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Age-related cognitive impairments in domestic cats naturally infected with Feline Immunodeficiency Virus (FIV)

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Abstract:

Background: Age-related dementia has been documented in domestic cats; however, its interaction with naturally occurring feline immunodeficiency virus (FIV) infection has been investigated only minimally. **Methods**: Visuospatial working memory (VSWM) and problem-solving (PS) ability were evaluated in FIV-infected (n=37) and control cats (n=39) using two cognitive tasks tested serially, which assessed the ability of cats to locate a baited container after a set delay, then evaluated the capability of the cats to manipulate the container to obtain the food within a time limit. Cats were categorized using 7-years-old as a cut-off to determine age-related differences. Relationship between cognitive performance and FIV viral load was investigated using real-time PCR Cycle Threshold (C_t) values. **Results**: Age significantly affected VSWM and PS ability. Younger cats had better VSWM performance and PS ability compared to the older cats with the same FIV status. There was no difference between younger FIV-positive and negative cats in either part of the task. Moreover, while older FIV-positive cats had significantly worse VSWM than older FIV-negative cats, no differences were found in PS ability. Additionally, C_t

values predicted VSWM but not PS ability. **Conclusion**: Age-related cognitive impairments and FIV-infection appear synergetic, causing greater cognitive deficits in older FIV-infected cats.

Introduction:

The relationship between the domestic cat (*Felis silvestris catus*) and Feline Immunodeficiency Virus (FIV) goes back to a time long before cats were domesticated by people in the Middle East's Fertile Crescent, around 9500 years B.C. (1, 2). Feline immunodeficiency virus is one of the most important infectious diseases of domestic cats, with the infection being transmitted predominantly through bite wounds from an infected cat during aggressive interactions; this has resulted in a worldwide prevalence of 2 to 14% (3, 4).

Age-related cognitive decline is a common feature of normal aging in people (5, 6), and has also been shown to occur in elderly domestic dogs and cats (7-14). The clinical features of feline dementia (previously called cognitive dysfunction syndrome; CDS) include increased vocalization, and other altered behaviours, plus a decline in learning, memory, sensorimotor, and perceptual skills (8, 10, 15, 16); however, the detection and quantification of these findings are lacking in the clinical context (10).

Amongst the immunodeficiency viruses, most is known about Human Immunodeficiency Virus (HIV), where infection has been shown to be associated with cognitive decline, such that HIV-associated neurocognitive disorder (HAND) is currently the most active topic for investigation into neuro-AIDS (17). The prevalence of neurocognitive disorders in HIV-infected people ranges between 15% and 64% (18). Thankfully, antiviral drugs slow the progression of disease in many HIV-infected patients, allowing them to live with stable cognitive function (19). The cause of cognitive disturbances in HIV-infected individuals is multifactorial, involving direct viral effects, persistent immune activation by the virus causing neuroinflammation, HIV-associated immunodeficiency, and secondary infections (20-23). In addition, there is mounting evidence that HIV and aging interact adversely to increase the risk of cognitive dysfunction (24-27).

Infection with FIV shares similar clinical features with HIV infection (28). The pathological effects of FIV infection on the central nervous system (CNS) of cats closely parallel the effects of HIV on the human CNS (29-32) and cognitive impairments have been documented in FIV-infected cats (33-36). Many of the current reports on cognitive deficits caused by FIV were specifically addressing experimentally infected cats (37). However, CNS lesions detected in experimentally infected cats are not always associated with obvious signs (31); hence, researchers believed that histopathological changes may exist without overt neuropsychological signs (38). While occasional cases of severe cognitive damage have been reported in cats with natural FIV infection (39), only 1-5% of naturally infected cats show clinical neurocognitive involvement (40). This low prevalence may be because detectable behavioural and cognitive changes likely occur late in infection and infected cats are euthanatized before the terminal stage of the disease. The reasons for euthanasia may vary from compassion for the cat's suffering, through to minimizing the risk of transmission of FIV to other cats, or cause opportunistic infections to immunocompromised people (41). Although changes in learning and memory may be subtle, it is probable that FIV-infected cats, like HIV-infected people (42), may develop reduced cognitive performance over time, with this being exacerbated by advancing age, although this hypothesis needs to be investigated.

Thankfully, effective supportive treatment and good management have transformed FIV into a manageable chronic disease (3). In a longitudinal study conducted by Ravi *et al.,* on 1205 domestic cats including both stray and pet cats, the effect of FIV on longevity (lifespan) of cats regardless of reasons for death was studied, and the median survival of 3.9 years was reported for FIV-positive cats (compared to 5.9 years in FIV negative cats) (43). Given that most cats become infected as adults (44), this means the population of older naturally FIV-infected cats is increasing rapidly. Cognitive impairment in these cats may become an increasingly important issue as this population ages, especially in owned cats because cognitive aging may cause many behavioural changes including changes in agitation and irritation, vocalization, and social responsiveness (9, 11). Forasmuch as the impact of FIV on aggressive behavior of cats is already documented (4), it is possible that FIV exacerbates these age-related effects on behavior of cats. Owners of pet animals consistently indicate that their pet's quality of life is of great importance to them; since affected cats may become less capable of communicating with their owners because of the behavioural changes following age-related dementia and possibly FIV, this may lead to breakdown of the cat-owner bond. Therefore, investigating the impact of FIV disease on behaviour and cognitive function is imperative.

Object permanence is one of the important cognitive processes for adept hunters such as cats (45); i.e. the understanding that something still exists even when you cannot see it. Working memory, which has multiple components, plays an important role in processing object permanence (45). One of the important components of working memory is visuospatial working memory (VSWM), which is the capacity to collect and recall the spatial information of a novel location that is essential for an animal's adaptation to its environment (46). It contains two main components, *Visual* that provides the capacity for the temporary storage of visual information (i.e. the memory of something's shape) and *Spatial* that allows the recall of something's position (47). Problem-solving (PS) ability is another important cognitive process, which is believed to be associated with learning and innovative abilities in animals (48). It involves finding a solution to a problem of locomotion or food finding through trial and error in an effective and timely manner (49). Although VSWM and PS are not the only indicators of an animal's cognitive ability, they provide important evidence of its ability to behave flexibly in response to environmental changes (45, 50). Impairments in these domains of cognition are believed to be early markers of age-related cognitive decline (51), and it is believed that decline in VSWM leads to decline in other domains of cognition over time (13). Therefore, evaluating these two cognitive processes may prove a promising way to understand cognitive abilities, and to evaluate the early stages of cognitive decline.

