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Treating the aging brain: cortical reorganization and behavior

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Summary

Aging comprises many physiological modifications, including structural and metabolic changes, yet little is known about how aging affects the way in which neurons process and integrate sensory information from the environments. Here the framework of "modified use" as a determinant of cortical reorganization was applied for the investigation of age-related modifications of cortical maps and processing, and of associated changes of behavior. The age-related changes of walking behavior in rats were contrasted with the parallel changes of sensorimotor processing developing at the cortical level. Based on the regional specificity of these changes attempts are made to separate age-related changes arising as a consequence of degeneration from a result of adaptable processes following reduced use at high age. Finally, findings from long-term treatment with the Ca^{2+}-blocker nimodipine, or from housing animals under enriched environmental conditions to ameliorate aging effects were described. Combined, these results show the general treatability of age-related changes. The data imply that age-related changes can be reversed by short periods of training and stimulation schedules even if they have developed. Clearly, the development of specific measures to delay aging processes and to rehabilitate aged brains depends on future progress in understanding mechanisms and effects of aging.

Keywords: Degeneration; plasticity; walking behavior; sensorimotor performance; enriched environment; training; cortical maps; reorganization; rats; nimodipine.

The aging brain: socio-political background

We witness a unique restructuring of the aging pattern in the societies of the industrial nations, characterized by an increasing probability to reach high age. Concomitantly, the probability to suffer from age-related disorders is raised dramatically, indicating an urgent need for increasing efforts towards 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 vital with respect to the innumerous implications for a wide range of social disciplines such as psychology, sociology, health care, and politics in general [1, 25].

Given this scenario, the preservation of every-day life competence of aged populations becomes increasingly important. In particular, the maintenance of sensorimotor abilities is a crucial prerequisite to be able to live largely independent. In this context it is of far-reaching consequences, whether age-related changes are due to the accumulation of degenerative processes and are by that largely irreversible, or whether age-related changes reflect plastic adaptations, and therefore allow for effective treatment [5, 6, 15, 23].

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, finds its 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 growing old is an old problem, the emergence of such a longevity for a substantial portion of the population is a fairly new phenomenon.

Aging theories

In search of an understanding of normal, not pathological aging processes, a number of "aging theories" have been developed. According to stochastic theories, aging processes are explained by a probabilistic accumulation of factors that progressively exert deteriorating effects onto the organism. On the other

hand, deterministic theories assume that aging is the consequence of endogeneous and/or genetically programmed processes. Among the stochastic theories are "tear and wear" [28], "free radicals" [16], "collagen/cross linkage" [44], "error and fidelity theory" [27] and the "immune theory" [45]. Deterministic theories are know as the "absolute metabolic scope theory" [36] and the "cell doubling theory" [17]. While each of these theories can account for some aspects observed during aging, there is now agreement that aging can not be explained by a single theory alone, but instead, that aging must almost certainly be regarded as caused by a multitude of factors.

Myths and facts

What do we know about the effect of aging on brain structures? "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 ref. 30). In fact, the idea that there is a significant loss of neurons during normal aging dates back to Brody [2]. However, recent studies revealed an amazingly degree of stability in neuron number [11, 26, 30]. Besides technical problems associated with an accurate estimation of neuron numbers, a great problem lies in the enormous variation in neuronal numbers between individuals. For example, the size of area 17 in the human or primate brain can vary by a factor of three among individuals [30, 31, 42]. This huge variability raises doubt about the significance of a loss of up to 10%, when individual variations can be as much as 100% [30]. Similarly, a recent study by Rapp & Gallagher [34], who studied neuron numbers of representative samples of the entire hippocampus of behaviorally tested rats, reported no age-related loss of neurons, even from those animals with the greatest age-related behavioral impairments.

The question remains, are there then no structural counterpart to the clear impairment seen functionally during aging? It had been suggested that certain subpopulations of neurons might undergo a dramatic loss. Also, there can be a substantial reduction of specific sets of dendritic spines [31]. Molecular shifts in intact circuits have been described in the dentate gyrus of the monkey [13]. Aged rats with spatial learning deficits displayed significant reductions in synaptophysin immunoreactivity in CA3 relative to either young controls or age-matched animals with preserved learning [39]. Combined it appears now accepted that an age-related decline might be attributable to modifications at the subcellular level rather than cell numbers.

Aging of sensorimotor behavior and associated cortical maps

Aging comprises a number of physiological modifications, including structural and metabolic changes. While there is a growing body of information about age-related changes at cellular and biochemical levels, little is known about how aging affects the way in which neurons process and integrate sensory information from the environments. According to the concept of "use-dependent" plasticity, the young and the adult brain is in a state of permanent changes: Even small adjustments in every-day life routines that are accompanied by changes in behavior, can lead to major reorganizational processes [6]. Therefore, a prevailing question is how plastic processes affect aging processes. Here, we applied the framework of "modified use" as a determinant of cortical reorganization for the investigation of age-related modifications of cortical representational maps, response properties and associated behavior and perception [5, 6].

