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≈*REVIEW PAPER*≈

Morphological and Functional Alterations in Cerebral and Cerebellar Cortices of Old Cats

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1 SUMMMARY

The cat brain undergoes significant structural and functional alterations during the normal aging process. This review focuses on the alterations in the cerebral and cerebellar cortices, including impairments in cortical architecture, changes in neuron quantity, degeneration in neuronal configuration, disorder of the neurotransmitter system, hyperplasia of glial cells, increase in neuronal firing and decrease in the signal-to-noise ratio, as well as retrogression in relevant behaviours. Among these changes, loss of neurons, degeneration of neuronal configuration, and disruption in neurotransmitter balance are believed to be the principal causes for age-related neural dysfunction, and ultimately lead to behavioural disability in aged cats; whereas age-related enhancement of glial activity might play a compensatory role in neural degeneration during brain aging.

2 INTRODUCTION

Cats are higher-order mammals with a well-developed nervous system and are frequently used in scientific studies. Many studies have demonstrated that the cat brain undergoes remarkable morphological and functional changes in their late lifespan (> 11 years old) (Hua *et al.,* 2006; Zhang *et al.,* 2006; Hua *et al.,* 2008; Williams *et al.,* 2010; Zhou *et al.,* 2011), which includes many age-related behavioural problems (Gunn-Moore *et al.,* 2006; Gunn-Moore *et al.,* 2007; Gunn-Moore and Gunn-Moore, 2010; Heuberger and Wakshlag, 2011). Cats are a widely popular pet, which has led to a marked increase in life expectancy due to improvements in nutrition and healthcare (Gunn-Moore, 2011). The proportion of cats >10 years old has increased to ~ 15% of the domestic cat population (Gunn-Moore, 2011). Some of these senile cats suffer from a multitude of neurological diseases, such as

anxiety, sleeplessness, walking disorder, and cognitive dysfunction syndrome (Landsberg *et al.,* 2010; Gunn-Moore, 2011; Landsberg *et al.,* 2011; Landsberg *et al.,* 2012). This paper is devoted to reviewing the morphological and functional changes in cat cerebral and cerebellar cortices during the normal aging process, which will increase our understanding of the mechanisms underlying brain aging and age-related neurodegenerative diseases.

3 GROSS EXAMINATION OF THE CHANGES IN THE AGING CAT BRAIN

It has been demonstrated that aging can lead to brain atrophy and ventricular system degradation. The cat brain is also reported to undergo these changes in aging. Significant cerebral and cerebellar atrophy has been found in the brain of cats aged > 14 years, which is characterized by marked retraction of cerebral gyri and widening of the sulci, with obvious meningeal fibrosis (Figure 1) (Özsoy and Haziroğlu, 2010). Moreover, aging cat brains have severe ventricular dilatation (Figure 1), marked ependymal denudation and notable subventricular rosettes, which rarely appear in young cats (Özsoy and Haziroğlu, 2010). Remarkably, these alterations are consistent with the observations from aging brains of humans and rodents (Andersen *et al.,* 2003; Ahmad *et al.,* 2004; Fjell and Walhovd, 2010; Chee *et al.,* 2011; Long *et al.,* 2012), indicating cat brains undergo the typical alterations seen in mammalian brains during the aging process. Brain atrophy and ventricular degeneration in aging may lead to decline of brain capacity and disorder of cerebrospinal fluid circulation (Li and Freeman, 2010; Bauer *et al.,* 2012); nevertheless, some degree of these changes may be associated with a range of neurological diseases.