While many studies have assessed cognitive impairment in dogs (11, 52-54), far fewer have measured aspects of cognition in domestic cats (15). Those that have, have used tasks originally designed for dogs or other animals, typically using puzzle boxes and object choice tasks with object-hiding paradigms (55-57). However, domestic cats often struggle with cognitive tasks, particularly those with of long testing sessions and repetitive trials (45). For the lack of a suitable test, evaluating cognitive function in cats has always been limited to laboratories where extensive training can be undertaken (15). Therefore, a simple and quickly performed task with a species-appropriate reinforcer is needed for cats. Vitale Shreve and colleagues studied domestic cat stimuli preference using free operant conditioning, and found that despite the presence of individual variation, food was the second most-preferred stimulus for cats, that is, after social interaction with humans (58). Therefore, food appears to function as a suitable reinforcer for cognitive tasks in many cats.

Tasks that are designed based on object-hiding paradigms (e.g., visible displacement tests) are usually the recommended way to test object permanence and working memory. This is because they measure the ability to reason about a hidden object and mentally reconstruct where it has moved to (59). These tasks generally involve the disappearance of an attractive object (e.g. food), behind or under an obstacle (e.g. box) (45). Success in these tests depends on searching for the disappeared object where the object was last seen (46). Piotti and colleagues recently published a study using a simple VSWM task for dogs, which requires no explicit training, and can be conducted within a few minutes (13). This simple task involves similar components of previous object permanence tasks, such as retention intervals and a species appropriate reinforcer i.e. food (58), and has the potential to test the ability of remembering the baited container and cognitively represent the object (i.e. food) even when the object is not visible.

Hunting behaviour requires complex motor skills for the successful capture and consumption of prey, and studies show that cats consistently use their dominant paw while performing certain cognitive tasks associated with this behaviour (e.g. food reaching tasks) (60, 61). The strength of lateralized behaviour, as expressed in skilled paw usage for object manipulation, is positively correlated with problem-solving ability in domestic cats (61). Puzzle boxes or a similar apparatus (e.g. hole board tasks) have been used as a quick and reliable test for measuring problem-solving and learning ability in cats; i.e. they require the cat to obtain a food reward that is inside a puzzle box using paw movements (62-64). However, many problem-solving tasks used in previous research on domestic cats use specific apparatus, which the cats needed to be trained to use, or the tests were not easily applicable to different experimental environments. González-Martínez and colleagues used a simple test, easily applicable to the clinical setting, to assess the PS ability of dogs, where dogs obtain food by manipulating an object (a transparent box) (12). More recently, Isparta and colleagues utilized two similar food searching tasks to study the association between the strength of lateralization and PS ability in cats, where cats needed to manipulate cups that were placed upside down to reach food rewards within them (61). This type of PS task has the potential to simply measure object manipulatory skills, which are directly related to cognitive motor skills and PS ability and can be performed in a fast and timely manner.

The VSWM and PS ability tasks described above have been successfully used for dogs (12, 13), and could, potentially, be modified and applied to cats in a shelter, home environment or clinical settings. If these tasks could be merged sequentially, this could allow for the assessment of two different cognitive processes in mere minutes, which could be feasible and species appropriate. This modified test could then be used to assess FIV-infected versus uninfected cats and compare them to younger versus older non-FIV-infected cats.

One of the main issues in studying neuropsychological impairments associated with FIV and HIV infections is that there are no specific biomarkers to quantify and track the course of neurocognitive dysfunction. However, viral load is significantly correlated with HIV and FIV disease progression (65, 66), so it may be a useful parameter for assessing the development of retrovirus-associated neurocognitive impairment. Real-time polymerase chain reaction (PCR) detects proviral DNA in diagnostic samples, providing quantitative data about the number of DNA copies (67). The PCR cycle threshold (C_t) value gives a semi-quantitative measurement of viral load that correlates with the amount of targeted proviral DNA copies in an inversely proportional and exponential relationship (68). While viral load has been shown to correlate with HIV-associated neurocognitive decline (69), to our knowledge, no study has demonstrated an association between viral load and FIV-associated cognitive impairment in naturally FIV-infected cats.

This study aimed to test the hypotheses that naturally FIV-infected cats develop cognitive impairments that progress with age, that impairments are more severe than those seen in aged-matched non-infected cats, that cognitive impairments in FIV-infected cats are correlated to their plasma viral load as determined by real-time PCR C_t values, and that FIV-infected cats with lower C_t values show poorer cognitive performance.

Materials & Methods:

Case recruitment

The cases were recruited from nine private small animal clinics and two veterinary hospitals in Iran. Owners and shelter caretakers who brought cats to the clinics/hospitals were asked to read a poster explaining the study objectives and methodology (which was written in plain language); if they agreed to take part in the study, they then gave written informed consent. Only healthy food-motivated cats were recruited. Exclusion criteria included having been previously referred for a behavioural consultation. Overweight cats were also excluded (i.e. having a body condition score of six or more, where one corresponds to emaciated, and nine to highly obese (70, 71)), as this could negatively affect mobility and affect the cat's performance. Cats with any health issues that might act as a confounding condition were also excluded. All cats were screened by routine physical and neurological examinations to exclude cats with reduced mobility. Ophthalmic examination excluded cats with impaired visual capacity. Cats were also excluded if they had any medical conditions that could cause significant pain, like traumatic injuries or arthritis (as assessed through physical examination and radiographs, if needed), or gingivostomatitis. For gingivostomatitis, lesions of the oral mucosa were graded according to the criteria published by Hung and colleagues (72); cats with moderate to severe oral lesions (grade 2 and 3) were excluded, along with any reported to have difficult or slow eating. Cats taking medication likely to influence their performance (e.g., gabapentin) were also excluded. The complete blood count and serum biochemistry profile were evaluated for each cat, along with further laboratory diagnostics (e.g. urine analysis) and clinical investigation (e.g. imaging and ultrasonography, if needed) to exclude those with primary organ failure. Any cats found to be positive on FeLV antigen testing were also excluded.

