ISSN: 1220-3173; E-ISSN: 2457-7618

THE AGEING BRAIN IMPAIRMENT AND THE USE OF DOGS IN BEHAVIORAL STUDIES

AFECTAREA CREIERULUI ÎN PROCESUL ÎMBĂTRÂNIRII ȘI UTILIZAREA CÂINILOR ÎN STUDII COMPORTAMENTALE

Mihaela Claudia SPĂTARU[1),*)], Luminița Diana HRIȚCU[1),*)], A.C. GRĂDINARU[1)], C. SPĂTARU[1)]

ABSTRACT | REZUMAT

The paper reviews literature data with respect to the importance of studies performed on dogs for in-depth knowledge of their behaviour and behavioural expression. Given the close cohabitation of dogs and humans, the study of dogs' behaviour is an important goal in selecting specialized breeds for various activities related to humans, where an aggressive or an unstable temperament should be avoided. Moreover, the nowadays dogs' lifestyle is similar to humans being even reported some behavioural disorders or developmental pathologies similar to humans. Therefore, considering the conditions and causes of these issues, most often similar to humans, the control, therapy or prevention of them in both humans and dogs may be discussed.

Keywords: behaviour, dog, health and well-being, anti-ageing

Această lucrare analizează datele din literatura de specialitate cu privire la importanța studiilor efectuate pe câini pentru o mai bună cunoaștere a comportamentului câinilor și modului lor de exprimare a manifestărilor comportamentale. Prin natura coabitării apropiate dintre câini și oameni, studiul comportamentului câinilor reprezintă un obiectiv important în selectarea raselor specializate pentru diferitele activități asociate oamenilor, unde un comportament agresiv sau un temperament instabil ar trebui evitat. Mai mult, condițiile actuale de viață ale câinilor sunt similare cu cele ale oamenilor, fiind chiar raportate unele tulburări de comportament și patologii comportamentale similare cu cele ale oamenilor. Așadar, considerând condițiile și cauzele acestor probleme, de cele mai multe ori similare cu ale oamenilor, controlul, terapia și prevenirea lor, atât la oameni cât și la câini, poate fi discutată.

Cuvinte cheie: comportament, câine, sănătate și stare de bine, anti-îmbătrânire

Over the time, the dog was the subject of many experiments which substantially contributed to the development of medicine, including pharmacology and various areas of cosmetics and food industry, leading to products nowadays certified to be safe for human and/or animal consumption or using. Additionally, dogs are important in certain domains such as criminology (13, 15, 49), detection of drugs or anti-personnel mines, as social animals or for the assistance of people with disabilities (31, 35, 36).

Domestic dogs are successfully used in upper and middle school to observe the behavioral and anatomical peculiarities, to study the functions of body apparats and systems, in learning medical manoeuvres and for developing specific skills and competences (2, 12, 18).

(51) suggested that through scanning the DNA of domestic dogs it is possible to approximately identify the time when the ancestral domestic dog had been separated from the group of wolves. The estimation of about 135,000 years ago cannot be correlated with the human activities in the absence of reliable evidence that can hardly be dated from that period (28). By selection, some breeds of dogs were obtained which certainly had desired qualities or were more specialized for one function and less skilled for another, developing dog breeds known as excellent companions, rescue dogs or hunting dogs (5, 14, 24, 27).

In this context, the aim of this paper is to highlight the importance of studies performed on dogs for in-depth knowledge of their behaviour and behavioural expression induced by ageing.

MATERIAL AND METHODS

This paper is a review study based on several databases checking and in which papers about the use of dogs in biomedical experimentation were published. According to (9), the capacity of searching of specific literature actively stimulate the complete knowledge of a domain, increasing thus the potential for a pros-

1) University of Life Sciences "Ion Ionescu de la Brad", Faculty of Veterinary Medicine, Iași, Romania
*) *Corresponding authors: mspataru@uaiasi.ro; lumidih@uaiasi.ro*

pective exploration of the researched topics. The open-access systems of databases and increasingly free access of information on social networks have led to the accumulation and comparison of information in each field.

RESULTS AND DISCUSSIONS

A better understanding of the dog behaviour would be beneficial in a society that considers the dog attacks on people and the deaths that result from them to be an ongoing problem. *The Humane Society of the United States* estimates that 2% of the population is yearly bitten by dogs (over six million people) and between ten to twenty percent of these bites are fatal, the victims usually being children (20). Also, in order to increase the degree of individual security in the USA, the number of dogs considered to be of aggressive breeds (especially of Pit Bull breed) increased by 36% from 1986 to 1994 (34) fact which led the authorities to prohibit dogs of these breeds.

