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Visuospatial function in the beagle dog: An early marker of cognitive decline in a model of human aging and dementia

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Abstract

Visuospatial learning and memory impairments are an early marker for age-related cognitive decline and Alzheimer's disease. Similar to humans, aged dogs show visuospatial learning and memory deficits (Adams et al., 2000b). One hundred and nine beagle dogs ranging between 0.25 and 11.99 years were tested on a visuospatial delayed non-matching to position (DNMP) task to better characterize the progression of visuospatial deficits in the dog. Age predicted 48.2% of the variability in learning the DNMP, with dogs ranging from 1 to 11.99 years generally making more errors with increasing age. By contrast, puppies (<1 year) likely were showing developmental deficits, possibly due to an immature prefrontal cortex. Mild visuospatial deficits were detected by 6 years, which precedes the typical onset of amyloid-β (Aβ) accumulation in the dog brain by two years, and can serve as an early marker for cognitive decline in the dog. These findings suggest that (1) age-related changes in visuospatial function in the dog models that seen in humans, further validating the dog as a model for human aging and dementia; and (2) other mechanisms, such as oxidative stress, soluble Aβ oligomers or cholinergic deficits, are likely contributing to the early impairment.

Keywords: Aging; Dog; Visuospatial function; Learning; Memory; Spatial; Dementia; Delayed non-matching to position

1. Introduction

For the past 15 years, our laboratory has studied the dog as a model of human cognitive aging and dementia. Aged dogs show a broad range of cognitive impairments (Adams et al., 2000b; Chan et al., 2002; De Rivera, Boutet, Zicker, & Milgram, 2005; Head et al., 1995; Milgram et al., 1999, 2002a, 2002b; Tapp, Siwak, Estrada, Holowachuk, & Milgram, 2003b; Tapp et al., 2003a) but not all abilities deteriorate equally with age (Christie et al., 2005; Milgram, Head, Weiner, & Thomas, 1994). Visuospatial function is of particular interest because spatial learning and memory are impaired in aged humans (Barnes, 1988; Olton, 1988; Rutledge, Hancock, & Walker, 1997; Sharps & Gollin, 1987; Uttl & Graf, 1993; Weber, Brown, & Weldon, 1978; Wilkniss, Jones, Korol, Gold, & Manning, 1997) and in Alzheimer's disease (AD) (Flicker, Ferris, & Reisberg, 1991; Freedman & Oscar-Berman, 1989). Age-associated impairments in these cognitive abilities also are present in non-human primates (Bachevalier et al., 1991; Bartus, Fleming, & Johnson, 1978; Rapp, Kansky, & Roberts, 1997) and rodents (Barnes & McNaughton, 1979; Barnes, Nadel, & Honig, 1980; Colombo & Gallagher, 1998; Dunnett, Evenden, & Iversen, 1988; Dunnett, Martel, & Iversen, 1990; Frick, Baxter, Markowska, Olton, & Price, 1995; Gage, Dunnett, & Bjorklund, 1984; Gage, Dunnett, & Bjorklund, 1989; Gallagher & Pelleymounter, 1988; Gallagher, Burwell, & Burchinal, 1993; Rapp, Rosenberg, & Gallagher, 1987). The impairments in visuospatial learning

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and memory are detected before any other cognitive deficits are observable (Bachevalier et al., 1991; Bachevalier, 1993; Herndon, Moss, Rosene, & Killiany, 1997; Rapp & Amaral, 1989; Rapp et al., 1997) and are early indicators of memory disorders such as mild cognitive impairment (MCI) and AD (Becker, Huff, Nebes, Holland, & Boller, 1988; Martin, 1987).

We previously have shown that aged dogs are impaired on the delayed non-match to position (DNMP) task using two versions of the task (Chan et al., 2002). Similar to humans, aged dogs have impaired spatial learning and spatial memory capacity (Adams, Chan, Callahan, & Milgram, 2000a; Adams et al., 2000b; Chan et al., 2002). They also show inter-individual differences; aged dogs can be classified as aged unimpaired, mildly impaired or severely impaired based on their acquisition of the DNMP (Adams et al., 2000a; Chan et al., 2002). The current study further extends these findings by examining a wider range of age groups and by determining when the visuospatial impairments may first be detected. Previous work has focused mainly on young dogs (between 1 and 4 years) and old dogs (8 and 12 years) (Adams et al., 2000b; Chan et al., 2002; Head, Callahan, Muggenburg, Cotman, & Milgram, 1998) but not middle-aged dogs (between 5 and 7 years). By contrast, human findings suggest that visuospatial deficits occur early in aging, which prompted us to examine whether a similar pattern is present in our dog model of cognitive aging and dementia. Therefore, we measured spatial learning and spatial memory capacity using the DNMP in 109 beagle dogs ranging in age from 0.25 to 11.99 years.