Rats are a convenient animal model as they age within 2 to 3 years. We therefore used aged rats to investigate the degree and the type of age-related changes at the level of sensorimotor cortical maps and processing by means of single cell recordings. To explore aspects of sensorimotor performance related to every-day life competence, we studied walking behavior. In old rats, the characteristic impairment of the sensorimotor state is most strikingly expressed in a walking impairment of the hindlimbs [15, 38, 41]. They show severe walking impairments – similar to old humans consisting of limping and dragging their hindlimbs (Fig. 1), while the forelimbs show little of these impairments [41].

Using electrophysiological recordings we demonstrated that the behavioral changes were paralleled by massive reorganizations of the somatosensory cortex such as an enlargement of receptive fields (RFs) of neurons of the cortical hindpaw representation, an increase of RF overlap and a deterioration of the topographic orderliness of the cortical maps (Fig. 2; refs. 6, 15, 41). In addition, temporal processing of the single neurons became impaired as indicated by a reduced capability to follow fast input sequences [6, 19].

In case of degeneration one would expect compa-

Fig. 1. 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 ref. 41; Lippincott Williams & Wilkins)

rable changes to occur in both the fore- and the hindpaw representation. However, analysis of RFs in the cortical forepaw representation of animals of high age revealed no alterations [15, 20]. At the same time, the sensorimotor behavior of the forelimbs remains largely unaffected even in animals of high age, presumably as a result of the maintenance of feeding and cleaning behavior. These results imply that age-related changes can be regionally very specific, and implicate a link between age-related neural changes and specific behavioral alterations emerging during aging. More generally, these findings extend the concept of use-dependent plasticity to high age (cf. 5, 6).

Perspectives for a treatment

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 [40, 46]. 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 [47]. 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 revealed only in the next decades [10, 22].

Behavioral challenges through an enriched environment has been shown to exert beneficial effects on a wide range of morphological, molecular and physiologic features of the brain. Enriched environments, usually targeting sensorimotor modalities, have been shown to improve cognitive function [35], to facilitate recovery from injury or stroke [18] and to prevent age-related decrease in synaptic density in the aged brain [37]. When rats were housed under enriched conditions for their entire life beneficial effects on the development of age-related changes of cortical maps and RFs have been reported [4]. Even keeping aged rats under enriched environmental conditions for only a few months resulted in a significant amelioration of otherwise typical age-related alterations of sensory [3] and motor hindpaw representations [7]. These results indicate that the beneficial outcome of an enriched environment and thus the aspect of reinforced mobility and agility takes effect even in animals of high age. Comparable ameliorating effects on age-related changes in rats have been found after long-term treatment with the Ca^{2+}-blocker nimodipine [20, 38]. Accordingly, physical and mental training through enriched environments, or more direct pharmacological treatment is highly effective in interfering with age-related changes behaviorally and cortically.

Almost certainly, the severe changes in organization and processing of rat sensorimotor cortex must impair tactile perception. Pleger and co-workers could recently demonstrate that in humans the degree of functional organization in somatosensory cortex is linearly related with tactile discrimination abilities [32]. 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 2-point discrimination in elderly subjects revealed significant higher discrimination thresholds [43, 48, 49].

To test directly the reversibility, and thus the plastic, adaptive nature of age-related alterations in human subjects, we used a perceptual learning protocol based on coactivation that followed the idea of Hebbian learning: Synchronous neural activity, necessary to drive plastic changes, is evoked by co-activating neighboring skin sites simultaneously [14]. In adults,