The first behavioural research on dogs was published by (8), highlighting how domestication influenced the behaviour of dogs and diminished their fear of humans. He sustained the evolution of specialized cortical brain areas, fact which was demonstrated in recent years by MRI investigations (1, 48). In their research, (17) showed the relationship between the interacting factors that can determine the variation of the brain size in dogs in relation to the body size or their specialization, the external and internal morphology of the skull and the organization of internal brain networks. *Darwin* also studied the social behaviour of dogs, observing the affectionate expression manifestations for their human owners (8). According to (8), the dog's consciousness would appear as a result of a conflict between lasting social feelings (attachment) and transient desires (hunger, play etc.), being known that the moral behaviour in humans is based on the same foundation.

In a study of (37) it was investigated whether visual orders, as opposed to verbal ones, are more effective when dogs are trained to bring an object. Dogs responded better to visual hand gestures than to verbal orders, although the speed of response was faster when both types of commands were used together. While dogs use vocalization to communicate (vocalizations are usually context-specific, for example for attracting attention) (40), they also largely communicate using discrete body postures (23), both intra-specific (dog to dog communication) and interspecific (dog to man communication). Thus, dogs can respond to the intention of an activity by eyes suggestion or if we gesture from the head (21) or point the hand, head or foot towards a certain object (22). (10) showed that the effectiveness of the command was reduced when the person who gave the order turned his back. This implies that body postures appear to be important for dogs in understanding signals as part of human-dog communication, but may be context dependent. As for people, at least 30 repetitions are needed to strengthen the conditional factor and an accuracy of 80% of the previously exercise for a new activity learning (27, 43).

Although all mammals go through the physiological life stages from early development to puberty, ageing and death, the temporal dynamics with which these phenomena occur in relation to humans are different. (52) propose the mapping of common methylation changes in mammalian genomes as they age, mainly generating some relevant data on the associations and representativeness of ages in humans and dogs. The study of epigenetic "clocks" (11) was successful in determining age in humans but not accurate in estimating age in mice or dogs. Studies on dogs are a useful model for such comparisons because much of the dog's environment, diet, chemical exposure, physiological or developmental patterns are similar to those of humans. According to the NIH investigator, Dr. Elaine Ostrander, "dogs experience the same biological hallmarks of aging as humans, but do so in a compressed period, around 10 to 15 years on average, versus over 70 years in humans. This makes dogs invaluable for studying the genetics of aging across mammals, including humans" (30). Thus, the life expectancy of the Labrador breed is 12 years and translates as 70 years in humans, which corresponds to the average life expectancy worldwide by establishing the formula "human age = 16 ln (dog age) + 31" (52).

Many breeds of dogs are used to study some aspects of ageing and the effects of degeneration of internal organs caused by aging. For this purpose, the Beagle dogs are the most often used. They have a lifespan of 12 to 14 years, individuals over 9 years are considered "old", being associated with people between 66 and 96 years (26, 33). As in humans, the cognitive and neurobiological changes are observed in dogs from middle age (6-8 years) and become more visible as they age, some dogs developing the early stages and symptoms of Alzheimer's disease (7, 16). Because the duration of studies on ageing in Beagle dogs is time consuming and leads to huge costs, scientists have resorted to models of accelerated ageing caused experimentally by chemical compounds, such as D-galactose (29). This kind of method has been used as a model of accelerated ageing in mice and rats (25, 41) and may be used to improve the efficiency of ageing studies in the case of Beagle dogs. In mice aged with D-galactose, progressively decreases in learning and memory capacity, mobility and cardiac dysfunction are observed, which are similar to mice that age naturally (19).