Each cat's FIV status was determined. Blood samples were collected in K2-EDTA microtubes and submitted for FIV antibody ELISA, using FIV Antibody ELISA kit 96, Agrolabo® S.p.A, Italy. A confirmation real-time PCR with FIV specific primers (73) was performed on extracted DNA samples following the direct method for blood as per manufacturer's instructions (AccuPrep® Genomic DNA Extraction Kit – Bioneer, South Korea). The temperature profile was 15 minutes at 95°C, followed by 45 cycles of 20 seconds at 95°C, 30 seconds at 54°C, and 35 seconds at 72°C (74, 75). The C_t values were provided for the positive samples following real-time PCR amplifications with Rotor-Gene Q – QIAGEN ® to assess FIV semi-quantitative plasma viral load. The cut-off C_t value was 40; C_t values $\leqslant 39.99$ were reported as positive (76). As all real-time PCR reactions were performed in triplicates, a mean C_t value was reported for each positive sample.

Subjects:

In an earlier study, 250 cats were randomly selected from all cats seen in the clinics and rescue centers described earlier (from May 2018 to July 2019) and tested for FIV antibody and FeLV antigen (this was to evaluate the prevalence of FIV and FeLV infections). For the current study, 80 cats (40 FIV-positive and 40 FIV-negative) were then randomly selected from the initial 250.

These 80 cats were assessed further. None were excluded as not being food motivated, and none were then excluded due to excessive body condition score. Three of the cats (two FIV-positive cats and one FIV-negative cat) were excluded due to mobility problems (n = 2) and having severe feline gingivostomatitis (n = 1). The remaining cats were recruited for the study; however, one of the FIV-positive cats was then excluded as it failed to reach the training criteria after four initial and four additional trials. Thus, 76 cats passed the criteria and contributed to the test (Table 1 details the FIV status, age, sex and breed of these cats): 37 FIV-positive cats ranging from 10 months to 10.2 years of age and 39 FIV-negative cats (controls) ranging from 8 months of age to 12.8 years of age. Age was normally distributed between both groups. Cats were from various breed types including DSH (n = 58), Persian (n = 16), and Maine coon cats (n = 2). The number of male and DSH cats were higher among FIV-infected cats compared to FIV-negative cats (χ^2 (1) = 4.415, $p = 0.036$ for sex, and χ^2 (1) = 17.561, $p < 0.001$ for breed).

Cognitive testing procedures

A VSWM task (13) and a PS ability task (12), both previously used with dogs, were chosen due to their speed and ease of use. The tasks were combined into one task and presented sequentially so that both VSWM and PS ability could be assessed quickly and in a single session within a few minutes.

The owners and shelter caretakers were asked to deprive the test cats of food for four hours prior to testing; water should be available *ad libitum*. The task was performed in a room with no external distractions. Each cat was trained and tested in the same room by the experimenter: pet cats were tested in a familiar room at their owners' home and shelter cats were tested in a room inside the shelter where they usually interacted with toys. During the whole experiment, only two people (the experimenter and the owner) were in the room with the cat. Four different shaped and colored, but similar sized, containers (approximately 8-10 cm in width and 6-8 cm in height), were positioned upside down on the floor. The containers were placed in a semi-circle shape at regular intervals (15-30 cm apart) depending on the size of the room, so that they were all equally distant from a pre-determined starting point that was 1.5 meters away from the subject (Figure 1). The session consisted of an initial *Training phase*, then the main *Examination phase,* which entailed *Exposure, Interval,* and *Testing phases*. Trials were not video recorded due to the owners' privacy and shelter regulations ("No camera" rule).

- ***Training phase:***

The training phase included four trials where each container was baited by the experimenter with a favorite food in a randomized order. This occurred while the cat was held by the owner at the starting point, and was looking at the baiting procedure. Baiting was performed only once the experimenter made sure that the cat was watching the procedure. The experimenter was positioned in front of the cat and behind the containers (to make the containers clearly visible for the cat), while the owner was positioned behind the cat while gently holding the cat's shoulders. Each cat was allowed to explore and try to eat the reward from the container they had just seen baited. The goal was to make subjects become familiar with the testing procedure and learn that to get the reward they had to manipulate the container by turning it over as the reward was placed under it. The containers were chosen based on their shape and their weight so that cats could not lift them easily with their paws. If a cat failed on three of the four training trials (i.e., they did not move towards the container or were unable to get the reward by manipulating it within a maximum of 10 minutes), the training phase was repeated for four additional trials. If the cat still failed to reach the training criteria (i.e., being successful in at least three trials), it was excluded from the experiment.

- ***Examination phase:***

During the *Exposure phase* the cat watched the experimenter baiting one of the containers. The owner or shelter caretaker held the cat to prevent it from moving away from the starting position. During the *Interval phase* (after the cat had witnessed which container was baited), the owner/caretaker was asked to distract the cat by taking it out of the room (77), keeping the containers out of the cat's sight for four minutes (78). For the *Testing phase*, the cat was placed back at the starting point, and was given 10 minutes to walk around freely, approach the containers, and make a choice. The cat's choice (the first container the cat tried to sniff or manipulate) was recorded during each testing trial as correct or incorrect; *this assessed the cat's VSWM performance*. The owner was asked to terminate the trial by immediately moving the cat away from containers if an incorrect container was chosen. However, if the correct (i.e. baited) container was chosen, the cat was given two minutes to manipulate the container in order to access to the reward. The cats were given a score based on the behavioural classification defined by González-Martínez and colleagues (12); *this assessed the cat's PS ability*. The scores were modified as follows: the cat obtains the reward within a maximum of two minutes (3 points); the cat tries to get the reward but does not obtain it within a maximum of two minutes (2 points); the cat sniffs the container but does not make any attempt to manipulate the container (1 point); and the cat made an incorrect choice, so the trial was terminated (0 point for PS ability).