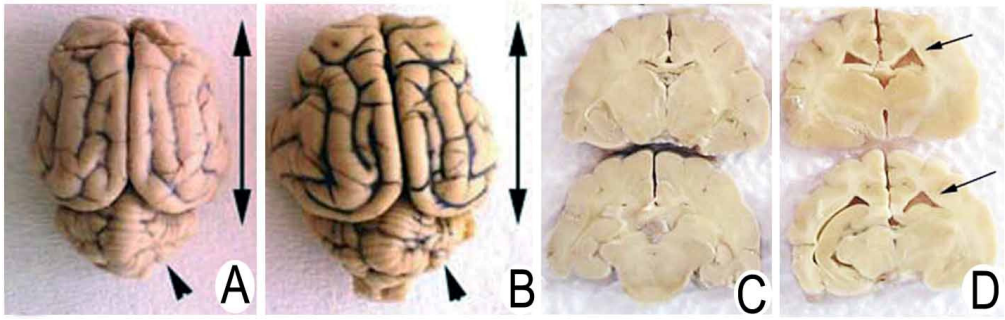

Figure 1: Compared with the young cat **(A, C)**, the old cat brain shows atrophy in the cerebrum (arrows) and cerebellum (arrowheads) **(B)**, and enlargement in the ventricles (small arrows) **(D)**. Adapted from Özsoy and Haziroğlu (2010).

3.1 Cortical architectural alterations in aging cat brain: It has been shown that the histological appearance of the cerebral and cerebellar cortices in senescent cats has marked alterations when compared to that in young cats. First, the blood vessels in the cortices of aged cats show fibrosis in the walls and some vessel lumens are completely occluded due to mineralization (Mandara, 2003; Özsoy and Haziroğlu, 2010). These alterations might directly attenuate vascular blood flow and lead to arteriosclerosis (Landsberg and Araujo, 2005), which will attenuate transportation of oxygen and nutrients in the brain tissue. Second,

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senescent cat brains have variable-sized vacuoles in the cortical tissues (Özsoy and Haziroğlu, 2010), which might arise from degeneration of the histological elements (such as loss of neurons and the matrix) in the aging cortex. Third, a significant decrease in the thickness of the cerebellar cortex has been found in old cats (Figure 2) (Zhang *et al.,* 2006), which implies the occurrence of heteromorphosis in the cortical architecture and correlation of functional disorder in the aging brain.

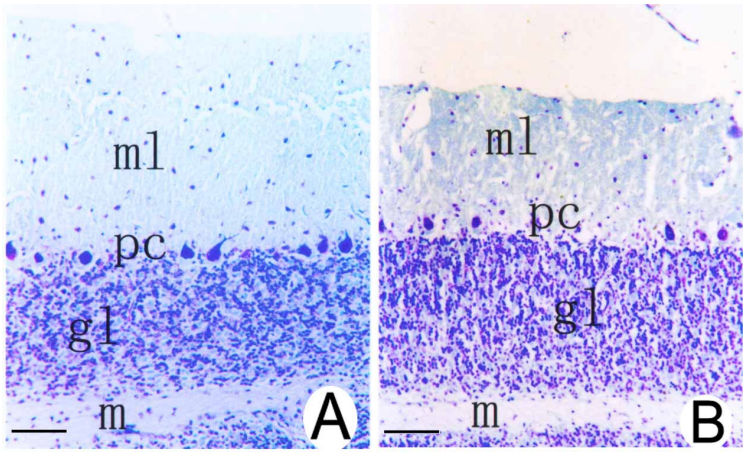

Figure 2: Compared with the young cat **(A)**, the old cat **(B)** shows significant decrease in the thickness of the cerebellar cortex. ml, molecular layer; pc, Purkinje cell; gl, granular layer; m, medulla. Bar scale = 100 μm. Adapted from Zhang et al. (2006).

3.2 Changes in the cortical neurons of old cats: Age-related change in the number of neurons is still under investigation. Some studies have revealed a significant loss of neurons in aging brains, while others have revealed no significant neuronal loss during aging. The total number of neurons in each cortical layer between the young and old cat brains does not differ significantly in the visual or auditory cortex (Luo *et al.,* 2006; Hua *et al.,* 2008), however, in old cats, the neurons in the anterior lobules of the cerebellar cortex are significantly decreased by 26.38%, 22.57% and 25.63% in the molecular, granular and Purkinje cell layers, respectively (Zhang *et al.,* 2006). This result is in line with a previous report that neurons remain relatively constant in most parts of the brain during aging, however, they do show a marked decline in some specific regions (Andersen *et al.,* 2003).

