following stimulation of pad. Normalized LFP-amplitudes are colour-coded and projected on to the cortical area of hindpaw representation reconstructed from [x,y] coordinates of penetration sites. Scale bar: 1 mm; each plot is oriented with rostral left and lateral up.

result in an overall increase of representational overlap. The average cortical area excited by tactile stimulation in old rats was 0.051 ± 0.018 mm^2 compared with 0.016 ± 0.011 mm^2 in young control rats. The relative overlap (percentage of cortical area evoked by three different stimuli) increased from 1.5 ± 0.8% in young rats to 10.2 ± 4.8% in old rats (Table 1).

To determine how far the observed changes of cortical organization in SI of old rats reflect changes in the degree of representational topography, we reconstructed somatosensory maps using an interpolation of sampling coordinates of penetration sites and corresponding receptive field centres.[10] The reconstructions of cortical maps in control rats (Fig. 4A) and in old rats (Fig. 4B) demonstrated a complete loss of topographic details of the hindpaw representations in old rats compared to the high-order topography in controls.

To strengthen the hypothesis of use/disuse dependent cortical changes, we correlated the functional parameters describing the individual rat's cortical organization with the state of each sensorimotor performance (cf. Fig. 1). This analysis confirmed the assumption that large deficits in sensorimotor per-