The task procedure was repeated twice per container for each cat (i.e. eight testing trials in total). Once each trial was completed, the cat was given a 3-minute time break (inter-trial interval), and then the cat went through the next trial, starting with the exposure phase (baiting another container while the cat was watching). The order for baiting the containers was randomized using an online random number generator (numbering the containers from left to right as 1 to 4), with the stipulation that each container should be baited twice through the experiment and the reward should not be placed in the same container for two consecutive trials. Both experimenter and owner refrained from making any eye contact with the cat while it was making its choice.

The total number of correct trials (response for VSWM performance) and an average of the PS ability scores obtained by the cat (response for PS ability) were recorded for each subject. For example, if a cat makes three correct choices out of the eight testing trials, the response variable for VSWM would be three. The second part of the task can only be conducted following each of these correct trials; for this example, the cat has three chances to obtain food. Based on the classification above, if the cat sniffs at the correct container, but makes no attempt to manipulate the container during its first chance (1 point), then successfully gains the food within the maximum time limit in the other two chances (3 points for each trial), the response variable for PS ability would be an average of these scores (in this case, this would be 2.333).

If the subject lost motivation and stopped collaborating during a trial or left the experimental area, the trial was paused and then re-attempted once the subject chose to take part again.

Previous research showed that domestic cats usually prefer visual cues over olfactory cues (79). Nevertheless, to avoid possible odor-induced bias of choices, the containers were all scented with a favorite wet food (depending on the subjects' preference) by smearing a small piece of this food onto their inner wall. This method was first used by Pisa and Agrillo (80) and subsequently utilized by Pongrácz and colleagues as an olfaction control (81).

Statistical analysis

The Chi-Square test of independence was used to determine if FIV-positive and negative cats differ in sex (male/female) or breed (non-pedigree i.e. domestic short-hair [DSH] versus pure breeds).

Generalized linear models (GLM) with linear probability distribution were run to predict the task performance based on FIV status, age (in months), sex, and breed, evaluating both main effects as well as a 2-way interaction between FIV status and other factors. The total correct trials (choices) for VSWM and the average score for the PS ability were considered separately as response variables, with FIV status, age, sex, and breed as fixed factors in each model. The PS response for each cat could only be assessed for the number of times it correctly identified the baited containers in the first part of the test, i.e. they only had the opportunity to manipulate the container if they had selected it correctly. Because of this, the natural log of the exposure variable (number of correct trials) was added into the model as an offset variable to adjust for differential exposure numbers among cats as they had different levels of exposure to the container.

Normality and homoscedasticity were assessed via residuals' distribution charts and plots of residuals against fitted values. The underlying distribution for the age variable based on FIV status was unintentionally found to be bimodal in both FIV-positive and FIV-negative cats, with the younger populations containing cats about five years of age or less, and the older populations starting at about seven years of age. A second analysis was therefore undertaken, to look for specific differences between age groups, as the categorical age might predict this data more perfectly. Different groups were compared to each other based on the mean of the total number of correct trials (the measure for VSWM performance) and the mean PS ability score. The dependent variables (total correct trials and PS scores) were normally distributed within each group of cats, and there was homogeneity of population variances of the dependent variable for all groups, so an independent sample t-test was used to determine the differences in their mean group performance (both for the VSWM and PS ability). Cochran's Q test was then used to determine whether the success rate for the VSWM task differed across the eight testing trials for each group.

Simple linear regression analysis was used to determine whether cognitive task performance could be predicted by C_t values in FIV-infected cats or not. The total number of correct trials and PS ability scores served as the dependent variable, separately, and the C_t values served as the independent variable.

Statistical analysis was performed using the analytical software package SPSS® 22.0 for Windows® (SPSS Inc., Chicago, IL, USA). Data are presented as mean ± standard error of the mean (SEM) and all t-tests used were two-tailed. A p value less than 0.05 denoted as statistical significance.

Results:

Part 1 of the Task: Visuospatial working memory

The subject's first choice during each trial (correct/incorrect) and total correct choices following eight testing trials were recorded for each subject. The GLM analysis showed that VSWM performance was negatively influenced by age ($\chi^2(1) = 23.404$, $p < 0.001$) and FIV status ($\chi^2(1) = 5.735$, $p = 0.017$) (Figure 2). There was also a statistically significant interaction between FIV status and age ($\chi^2(1) = 4.306$, $p = 0.038$) on VSWM performance, with FIV-positive cats performing worse with increasing age. However, the impact of sex ($\chi^2(1) = 1.390$, $p = 0.238$) and breed ($\chi^2(1) = 0.741$, $p = 0.389$), and their interaction with FIV ($\chi^2(1) = 3.265$, $p = 0.071$ for sex; $\chi^2(1) = 3.054$, $p = 0.081$ for breed) did not reach significance.

Different subsamples of cats were then compared to each other to assess categorical age/FIV differences (Figure 3). As a group, the younger FIV-positive cats (mean = 4.27 ± 0.28; SD = 1.22) chose the correct container significantly more often ($t\,(29) = 3.411$, $p = 0.002$, Cohen's $d = 1.09$) than the older FIV-positive cats (mean = 2.68 ± 0.18; SD = 0.8); over 66% of the younger and 26% of the older FIV-positive cats chose the correct container in at least four of the eight testing trials. The younger FIV-negative cats (mean = 4.15 ± 0.3; SD = 1.34) also performed significantly better than the older FIV-negative cats (mean = 3.36 ± 0.2; SD = 0.89) in the first part of the task (t (33) = 2.142, p = 0.04, Cohen's d = 0.683); over 65% of the younger and 31% of the older FIV-negative cats chose the correct container in at least four of the eight testing trials. There was also a statistically significant difference in the mean number of correct choices between the older FIV-positive and the older FIV-negative group (t (36) = -2.29, p = 0.028, Cohen's d = 0.92). However, no significant difference was found when the younger FIV-infected cats were compared to the younger FIV-negative cats (t (36) = 0.3, p = 0.76, Cohen's d = 0.093).