3.3 Neuronal morphological alterations in cerebellar Purkinje cells in old cats: It is believed that aging is strongly associated with alterations of neuronal morphology (Zhang *et al.,* 2010; Pannese, 2011; Samuel *et al.,* 2011). Zhang et al. (2008b; 2011b) have examined the structural and ultrastructural changes in the cerebellar Purkinje cells in brains from young and old cats. The volumes of the soma and nuclei of Purkinje cells are significantly decreased in aged cats, with a marked loss of Nissl granules in the perikaryon (Zhang *et al.,* 2011b). The height, width, and area of dendritic arborizations in Purkinje cells are significantly reduced, with loss of spine density (Figure 3) (Zhang *et al.,* 2011b). Moreover, the dendritic branchlets in old cat Purkinje cells contain

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various swellings and nodules in many segments (Figure 3), while the dendrites in young cats are almost homogeneous (Zhang *et al.,* 2011b). Additionally, Purkinje cells in senescent cats have organelle degeneration. For example, the rough endoplasmic reticulum collapses with loss of the ribosomes; the mitochondria show marked swellings with notable decomposition of the cristae; the sacs in the Golgi apparatus appear dilated with obvious abnormal polarities; lipofuscin and metabolic substances accumulate significantly in the perikaryon; the chromatin emerges in condensation; and biomembrane structures are destroyed (Zhang *et al.,* 2008b). Zhang *et al.* (2010) speculate that age-related retraction in the neuronal dendritic arborizations attenuates neural information transportation, while degeneration in the organelles may affect neuronal functions of energy metabolism, substance synthesis and intraneuronal homeostasis in the aging brain. These alterations might lead to neuronal apoptosis and subsequent brain dysfunction in senile cats.

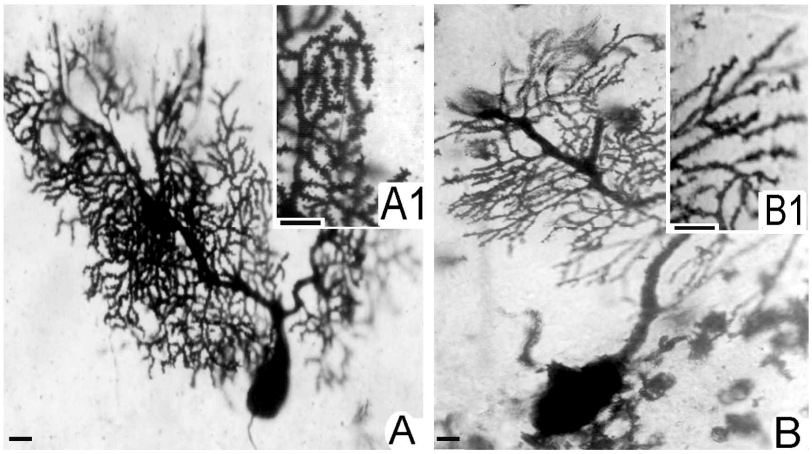

Figure 3: Compared with the young cat **(A, A1)**, the old cat Purkinje cell shows significant retraction in dendritic arborizations **(B)**, loss of dendritic spines and occurrence of nodulations or swellings in some branchlets **(B1)**. Scale bar = 10 μm. Adapted from Zhang et al. (2011b).