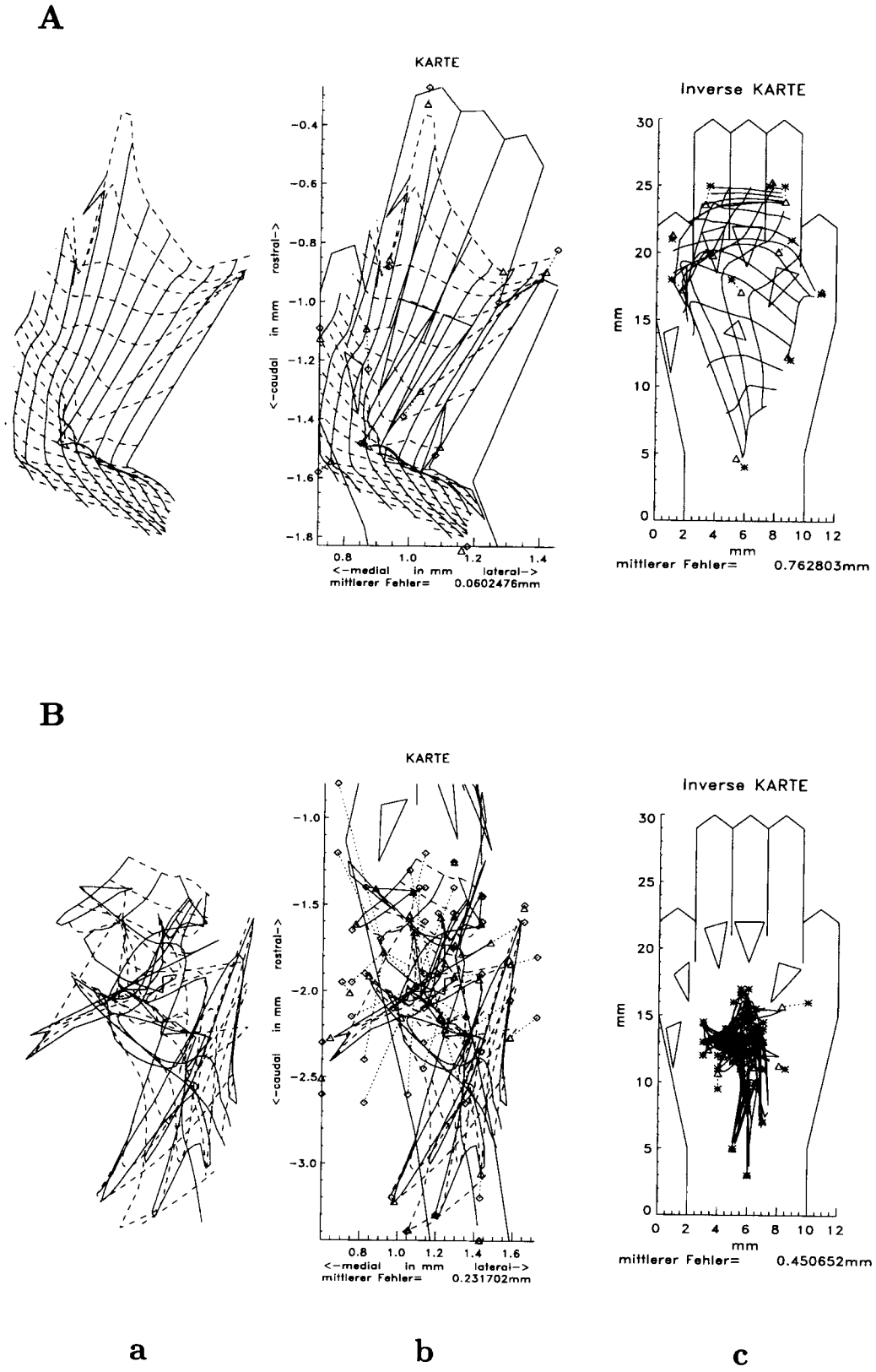

FIG. 4. Reconstructions of a cortical hindpaw representation of a control (**A**) and of an old rat (**B**) by the interpolation of RF centres and the cortical coordinates of corresponding penetration sites. (**a**) Examples of cortical topographies represented as a regular lattice within SI. (**b**) 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. ◇, indicate penetration sites; □ give the interpolated RF centres. Dotted lines give the deviation between them. (**c**) Back projection of the regular lattice of the cortical map on to the hindpaw. □ give the interpolated, asterisks the measured RF centres. One square of the lattice represents the skin portion represented by 0.01 mm^2 cortical area.

formance are associated with severe degradation of cortical topography. There was a correlation between RF size and walking patterns ($r = 0.59$; $p < 0.07$). In contrast, age and walking pattern ($r = 0.125$) and age and RF size ($r = 0.177$) were not correlated, indicating that the degradation of cortical organization is primarily associated with sensorimotor deficits, but not *a priori* with age. In other words, aged rats with fairly normal walking behaviour had fairly normal RFs.

Discussion

In old rats, which are a well-established animal model for studies of age-related modifications, cortical organization is severely affected. There is a loss of small and distinct receptive fields and a loss of the fine grained topography in the hindpaw representation of primary somatosensory cortex, which is usually found in normal, adult rats. Instead, old rats have highly enlarged and overlapping receptive fields and have coarse representational maps that do not contain topographic details about the skin. Most interestingly, these changes are associated with a behaviourally defined decline of sensorimotor performance of the hind leg, indicating that such changes cannot be entirely attributed to non-specific, age-related, degenerative breakdown of cortical functions independent of the behavioural performance and the overall state of the animal. As described above, this assumption was further substantiated by the lack of correlation between cortical changes and age (within the group of aged animals) and between age and behavioural performance.

There is a general agreement that mechanisms of adult neuronal plasticity are input based.[8–12,15,16] In this first study of age-related changes of cortical organization we demonstrate that the hindpaw representations in aged rats display representational changes comparable to or even more extensive than those induced by experience and use or by lesions in the normal adult nervous system.[5–12,15,16] According to the established relationship between functional changes of the somatosensory cortex in old rats and the age-related changes of sensorimotor performance, a type of walking that simultaneously engages larger skin surfaces appears to generate large receptive fields, considerable overlap and an overall topographic breakdown. These modifications indicate that the ageing nervous system maintains the capacity of input-selective, use/disuse-dependent neuronal plasticity. The maintenance of functional plasticity in aged nervous systems is also supported by the partial reversibility of impaired sensorimotor performance by pharmacological treatment.[13,14,19] So far, studies on the effects of ageing on information processing, i.e. functional changes at higher, cortical levels are rare. We propose that the age-related impact of neuromodulatory mechanisms and physiological changes at multiple levels, including structural and sensory changes of the skin, muscle atrophy and neural degeneration[20–25] may interact in a complex manner with input-dependent functional changes to effect the topographies in the cortical representations. According to this hypothesis, deteriorated topographies as a result of temporally and spatially deteriorated sensory inputs of aged rats reflect active, adaptive-plastic capacities and processes. Further studies on cortical plasticity in ageing individuals are required to clarify the basic mechanisms of active and degenerative processes involved in the ageing of the brain.

Conclusions

Rats older than 24 months show a striking degradation of their cortical organization. These changes are correlated with deficits in limb coordination and with decreased motor activity. It is assumed that age-related behavioural decline generates modified sensory inputs and that their impact is causally related to the breakdown of cortical representational topographies. Similar mechanisms can be hypothesized to be involved in various aspects of elderliness. Accordingly, age-related changes reflect diversified, complex processes, which beside degenerative phenomena include active, adaptational processes. The experimental findings support the hypothesis that experience and use/disuse are crucial factors which affect the idiosyncratic layout of cortical representations in adults, and that these factors are similarly involved in the process of ageing.

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