Cochran's Q tests were conducted for each group to see whether the success rate for choosing the correct container changed over the eight testing trials as the trials progressed. Results showed that the proportion of cats choosing the correct containers within each group was not significantly different across the trials suggesting that there was no learning effect (younger FIV-positive cats: $\chi^2(7) = 6.410$, p = 0.49; older FIV-positive cats: $\chi^2(7) = 5.712$, p = 0.54; younger FIV-negative cats $\chi^2(7) = 6.758$, p = 0.45; older FIV-negative cats: $\chi^2(7) = 3.972$, p = 0.78).

Part 2 of the Task: Problem-solving ability

An average PS ability score was calculated for each subject. While GLM analysis revealed that PS ability scores were significantly affected by age (Fig 2) ($\chi^2(1) = 18.646$, $p < 0.001$), the effect of FIV status ($\chi^2(1) = 0.686$, p = 0.408) and its interaction with age ($\chi^2(1) = 0.177$, p = 0.674) did not reach significance. In addition, the impact of sex ($\chi^2(1) = 3.167$, p = 0.075) and breed ($\chi^2(1) = 1.609$, p = 0.205), as well as their interaction with FIV ($\chi^2(1) = 2.930$, p = 0.087 for sex, and $\chi^2(1) = 3.429$, p = 0.064 for breed) on PS ability score were not significant.

To evaluate categorical age differences in PS ability, the younger and older FIV-positive and negative cats were compared to each other (Figure 4) and results revealed that PS ability score was significantly higher in the younger FIV-positive cats (mean: 2.35 ± 0.07; SD = 0.1) than the older FIV-positive cats (mean: 2.03 ± 0.1; SD = 0.47) (t (31) = 2.437, p = 0.021, Cohen's d = 0.795), and in the younger FIV-negative cats (mean: 2.44 ± 0.06; SD = 0.29) than the older FIV-negative cats (mean: 2.05 ± 0.11; SD = 0.51) (t (29) = 2.946, p = 0.006, Cohen's d = 0.949). However, there was no statistically significant difference when younger and older FIV-positive cats were compared to FIV-negative cats in the same age category (younger FIV-positive vs. younger FIV-negative: t (36) = -0.962, p = 0.34, Cohen's d = 0.3; older FIV-positive cats vs. older FIV-negative cats: t (35) = -0.082, p = 0.93, Cohen's d = 0.026).

Predicting cognitive performance in the FIV-infected cats based on C_t values:

The lowest C_t value in the study was 7.19 and the highest was 29.98. The mean C_t value were 22.36 and 12.25 for the younger FIV-positive cats and older FIV-positive cats respectively. Simple linear regression analysis revealed that the VSWM performance of the FIV-infected cats was significantly influenced by C_t values (Fig 5), $F(1, 35) = 98.714$, $R^2 = 0.738$, $p < 0.001$. However, C_t value was not a significant predictor for the PS task performance (Fig 6), $F(1, 35) = 2.433$, $R^2 = 0.065$, $p = 0.128$.

Discussion:

The current study creates the first link between cognitive aging and FIV disease in naturally infected cats, and it highlights the negative impact this infection may have on domestic cat welfare. Understanding how cognitive function is compromised following FIV disease progression is essential when appreciating the full impact of this disease. This should lead to new insights into the neuropsychological dimension of FIV disease following natural infection.

Devising a test that could be used to assess the effect that FIV infection may have on a cat's memory was challenging; one of the first factors that had to be considered was the duration of the retention interval. Tests to evaluate working memory for hidden food were first administered to domestic cats with a maximum retention interval of 60 seconds (82). More recently, Takagi and colleagues (77) studied working memory in domestic cats with a delay phase of approximately 15 minutes (a range of 12-23 minutes): subjects were required to retrieve and utilize incidentally encoded information from a single past experience in a simple food-exploration task. While Fiset and Doré (82) showed that cats' working memory declines between 10 to 30 seconds, results from Takagi and colleagues (77) suggested that cats could retrieve not only "where" information but also "what" information from a single past event for much longer periods, even beyond the previously believed working memory capacity of cats for retaining information. The other important factor for choosing an appropriate cognitive test for cats is the test's sensitivity to cover aspects of domestic cat cognitive function. Combining the two tests used in the current study created a simple and fast test using an object-hiding paradigm, which is an appropriate approach to test the working memory of cats (similar to a visible displacement task where the hiding object was accessible under the container). At the same time, the test could evaluate PS ability of cats by using a similar approach that Isparta and colleagues used through object manipulation (61). However, it is also possible that the PS task used in the current study, despite showing a significant impact of age, is not sensitive enough to measure changes in PS ability in cats.

During the testing trial, the owner / caretaker held the cat by its shoulders while the cat was watching the experimenter baiting one of the containers. This procedure has been previously used as a part of similar cognitive experiments in domestic cats (82, 83). Although this partial restraint may cause mild stress for some cats (84), the cats in our study were held by their owners / caretakers (who they are more comfortable with, compared to an unfamiliar experimenter), and the cats were only held for a few minutes while the experimenter baited the container. Although being unwilling to continue the experiment had been set as an important reason to terminate the testing session, none of the cats refused to take part, with only a small number needing an occasional 'time out' to relax.