As in humans, memory decreases in dogs with age and manifests itself by affecting the ability of spatial orientation, this stage being recorded at the beginning of the aging process, between 6 and 7 years (44). In vivo brain imaging studies show that in the brain of older dogs there is a cortical atrophy and an enlargement of the ventricles (45), atrophy occurring through the destruction of neurons and changes in neuronal density, as in humans (42, 52). In dogs, the volume of white matter in the brain also decreases with age and, interestingly, appears to have a different pattern in males and females (46). Frontal lobe atrophy intensifies with age, especially in older males, while in females the temporal lobe atrophy was reported to be more evident. Given that myelin loss is observed in dogs as they age, the frontal cortex being particularly vulnerable, this may be critically involved in cognitive decline in both sexes (6, 38, 50). Both in humans and dogs, the Alzheimer's disease is accompanied by progressive dementia and the accumulation of senile plaques and neurofibrillary tangles. Plates contain beta-amyloid (Aβ) (39) that forms either extracellular or deposits in the cytoplasm of neurons, leading to their degeneration. Dogs develop a type of Aβ pathology similar to that of humans. Aβ deposition occurs progressively, firstly affecting the prefrontal cortex of the dog and later the temporal and occipital cortex, similar to aspects reported in humans (38, 47).

Because dogs may develop Alzheimer's disease, older dogs have been used to test some different therapies that have been tested in human clinical trials. A diet rich in antioxidants and mitochondrial co-factors improved cognition and reduced neuropathology in older dogs over a period of 2.8 years. Behavioural enrichment, which includes new and complex exercises, environmental improving, social enrichment and cognitive training, also lead to significant cognitive and neurobiological benefits. Statins have also been associated with a reduced risk of Alzheimer's disease by lowering cholesterol levels (3, 32).

CONCLUSIONS

The investigations on dogs' behaviour and changes induced by ageing and various brain pathologies revealed many similarities with those of humans. Therefore, in many cases, the dog may be used as an animal model for the evolution of these diseases. Moreover, various therapeutic strategies can be tested on dogs affected by natural brain impairment as a result of ageing, including here antioxidant diets and learning programs, interruption of beta-amyloid processing by anti-inflammatory drugs or statins etc.

REFERENCES

1. *Andics A., Gácsi M., Faragó T., Kis A., Miklósi Á.,* (2017), Voice-sensitive regions in the dog and human brain are revealed by comparative fMRI. Curr Biol, 27:1248-1249
2. *Arluke A.,* (2004), The use of dogs in medical and veterinary training: understanding and approaching student. JAAWS, 7(3):197-204
3. *Bosch M.N., Pugliese M., Gimeno-Bayon J., Rodriguez M.J., Mahy N.,* (2012), Dogs with cognitive dysfunction syndrome: a natural model of Alzheimer's disease. Curr Alzheimer Res, 9:298-314
4. *Bosch M.N., Gimeno-Bayon J., Rodriguez M.J., Pugliese M., Mahy N.,* (2013), Rapid improvement of canine cognitive dysfunction with immunotherapy designed for Alzheimer's disease. Curr Alzheimer Res, 10:482-493
5. *Bray E.E., Otto C.M., Udell M.A.R., Hall N.J., Angie M., Johnston A.M., MacLean E.L.,* (2021), Enhancing the selection and performance of working dogs. Front Vet Sci, 8:644431
6. *Chambers J.K., Urchida K., Nakayama H.,* (2012), White matter myelin loss in the brains of aged dogs. Exp Gerontol, 47(3):263-269
7. *Cotman C.W., Head E.,* (2008), The canine (dog) model of human aging and disease: dietary, environmental and immunotherapy approaches. J Alzheimers Dis, 15(4):685-707
8. *Darwin C.R.,* (1871), The descent of man and selection in relation to sex. London: John Murray. Volume 1. 1st edition, Available at: http://darwin-online.org.uk/content/frameset?pageseq=1&itemID=F937.1&viewtype=text [Accessed: December 02, 2021]
9. *Davis P.M.,* (2011), The impact of free access to the scientific literature: a review of recent research. J Med Libr Assoc, 99(3):208-217
10. *Fukuzawa M., Mills D.S., Cooper J.J.,* (2005), More than just a word: non-semantic command variables affect obedience in the domestic dog *(Canis familiaris).* Applied Animal Behaviour Science, 91 (1):129-141
11. *Grădinaru A.C., Davidescu M.A., Petrescu Mag I.V.,* (2020), DNA methylation – a common denominator in transcriptional repression, genome imprinting, X – inactivation, and carcinogenesis. HVM Bioflux, 12(4):193-197
12. *Grové C., Henderson L., Lee F., Wardlaw P.,* (2021), Therapy dogs in educational settings: guidelines and recommendations for Implementation. Front Vet Sci, 8:655104
13. *Handy W.F., Harrington M., Pittman D.J.,* (1961), The K-9 Corps: The use of dogs in police work. Crim L Criminology & Police Sci, 52:328-337
14. *Hare B., Tomasello M.,* (2005), Human-like social