3.4 Age-related changes in the expression of γ-aminobutyric acid (GABA)/glutamate in old cat brain: It has been widely reported that aging alters neurotransmitter expression. Studies on the cat visual cortex have demonstrated that GABA immunoreactivity in the neurons appears only in the perikaryon in old cats, while strong immunoreactivity is additionally visualized in the proximal dendrites and the initial segment of the axons in the GABA-positive neurons in young cats (Hua *et al.,* 2008). Moreover, the GABAergic neurons are significantly atrophied in the auditory cortex in aged cats compared to those in young cats (Luo *et al.,* 2006). These results indicate loss of GABAergic expression in aging cat brains, which is consistent with the results from other animals (Leventhal *et al.,* 2003; Burianova *et al.,* 2009). Moreover, the expression of GABA is decreased to a varied extent in different cortical layers. For example, in the old cat brain the GABAergic neurons in the visual cortex were decreased by 44.5%, 56.8%, 54.7%, 60.7%, and 50.9% in layers I, II – III, IV, V and

VI, respectively (Hua *et al.,* 2008). Considering that the total number of neurons in this cortex remains constant (Hua *et al.,* 2008), the proportion of GABAergic neurons to the total neurons is significantly lowered in old cat brains, which implies loss of intracortical inhibition during brain aging (Hua *et al.,* 2008; Zhang *et al.,* 2008a). The density of glutamate-immunoreactive neurons in the cerebral cortex also decreases significantly in old compared with young cats (Diao *et al.,* 2009). However, loss of glutamate-immunoreactive neuron appears less than that of the GABAergic neurons (Diao *et al.,* 2009), which suggests impairment of the excitatory/inhibitory balance in the brain of old cats. Similarly, glutamatergic loss has been observed in the cerebellar cortex of old cats (Zhang *et al.,* 2008c). Therefore, it seems that intracortical GABA/glutamate balance is disrupted in the aging brain, which may consequently affect the physiological functions in old cats.

3.5 Age-related alterations in the glial cells in cat brain: Glial cells in the central nervous system exhibit significant age-related hyperplasia in various species (Marquez *et al.,* 2010; Zhu *et al.,* 2010). Astrocytes are the most widely distributed and studied glial cells in the central nervous system. In old cat brain, there is a marked increase in the number of astrocytes and astrocytic processes, as well as anti-GFAP immunoreactivity in the cerebral and cerebellar cortices (Figure 4) (Zhang *et al.,* 2006; Zhang *et al.,* 2011a). Moreover, Bergmann's glial cells, a special type of astrocyte in the Purkinje cell layer, show similar proliferation in old cats, which is speculated to offset the gap caused by loss or shrinkage of Purkinje cells during aging (Negrin *et al.,* 2006; Özsoy and Haziroğlu, 2010). In addition, oligodendrocytes are also increased in the cerebrum and cerebellum in the aging cat brain (Özsoy and Haziroğlu, 2010). As glial cells have numerous active roles in the central nervous system, such as protecting synapse functions, maintaining extracellular substance homeostasis, and repairing the traumatized tissues (Theodosis *et al.,* 2008; Edwards and Gibson, 2010; Xia and Zhai, 2010; L'Episcopo *et al.,* 2011), it is supposed that age-related proliferation of glial cells might exert compensatory functions in aging cat brains.