The impact of age on cognitive function:

Age was a central component of the current study; it was analyzed for its effect in a number of ways. Methodology for grouping subjects by age varies in the literature. Most often, researchers treat age as a continuous variable (54, 85). However, there are also several studies that analyzed age as a categorical variable (13, 14, 64, 86, 87). The current study used both methods. This is in line with other studies in which they assessed age first as a continuous variable, and then by splitting the population into younger and older (dogs) using seven or eight years of age as a cut-off (88, 89). It is believed that cats show impairment in their cognitive function as early as 10 years of age, with deficits in spatial memory being identified as early as six to eight years of age (15). The current study aimed to evaluate the possible interaction between FIV and age, to see if FIV can lead infected cats to show age-related cognitive impairments at an earlier age than uninfected cats. Using 10 years of age as a cut-off was not feasible because there were too few cats that of 10 years of age or older; however, when the cats were categorized using seven years of age as a cut-off, it was resulted in balanced sample sizes in each group, which could be considered as younger and older (i.e. senior adult) cats (64).

Results from the current study showed that both VSWM and PS ability were significantly impacted by age and results of the categorical age analysis showed that younger cats, whether FIV-positive or negative, had a better performance in both parts of the task compared to the older cats within their same FIV-status category. These results are broadly consistent with previous reports indicating that both cats and dogs experience age-related deterioration of cognitive abilities as they become geriatric (12, 15, 34, 90, 91).

Age related differences in cognitive performance between FIV-positive and negative cats:

The current study found a significant interaction between age and FIV status when assessing VSWM performance, albeit the cognitive decline was mild and subclinical. It is believed that HIV-associated neurocognitive decline is a gradual process that presents with high variability, and changes over time (92). In its terminal stages, HIV infection causes cognitive disturbances that interact with age-related cognitive decline (93). Similarly, the paper by Podell and colleagues demonstrated that the encephalopathy following experimental FIV infection was associated with the onset of acquired immunodeficiency late in the duration of infection (94). It is therefore probable that FIV interacts with age-related neurodegeneration and cerebrovascular disease in a similar way to that already documented in HIV-infected individuals (95). It is also likely that FIV-associated cognitive impairment and age-associated neurodegenerative disorder may accelerate the cognitive aging process in cats. While the mechanism behind this process is yet to be determined, the current study supports the recognition of early cognitive decline in FIV-positive cats as they age.

In the categorical age analysis, the younger FIV-positive and negative cats showed no significant difference in the VSWM and PS performance when compared to each other. Based on these data, it appears likely that younger FIV-infected cats do not exhibit a higher risk of cognitive impairment than younger cats without FIV infection, which is in agreement with previous research on VSWM in FIV-infected cats (78).

The current study also found that the older FIV-infected cats had poorer VSWM performance than the older FIV-negative cats. Such results suggest a progressive deterioration in the VSWM of older FIV-infected cats that is likely to interact with the cognitive aging process. This may reflect the initiation of cognitive impairments at an earlier age and the possible synergistic effect of age and FIV that may become more obvious over time (78, 94). However, the current study results also demonstrate no significant difference in the PS ability between the older FIV-positive and older FIV-negative cats, which means that their overall reaction and manipulation time did not appear to differ from each other. Steigerwald and colleagues found that FIV-infected cats committed more errors than controls in the 'hole board task' where cats had five minutes to retrieve food reinforcements from a chamber with cylindrical holes. Their open-field observations showed that FIV-infected cats demonstrate compulsive roaming and agitated hyperactivity which can affect their ability to focus on a task and consequently, their task performance may be affected by their higher distractibility levels and loss of attention, as was supported by differences found between the performance of FIV-infected cats and controls in the plank walking test they used in this study (37). Sherman and colleagues also found distraction to be one of the difficulties when using the T-maze task for evaluating cognitive-motor function in FIV-infected cats (96). Although easy distraction of attention might have impacted task performance in some of the FIV-infected cats in our study, our PS task result did not support this hypothesis. In addition, object manipulatory skills can have substantial influence on the animal's physical PS performance (12, 97). Previous life experiences may affect the manipulatory skills of animals, causing variation across individuals (12). With that being said, learning through previous experiences appears to have the potential to influence task performance, especially in cognitive tasks that are based on manipulating objects (98). Although no information about the environmental/housing condition was collected for cats in the current study, previous research showed that cats with FIV infection are more likely to live outdoors or to some degree have access to the outdoor environment (99). Previous studies found that environmental changes enhance cognitive abilities in animals (100, 101). While, to the authors' knowledge, it is still not clear how the outdoor access can influence learning and cognitive function through life experiences in cats, it is possible that the past and current environmental conditions influenced cognitive abilities of cats in the current study. Therefore, further investigation is needed to determine whether cats with outdoor access perform better in cognitive tasks or not.

Cognitive impairments and FIV viral load:

Viral load in the cerebrospinal fluid (CSF) is likely to be a more accurate and important predictor for cognitive disturbances associated with FIV infection as it was reported to be elevated in HIV-infected individuals with cognitive impairments (102-104); however, its collection is not without risk. Plasma viral load has been reported to have a significant interaction with behavioural disturbances, such as extreme aggressive tendencies in FIV-infected cats (4); however, the relationship between plasma viral load and cognitive function is still unclear. It is possible that higher plasma viral loads reflect higher numbers of infected monocytes circulating in the blood stream, which can affect CNS function as these cells bring virus into the brain and induce neuroinflammation (20). Plasma viral load might therefore predict the likelihood of clinically significant neuropsychological disturbances, and its collection is far simpler than that for CSF.