skills in dogs? Trends Cogn Sci, 9(9):439-444
15. *Hart L., Zasloff L., Bryson S., Christensen S.L.*, (2000), The role of police dogs as companions and working partners. Psychological Reports, 86(1): 190-202
16. *Head E.,* (2013), A canine model of human aging and Alzheimer's disease, Biochim Biophys Acta, 1832(9):1384-1389
17. *Hecht E.E., Smaers J.B., Dunn W.D., Kent M., Preuss T.M., Gutman D.A.,* (2019), Significant neuroanatomical variation among domestic dog breeds. Journal of Neuroscience, 39(39):7748-7758
18. *Henderson L., Grové C., Lee F., Trainer L., Schena H., Prentice M.,* (2020), An evaluation of a dog-assisted reading program to support student well-being in primary school. Child Youth Serv Rev, 118: 105449
19. *Ho S.C., Liu J.H., Wu R.Y.,* (2003), Establishment of the mimetic aging effect in mice caused by D-galactose. Biogerontology, 4:15-18
20. *Humane Society of the United States,* (2007), Questions and answers about dog bites. Available at: http://www.hsus.org/pets/pet_care/dog_care/stay_dog_bite_free [Accessed: December 02, 2021]
21. *Kaminski J., Nitzschner M.,* (2013), Do dogs get the point ? A review of dog-human communication ability. Learning and Motivation, 44:294-302
22. *Lakatos G., Gácsi M., Topál J., Miklósi A.,* (2012), Comprehension and utilization of pointing gestures and gazing in dog-human communication in relatively complex situations. Animal Cognition, 15:201-213
23. *Landsberg G.M., Hunthausen W.L., Ackerman L.J.,* (2012), Behavior problems of the dog and cat, 3rd Edition, Elsevier Health Sciences, Oxford, UK
24. *Larson G., Karlsson E. K., Perri A., Webster M.T.*, (2012), Rethinking dog domestication by integrating genetics, archeology, and biogeography. Proc Natl Acad Sci USA, 109:8878-8883
25. *Liu C., Hu J., Mao Z., Kang H., Liu H., Fu W., Lv Y., Zhou F.,* (2017), Acute kidney injury and inflammatory response of sepsis following cecal ligation and puncture in D-galactose-induced aging rats. Clin Interv Aging, 12:593-602
26. *Lowseth L.A., Gillett N.A., Gerlach R.F., Muggenburg B.A.,* (1990), The effects of aging on hematology and serum chemistry values in the beagle dog. Vet Clin Pathol, 19(1):13-19
27. *Miklósi A., Pongracz P., Lakatos G., Topál J.,* (2005), A comparative study of the use of visual communicative signals in interactions between dogs *(Canis familiaris)* and humans and cats *(Felis catus)* and humans. J Comp Psychol, 119(2):179-186
28. *Morey D.F.,* (2006), Burying key evidence: the social bond between dogs and people. Journal of Archaeological Science, 33:158-175
29. *Musi J., Su X., Liu J., Zhao Y., Li Z., Xu X., Li H., Nashun B.,* (2017), Comparison of naturally aging and D-galactose induced aging model in beagle dogs, Exp Ther Med, 14(6):5881-5888
30. *NIH Record*, (2020), NIH researchers reframe dog-to-human aging comparisons, Available at: https://nihrecord.nih.gov/2020/08/07/nih-researchers-reframe-dog-human-aging-comparisons [Accessed: December 02, 2021]
31. *O'Haire M. E., Rodriguez K. E.,* (2018), Preliminary efficacy of service dogs as a complementary treatment for posttraumatic stress disorder in military members and veterans. J Consult Clin Psychol, 86:179-188
32. *Opii W.O., Joshi G., Head E., Milgram N.W., Muggenburg B. A., Klein J.B., Pierce W.M., Cotman C.W., Butterfield D.A.,* (2008), Proteomic identification of brain proteins in the canine model of human aging following a long-term treatment with antioxidants and a program of behavioral enrichment: relevance to Alzheimer's disease. Neurobiol Aging, 29(1):51-70
33. *Patronek G.J., Waters D.J., Glickman L.T.,* (1997), Comparative longevity of pet dogs and humans: implications for gerontology research, J Gerontol A Biol Sci Med Sci, 52(3):B171-178
34. *Philips K.M.,* (2007), Dog bite statistics, Available at: www.dogbitelaw.com, [Accessed: December 02, 2021]
35. *Rintala D.H., Matamoros R., Seitz L.L.,* (2008), Effects of assistance dogs on persons with mobility or hearing impairments: a pilot study. J Rehabil Res Dev, 45:489-503
36. *Rodriguez K.E., Bibbo J., O'Haire M.E.,* (2020), The effects of service dogs on psychosocial health and wellbeing for individuals with physical disabilities or chronic conditions. Disabil Rehabili, 42:1350-1358
37. *Scandurra A., Alterisio A., Aria M., Vernese R., D'Aniello B.,* (2018), Should I fetch one or the other? A study on dogs on the object choice in the bimodal contrasting paradigm. Animal Cognition, 21(1):119-126
38. *Schütt T., Helboe L., Pedersen L.O., Waldemar G., Mette B., Pedersen J.T.,* (2016), Dogs with cognitive dysfunction as a spontaneous model for early Alzheimer's disease: a translational study of neuropathological and inflammatory markers. J. Alzheimers Dis, 52:433-449
39. *Selkoe D.J.,* (1994), Normal and abnormal biology of the beta-amyloid precursor protein. Annu Rev Neurosci, 17:489-517
40. *Serpell J.,* (2016), The domestic dog: its evolution,