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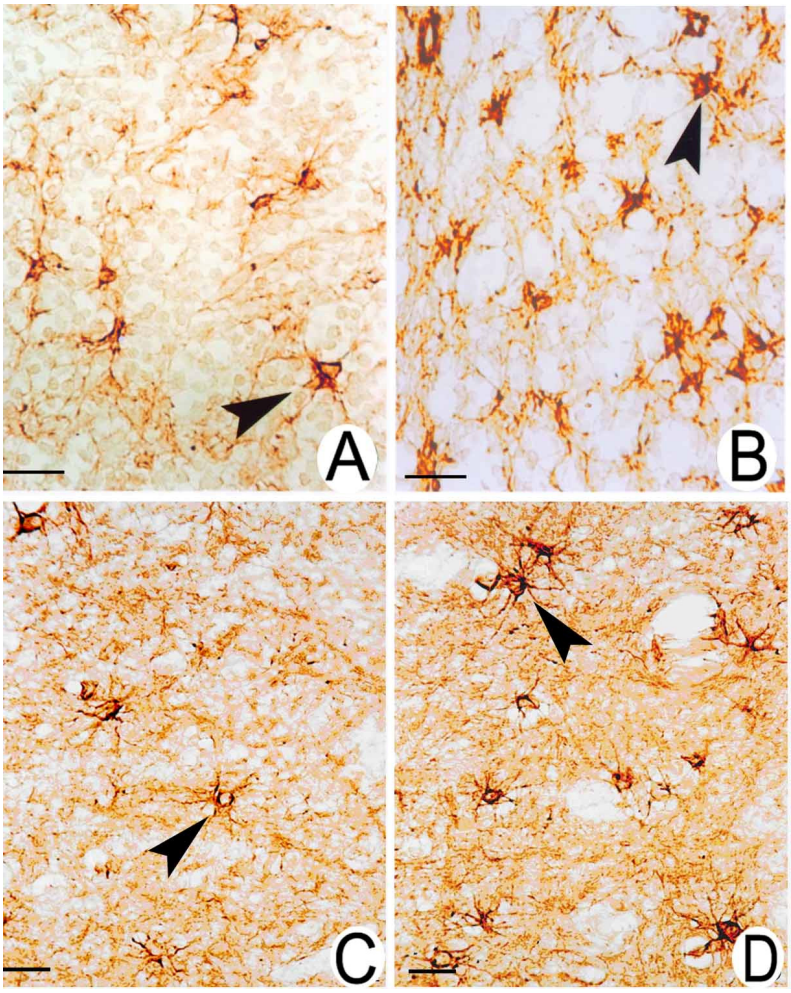

Figure 4: GFAP-immunoreactive astrocytes (arrowhead) in cerebellar cortex of young **(A)** and old cat **(B)**, and in the visual cortex of young **(C)** and old cat **(D)**. In the old cortex, the GFAP-immunoreactive astrocytes not only increase in the size and number but also in the intensity of GFAP immunostaining. Scale bar: A and B = 25 μm; C and D = 20 μm. Adapted from Zhang et al. (2006) and Zhang et al. (2011b).

4 PATHOLOGICAL ALTERATIONS IN AGING CAT BRAIN

The aging brain develops some degree of pathological alterations, such as amyloidal deposition, senile plaques, and neurofibrillary tangles, which are the prominent histopathological characteristics of Alzheimer's disease (Gunn-Moore *et al.,* 2006; Özsoy and Haziroğlu, 2010; Chambers *et al.,* 2011). Aged cat brains have evidence of amyloid β (Aβ) deposits in the cortex (Brellou *et al.,* 2005; Head *et al.,* 2005; Gunn-Moore *et al.,* 2006; Özsoy and Haziroğlu, 2010). Aβ is a long-lived peptide, and once deposited in the extracellular space, it becomes spontaneously isomerized and undergoes a conformational change that can lead to further Aβ aggregation (Gunn-Moore *et al.,* 2006). In addition, senile plaques have also been found throughout the cerebral cortices (Brellou *et al.,* 2005), and even in a few cortical

arterioles (Nakamura *et al.,* 1996) of old cats. It is believed that the extracellular accumulation of Aβ or emergence of senile plaques in the brain may initiate inflammatory changes and neurotoxicity, which ultimately results in τ hyperphosphorylation, formation of neurofibillary tangles, and further neurological dysfunctions (Gunn-Moore *et al.,* 2007; Chambers *et al.,* 2011). Therefore, these age-related alterations in aging cat brain may indicate a transition status from the normal aging changes to pathological initiation.