In the present study, Ct values were related to VSWM and negatively correlated with the number of errors committed; however, no relationship was found between C_t values and PS ability in FIV-infected cats. Contradictory results regarding the relationship between plasma viral load and cognitive decline associated with immunodeficiency virus infections have been reported previously. A study of 140 HIV-infected people that were grouped into three categories based on their plasma viral load revealed no difference in their neuropsychological test performance (including tests to evaluate attention, executive function, and working memory) (105). Ellis and colleagues also found no relationship between plasma viral load and neurocognitive impairment in HIV-infected patients (106). In contrast, HIV plasma viral load has been associated with neurocognitive impairment in other studies: for example, Robertson and colleagues found that subjects with high viral load had more reduction in their neuropsychological performance than the low viral load group (104). Other studies also found HIV plasma viral load to be a significant modifier and a strong determinant of neurocognitive function in HIV-positive individuals (107, 108). Our results on the inverse relationship between FIV viral load and VSWM performance are consistent with those reported by Maingat and colleagues (109). They found that the FIV-infected group exhibited more errors compared to the control group in spatial memory performance and an object memory task (where cats were trained to walk down a narrow alley toward a 6-cm-high removable barrier to obtain food); both task performances were inversely correlated with neural tissue viral load in FIV-infected cats. More studies are needed on the relationship between cognitive function and viral load. In addition, research examining other factors, such as $CD4^+$ nadir, which has a direct relationship with FIV disease progression, might be helpful in this matter (110, 111).

Study limitations:

While this study was novel and contributes important new findings to the field, it was not without limitations. The biggest weakness was the lack of blinding during the VSWM and PS tasks; all individuals in the room knew which containers were baited. An attempt to mitigate human influence was made by asking all researchers and caretakers to refrain from making eye contact with the cat so the cats could not gaze track humans for referential information (81); however, it is possible that other non-intentional cueing could have occurred. It would have been better to have put a blindfold on the owners and caretakers while they held the cat to have it watch which container was baited, then used two separate experimenters (one who baits, one who records), or one experimenter who baits then leaves the room, while a camera then records the cat's choice. Improved blinding procedures would also eliminate other potential cueing by researchers or caretakers. Moreover, the experimenter was not blind to the FIV status or age of the cats. The results would be more robust if these opportunities for experimenter bias were eliminated, or if video-recorded sessions were provided to be double coded by a blinded research assistant. However, due to lack of experienced human resource, and the "no camera" rules in shelters these methods could not be adopted. Future studies will incorporate these controls. Other limitations include not considering the environmental/housing condition of cats, not testing for Toxoplasmosis (see below), and not using a preliminary behavior assessment as factors in the study. Factors such as sex status (being sexually intact) and aggressive behavior are important risk factors that can predispose cats to FIV infection and lead to having more cats with certain characteristics in FIV-positive compared to FIV-negative groups (4). Therefore, these factors can be considered as possible confounds impacting cognitive performance in cats and should be considered in future study designs. To overcome this issue, future studies can recruit cats as a case-cohort (one by one), which means to recruit a FIV-negative cat with similar characteristics of a recruited FIV-positive cat.

Other limitations include not controlling for time-of-day effects, and not assessing FIV biomarkers (see below). Of note, the number of male and DSH cats were significantly higher among FIV-infected cats, compared to the controls. This is likely to have occurred because both sex and breed are important risk factors for FIV, with mixed breed male cats being more predisposed to FIV infection (112). However, none of these factors influenced cognitive task performance in FIV-positive or negative cats, so this population bias does not appear to have negatively affected this study.

Future research:

- ***Other contributing factors of FIV-associated cognitive impairments:***

The variability in task performance and the level of cognitive impairments may vary based on a combination of different factors. For instance, FIV has different clades and each can express different tendencies towards the development of neurocognitive impairments (113); FIV isolates of clade A have been associated with the development of neurologic diseases in experimentally infected cats, while clade C isolates have not (114). The variability in the neuropathogenesis of FIV in cats may occur for similar reasons to those seen in HIV-infected people, some of whom develop unique neurovirulent quasi-species (29). This may also be happening in FIV-infected cats, where FIV infection allows uniquely adapted quasi-species to emerge that may account for neurotropism and neurovirulence. Neurologic disorders may also be caused by opportunistic complications of immunodeficiency; some naturally FIV-infected cats with neuropsychological impairments may have concurrent opportunistic infections (such as Toxoplasmosis). However, it is not known whether cognitive decline results mainly from the FIV itself, or the secondary infections (94). It could be theorized that exposure to a potential infection or toxic agent could result in an increase of aggressive behaviour when young (hence increasing the risk of becoming infected with FIV), while also being neurotoxic, hence predisposing the same group of cats to develop cognitive decline when older. The only infection with a realistic potential to do this is Toxoplasmosis. It can mimic and exacerbate signs of dementia in older cats (16). Since it has been shown to alter the behaviour of young adult rodents and people, making them less risk adverse (115), it is at least theoretically possible that it could cause aggression in younger cats, increasing their risk of catching FIV infection. Hence Toxoplasmosis could potentially increase the risk of FIV infection and the development of later cognitive decline. Whether a toxic agent could have the same effect is unknown. These complications are a substantial challenge in naturally infected cats, especially where many of them are strays. Thus, future research should also focus on FIV clades, the presence of quasi-species clouds, and the impact that any opportunistic infections may exert on neurocognitive function in naturally FIV-infected cats. A diagnosis of FIV-associated neurocognitive decline based on the cognitive task performance is unlikely to be as sensitive as neuroimaging or CSF markers of CNS injury, such as neopterin (116). Where neuroimaging is assessed, it should evaluate structural changes correlating with inflammation and neuronal injury and utilize Volumetric Analysis of MRI to investigate volume loss in the basal ganglia, posterior cortex, and total white matter, comparing infected individuals to age-matched controls (117). These factors should also be considered for future research studies.

Another factor that might affect cognitive task performance in cats is "time-of-day." Previous studies revealed that rodents perform better in spatial memory tasks during their active phase of the day, rather than the rest period (118). Cats in the current study were tested at times of the day based on the availability of the owners and caretakers. However, it may be better to test cats during their optimal functioning times of the day as this may influence their motor or visual abilities. Since they are naturally crepuscular animals, it might be best to test them early in the morning or late in the evening (119).