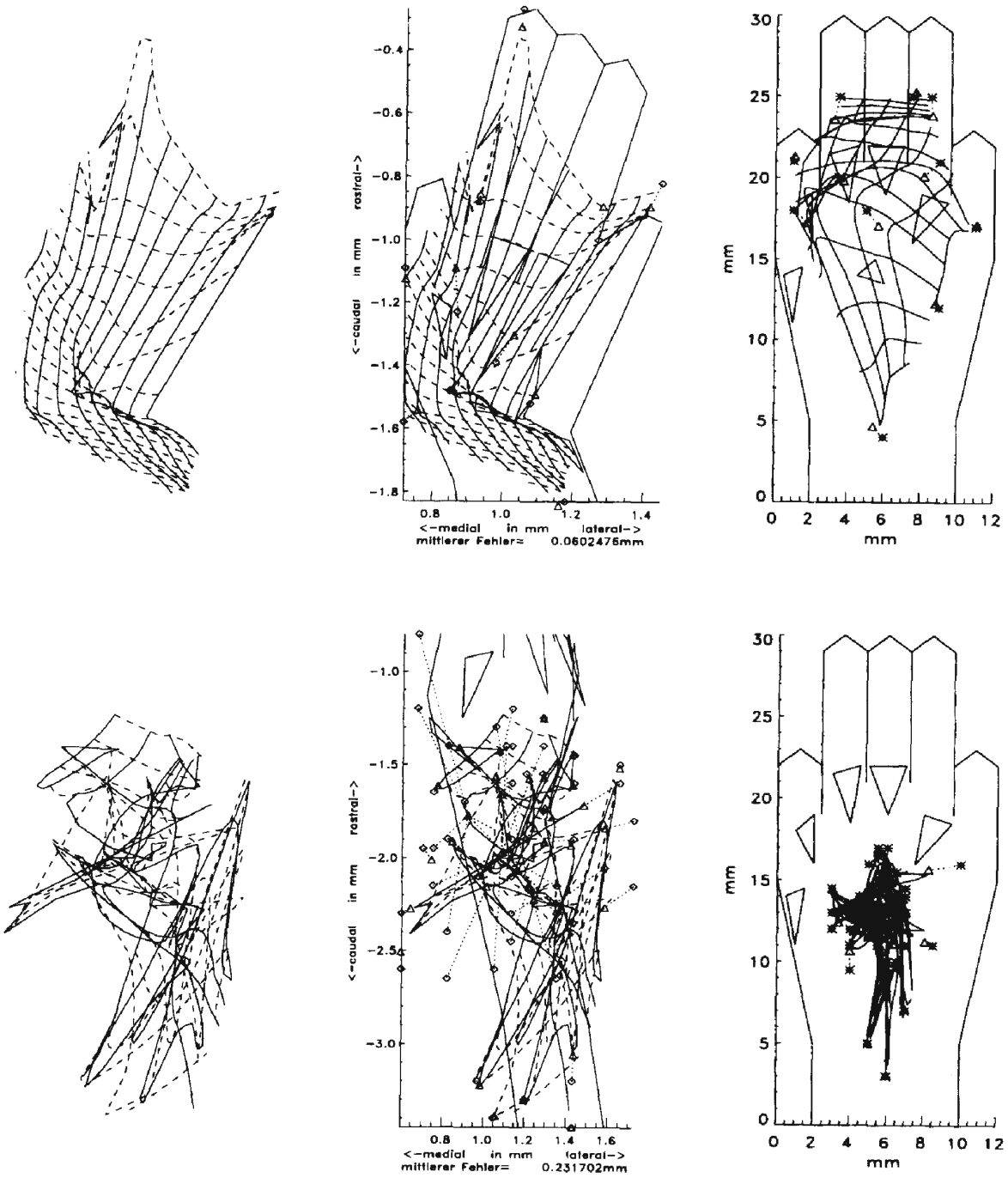

Fig. 2. Effects of age on cortical maps of the hind paw recorded in somatosensory cortex of aged rats. To visualize the effects of aging on the topography of the underlying cortical representations, we reconstructed somatosensory maps using a computer-based interpolation algorithm based on a linear least square approximation of sampling coordinates of penetration sites and corresponding receptive field centers. Reconstruction of a cortical hind paw representation is shown for control (top) and for old rat (bottom), respectively. Examples of cortical topographies represented as a regular lattice within somatosensory cortex (left). Extrapolated cortical representation of a schematic and standardized drawing of the hind paw (middle). Dashed lines indicate horizontal, and 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. Back projection of the regular lattice of the cortical map onto the hind paw (right). Squares give the interpolated, and stars the measured, RF centers. One square of the lattice represents the skin portions that is represented by 0.01 mm^2 cortical area. According to these reconstructions, maps of the hind paw representation recorded in old animals, characterized by a selective impairment of the hindlegs show a dramatic distortion of their representational maps and a loss of topographic order. (Modified from ref. 41; Lippincott Williams & Wilkins)

coactivation of a few hours improves discrimination performance of the coactivated finger [8, 14, 32]. We found similar effects in subjects of high age. In detail, coactivation for 3 hours restored tactile acuity to the level of performance typically seen in subjects 50 years of age [9, 21]. Combined, the results show the general treatability of age-related changes and imply that age-related changes can be reversed even if they have developed.

A comforting outlook

According to the "Berlin study", there exists a clear negative correlation between age and measures of intelligence [24]. However, in spite of this overall correlation, the inter-individual variability in the population of subjects that ranged between 70 and 103 years of age, is enormous. As a result, despite the negative correlation, the highest rating in intelligence performance is reached by a woman aged 87. In fact, one of the basic accomplishments in gerontology relate to the acknowledgement of tremendous heterogeneity and inter-individual variability. This variability appears to be a rather general characteristic and has been observed in humans, primates and rats [12, 33]. Additional evidence that aging must not automatically imply a general decline comes from studies of the so-called "oldest old", i.e. subjects 100 years and older, who characteristically display a considerable mental and physical fitness. They almost without exception report a high degree of subjective wellness that include active participation in social and cultural life. Interestingly, so far no correlations could be established between events and the individual life-span history on the one hand and the amount of vitality at very high age on the other hand [29].

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