5 AGE-RELATED CHANGES IN ELECTROPHYSIOLOGICAL CHARACTERISTICS OF NEURONS IN CAT BRAIN

Neurons in aging cat brains not only undergo morphological alterations but also exhibit electrophysiological modifications. Neurons in the visual cortex of old cats have a wider (increased by 464%) range of spontaneous responses when compared to those in young cats (Hua *et al.,* 2006). Bias in orientation and direction are significantly decreased in the aged neurons, which is accompanied by increased visual responsiveness to non-optimal stimuli and a decreased signal-to-noise ratio in old cats (Hua *et al.,* 2006). The increased visual responsiveness in the aged cat brain might be an important mechanism mediating the reduction in stimulus selectivity during aging, while the decreased signal-to noise ratio indicates a decreased ability of aged cells to retrieve signals from noisy backgrounds (Hua *et al.,* 2006). Moreover, the mean optimal spatial frequency and high cut-off spatial frequency of the neurons in the visual cortex of old cats are significantly smaller than those in young cats (Hua *et al.,* 2011), which may contribute to decline in visual acuity during aging. Furthermore, neurons in the visual cortex of the aged cat brain have a stronger adaptation to visual stimulation than the neurons in young cats, indicating that old cats are more easily adaptive to visual signals that appear continuous in the environment than the young ones (Hua *et al.,* 2009). This kind of enhancement in the aging brain might compensate for a decrease in metabolic rate during aging (Hua *et al.,* 2009). In addition, the contrast sensitivity of the neurons to visual stimuli in the visual cortex of old cats decreases significantly relative to that in young cats, which might contribute to the reduction in visual contrast sensitivity in senescence (Zhou *et al.,* 2011). These age-related alterations of the electrophysiological properties may account for, to some extent, the neural disorders in aging cat brains.

6 BEHAVIOURAL DISORDERS IN AGING CATS

A large number of studies have demonstrated that some behavioural disorders are consistent with the direct consequences of brain aging. In cats, almost one-third of the population aged 11 – 14 years develop at least one geriatric-onset behavioural problem, and this ratio increases to > 50% in cats aged ≥ 15 years (Landsberg *et al.,* 2010; Gunn-Moore, 2011). These behavioural dysfunctions include cognitive impairments, sensory degeneration, motor disorders, conditioned reflex deficit, inappropriate vocalization, and alteration in social interactions with people or other pets (Harrison and Buchwald, 1983; Levine *et al.,* 1987; Landsberg and Araujo, 2005; Negrin *et al.,* 2006; Gunn-Moore *et al.,* 2007; Gunn-Moore and Gunn-Moore, 2010; Landsberg *et al.,* 2011). Many aged cats have cognitive syndromes, which

might be related to the compromised cerebral blood flow, chronic free radical damage, alteration of proteins within nerve cells (such as τ hyperphosphorylation), as well as the deposition of protein plaques outside the nerve cells (Gunn-Moore, 2011). Some old cats show decline in sensory and motor ability, which might be associated with the decrease in the conduction velocity of fiber tracts and accumulation of neurofilaments in the fibers (Zhang *et al.,* 1998; Xi *et al.,* 1999). It has been noticed that aged cats are easily engendered with jittering or even aggression especially when their environment is changed, which is speculated to be related to the heightened nervous sensitivity in aging (Houpt and Beaver, 1981; Landsberg and Araujo, 2005; Sparkes, 2011). However, these behavioural problems might be associated with some degree of age-related pathological alterations in the brain; for example, one study has shown that aging cats with signs of behavioural problems have notable senile plaques and other neurological changes in the brain (Gunn-Moore *et al.,* 2006).

7 CONCLUSIONS

The aging brain experiences great changes in the morphology and function that is a major risk factor for most neurodegenerative diseases. Although much research has focused on brain aging of rodents, monkeys and humans, there are few informative studies on the brains of aging cats. Intriguingly, this research suggests that the aging process is associated with severe structural and functional alterations in cat brains, and correlates with several behavioural degenerations.

8 ACKNOWLEDGEMENTS

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