- ***Suggestions and modifications for the cognitive task and experimental design:***

A key advantage of using two tasks sequentially by merging them together is that it improves time efficiency. However, using only two tasks may not be sufficiently sensitive and reliable to identify subtle effects of FIV on cognitive function. It is believed that working memory tasks and tasks evaluating executive function share a common executive attention component, and age-related deficits of executive attention are associated with age-related declines in working memory (120). Thus, it would be beneficial for future studies to assess executive function as well. A greater breadth in exploratory behaviour is related to success and cognitive accuracy in the PS ability of both human infants and non-human animals (121, 122). Forasmuch as manipulation was the only approach to the reward in the PS task used in the current study, it is possible that the cats' PS performance was affected by variabilities in their exploratory behaviour that generally involved movement and locomotor activity. Future studies would be better to consider a curiosity test along with the PS task to see whether locomotion and exploratory behaviour vary between groups that had different PS ability scores.

Longitudinal changes in VSWM and PS ability could be evaluated in subjects with and without FIV infection to assess the speed of progression of any cognitive impairments. In this regard, the VSWM part of the task could have a scoring system based on cat's behaviour during the task to categorize subjects regarding the level of cognitive performance; FIV-infected cats could then be categorized by baseline assessment to see whether mild cognitive impairment is a predictor of decline to a more severe form of cognitive impairment through time or not. For instance, Grant and colleagues studied 347 HIV-infected people over a mean of 45 months (although they had no uninfected controls for comparison). They used a comprehensive neurocognitive test battery to categorize the individuals based on their cognitive status. Results revealed that subjects with milder forms of HAND (termed asymptomatic neurocognitive impairment) were faster to develop symptomatic HIV-associated neurocognitive disorder than the neurocognitively normal group (123). Accepting that the challenge of measuring cognitive performance in cats complicates the interpretation of the results, a similar study could be performed in cats. Therefore, developing a detailed scoring system for the first part of the task is planned for the future.

Conclusion:

The current study is important as it is the first to investigate PS ability and VSWM performance among older naturally FIV-infected cats, comparing them to younger FIV-infected individuals, as well as to younger and older uninfected controls. The study provides valuable information into the feasibility of repurposing neuropsychological tests that have been characterized for other species, then using them with cats. The results showed that increasing age exacerbated the negative effect that FIV exerts on cognitive function and the deterioration in VSWM performance was echoed by increasing viral load. This is in agreement with data from studies of HIV patients and experimental models of FIV infection in cats. Finally, it appears that older FIV-infected cats do not exhibit a higher risk for impairments in the PS ability compared to FIV-negative cats.

Exploring the impact of FIV infection on the course of age-related cognitive impairments in naturally infected cats can help us to foster a greater understanding of the potential importance of FIV neurodegeneration as an issue in domestic cat welfare. More studies are needed to understand how age-related and FIV-associated cognitive impairment are involved in the multifaceted causes of cognitive dysfunction in cats (i.e. feline dementia) and how these may negatively affect the cat-owner bond.

Conflict of interest: The authors declare that they have no conflict of interest.

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Ethical note

The experimental methods were approved by the ethical committee of the faculty of Veterinary Medicine, University of Tabriz (approval code: FVM.REC/1397.84). All owners and shelter caretakers signed an informed consent form and agreed to their cats' participation in the current study.

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Demographic characteristics	Younger FIV-infected cats: n = 18	Older FIV-infected cats: n = 19	Younger uninfected control cats: n = 20	Older uninfected control cats: n = 19
Mean age (in years) [age range]	2.6 (1.4) [10 months to 4.8 years]	8.44 (0.87) [7.4 to 10.2 years]	2.7 (1.35) [8 months to 5.2 years]	8.51 (1.41) [7.3 to 12.8 years]
Sex (m/f)	11/7	14/5	7/13	10/9
Sexual status	Intact male = 10 Intact female = 5 Neutered male = 1 Spayed female = 2	Intact male = 11 Intact female = 5 Neutered male = 3 Spayed female = 0	Intact male = 3 Intact female = 6 Neutered male = 4 Spayed female = 7	Intact male = 2 Intact female = 1 Neutered male = 8 Spayed female = 8
Breed:	DSH = 18	Persian = 1 DSH = 18	Persian = 9 DSH = 11	Maine coon = 2 Persian = 6 DSH = 11

Table 1. Demographic characteristics of the study population. Data are presented as means, with standard deviations in parentheses; m = male; f = female; DSH = Domestic short-haired.

Figure 1. Representation of the experimental procedure. During each experimental trial, cats were only allowed to have one choice, and then to manipulate the correctly selected container they had seen baited four minutes previously.

Figure 2. The relationship between Age and Visuospatial working memory (VSWM) performance (upper graph) **and between Age and Problem solving (PS) score** (lower graph). FIV-positive cats - blue circles and trendline, FIV-negative cats - green circles and trendline.

Figure 3. Visuospatial working memory (VSWM) performance of the younger and older FIV-positive and negative cats based on the average number of correct choices (error bars represent 95% confidence intervals).

Figure 4. Mean Problem-solving (PS) scores for younger and older FIV-positive and negative cats (error bars represent 95% confidence intervals).

Figure 5. The relationship between C_t values and total number of correct choices of the FIV-infected cats. A positive linear relationship is present between C_t values (the C_t is the Cycle threshold, which represents the inverse of the FIV proviral DNA load) and the total number of correct choices. This means that the C_t value could statistically significantly predict the total correct number of choices by the FIV-infected cats, and the C_t value accounted for 73.8% of the explained variability in Visuospatial working memory (VSWM) performance based on the total number of correct choices.

Figure 6. The relationship between C_t values and mean PS scores of the FIV-infected cats. There is no relationship between the Cycle threshold (C_t) value and the mean PS score and the C_t value could not statistically significantly predict PS ability of the FIV-infected cats.

Authors contribution: Conceptualization, A.A. and D.GM.; methodology, A.A. and D.GM.; data collection and analysis A.A.; supervision, D.GM.; writing – original draft, A.A.; writing – review and editing, D.GM.

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