behavior and interactions with people, (Ed.) Cambridge University Press, Cambridge, UK
41. *Shahroudi M.J., Mehri S., Hosseinzadeh H.,* (2017), Anti-aging effect of *Nigella sativa* fixed oil on D-galactose-induced aging in mice. J Pharmacopuncture, 20:29-35
42. *Simić G., Kostović I., Winblad B., Bogdanović N.,* (1997), Volume and number of neurons of the human hippocampal formation in normal aging and Alzheimer's disease. J Comp Neurol, 379(4):482-494
43. *Soproni K., Miklósi A., Topál J., Csányi V.,* (2001), Comprehension of human communicative signs in pet dogs *(Canis familiaris).* Journal of Comparative Psychology, 115:122-126
44. *Studzinski C.M., Christie L.A., Araujo L.A., McIntyre Burnham W., Head E., Cotman C.W., Milgram N.W.,* (2006), Visuospatial function in the beagle dog: an early marker of cognitive decline in a model of human aging and dementia. Neurobiol Learn Mem, 86(2):197-204
45. *Su M.Y., Head E., Brooks W.M., Wang Z., Muggenburg B.A., Adam G.E., Sutherland R., Cotman C.W., Nalcioglu O.,* (1998), Magnetic resonance imaging of anatomic and vascular characteristics in a canine model of human aging. Neurobiol Aging, 19(5):479-485
46. *Tapp P.D., Head K., Milgam N.W., Muggengurg B.A., Su M.Y.,* (2006), Application of an automated voxel-based morphometry technique to assess regional gray and white matter brain atrophy in a canine model of aging. Neuroimage, 29(1):234-244
47. *Thal D.R., Orantes M., Braak H.,* (2002), Phases of a beta-deposition in the human brain and its relevance for the development of AD. Neurology, 58 (12):1791-1800
48. *Thompkins A.M., Ramaiahgari B., Zhao S., Gotoor S.S.R., Waggoner P., Denney T.S., Deshpande G., Katz J.S.,* (2018), Separate brain areas for processing human and dog faces as revealed by awake fMRI in dogs *(Canis familiaris).* Learn Behav, 46: 561-573
49. *Toffoli C., Rolfe D.,* (2006), Challenges to military working dog management and care in the Kuwait theater of operation. Mil Med, 171(10):1002-1005
50. *Vikartovska Z., Farbakova J., Smolek T., Hanes J., Zilka N., Hornakova L., Humenik F., Maloveska M., Hudakova N., Cizkova D.,* (2021), Novel diagnostic tools for identifying cognitive impairment in dogs: behavior, biomarkers, and pathology. Front Vet Sci, 7:551895
51. *Vilà C., Savolainen P., Maldonado J.A., Amorim I.R.,* (1997), Multiple and ancient origins of the domestic dog. Science, 276(5319):1687-1689
52. *Wang T., Ma J., Hogan A.N., Fong S., Licon K., Tsui B., Kreisberg J.F., Adams P.D., Carvunis A.R., Bannasch D.L., Ostrander E.A., Ideker T.,* (2020), Quantitative translation of dog-to-human aging by conserved remodeling of the DNA methylome, Cell Syst, 11(2):176-185.