The DNMP task used in this study involves three spatial positions (Chan et al., 2002). The dog must remember the position of a sample block over a brief delay and, after the delay, when the animal is presented with two identical blocks, it must displace the block in the novel spatial position to obtain the food reward. Acquisition errors at a short delay of 10-s provide a measure of spatial learning. Spatial memory capacity is measured by progressively increasing the delay over a set number of sessions.

2. Materials and methods

2.1. General experimental design

Spatial learning and maximal spatial memory capacity were assessed using the DNMP in 109 beagle dogs ranging in age from 0.25 to 11.99 years. After completing our standard pretraining protocol (Milgram et al., 1994), the dogs were trained on the DNMP at a short delay of 10-s. After achieving our predetermined learning criterion, the dogs' maximal spatial memory capacity was assessed by progressively increasing the length of the delay. A subset of dogs ($n = 6$) unable to learn the task at a delay of 10-s received remedial training at a delay of 5-s and then progressed onto the maximal memory paradigm.

2.2. Subjects

Subjects were 109 beagle dogs, of which 58 were female. They ranged in age from 0.25 years to 11.99 years. See Table 1 for a breakdown of the age groups. Thirty-one animals of known pedigree originated from colony A.

Table 1
Age groups for DNMP analyses

Group	Age range (years)	DNMP acquisiton (*N*)	Maximal spatial memory (*N*)
Puppies	<1	9	9
Young	1–2.99	18	18
Adult	3–5.99	19	17
Middle-aged	6–7.99	14	13
Old	8–9.99	29	11
Senior	10–11.99	20	0

Forty-nine animals of known pedigree were obtained from colony B and the remaining 29 animals came from a random source beagle breeder (colony C). The animals were housed in USDA-approved kennels at one of three facilities: (1) Lovelace Respiratory Research Institute (LRRI), (2) University of Toronto Scarborough campus (UTSC), or (3) Division of Comparative Medicine (DCM) at the University of Toronto. Each kennel differed slightly. At the LRRI facility, animals were housed singly or in pairs in indoor/outdoor runs and were walked twice per week. At UTSC, the animals were group housed in rooms with up to five animals per room. At DCM, animals were housed singly or in pairs and received toys in their cages. In all three facilities, animals received water ad libitum and were fed appropriate quantities of dog chow. Prior to the start of testing, all of the animals underwent a complete physical by the facility veterinarian, which included a neurological assessment.

The animals were tested in small cohorts over a period of 5 years. All subjects had previous cognitive testing experience on our standard pretraining protocol (Milgram et al., 1994). The first two pretraining tasks trained the animal to displace objects with their nose to obtain food rewards. The remaining two tasks were a visual object discrimination and reversal, which required the dogs to discriminate between two objects that differed in color, shape, and size. Only animals that successfully passed all four pretraining tasks were tested on the DNMP. This ensured that the animals' sensory processing skills were intact. Once the animals completed the pretraining protocol, they were tested on the DNMP task.

2.3. Testing apparatus

Milgram et al. (1994) previously have described the testing apparatus. Briefly, it consisted of a large wooden box measuring 0.609 m × 1.15 m × 1.08 m with three height-adjustable gates through which the animal was allowed to respond. The experimenter was separated from the animal by a one-way mirror and a hinged door that was opened during tray presentation. The Plexiglas tray contained three food wells—two lateral and one medial. A dedicated computer program indicated pseudo-random stimulus locations and calculated inter-trial intervals and delays. This program also recorded response locations and latencies. The food reward consisted of 1 cm^3 of Hill's Prescription Diet® p/d canned food.

2.4. DNMP

The DNMP testing procedures were similar to those previously described (Chan et al., 2002). This task provided two separate measures of cognition: spatial learning and maximal spatial memory capacity. Each trial consisted of two tray presentations. On the first presentation ('sample presentation'), a single red block covered one of three spatial locations (right, center, and left) and a food reward. After the animal displaced the object with its nose and ate the food reward, the tray was removed and a delay began. After the delay, the second tray presentation ('pair presentation') occurred. This presentation consisted of two identical red blocks, one of which covered the spatial location that was rewarded on the sample presentation. The animal had to remember the location of the sample block and, on the pair presentation, select the block covering the novel spatial location. This was considered a correct response and the animal obtained a food reward. The animals received 12 such trials per session and each trial was separated by a 60-s inter-trial interval. If an animal