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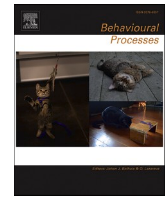

A rapid serial reversal learning assessment for age-related cognitive deficits in pet dogs

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A B S T R A C T

Assessments for behavioral inhibition in pet dogs that can rapidly detect age-related cognitive deficits (ARCD) using inexpensive and accessible materials may aid in diagnosing canine dementia and may facilitate translational research on Alzheimer's disease in humans. In this study, we designed and deployed a spatial serial reversal learning test in which 80 pet dogs were required to learn which of two identical boxes contained a hidden food treat. Each time the dog chose the correct box in three consecutive trials the procedure was repeated using the other box. All dogs that completed shaping ($n = 62$) also completed the 30-minute assessment. Middle-aged dogs chose the correct box more often than younger and older dogs. This cognitive decline was detectable with a stand-alone score for perseveration that can be easily measured and interpreted by clinicians and dog owners. Age did not predict how frequently the dog learned the serially-reversing reward contingency but older and younger dogs displayed longer streaks of perseverative errors. Thus, ARCD in dogs may be better characterized by bouts of severe cognitive dysfunction rather than temporally-consistent cognitive deficits. We suggest that future ARCD assessments for pet dogs should include measurements for intra-individual variability.

1. Introduction

Some dogs spontaneously develop retrogressive neurological and cognitive deficits that resemble early-stage Alzheimer's Disease (AD) in humans (Head, 2001). Dogs are highly tractable, widely accessible, and share a number of anatomical similarities with humans (Kaeberlein et al., 2016) but have shorter lifespans (Gilmore and Greer, 2015) and may thus provide a strong animal model for translational AD research (Araujo et al., 2017). Given that pet dogs share their environments with their owners, research on age-related cognitive deficits (ARCD) in pet dogs may also provide insight into the environmental factors that contribute to dementia in humans (Kaeberlein et al., 2016). Cognitive tests typically carried out on aging colony dogs require weeks or months of daily testing sessions and specialized laboratory equipment (e.g., Adams et al., 2000). Thus, to facilitate veterinary care for aging dogs while expanding the utility of pet dogs as a model population for AD research, new cognitive tests must be designed which can be administered in a single session using only cheap and accessible materials (Chapagain et al., 2018).

In both humans and dogs, executive functions like inhibitory control and working memory are particularly sensitive to ARCD (Head, 2013). Behavioral inhibition requires selective attention towards task-relevant information and the suppression of irrelevant or conflicting behaviors (McDowd and Oseas-Kreger, 1991). Reversal learning tests evaluate an individual's ability to inhibit prepotent responses to previously reinforced stimuli and to shift responses towards a previously unreinforced stimulus (Lai et al., 1995).

Previous studies on size- and object-reversal learning in colony beagles have found robust evidence that older dogs are more persistent in responding to previously rewarded objects following reversals of task contingencies, and exhibit stronger position biases (e.g., Chan et al., 2002; Tapp et al., 2003). However, the relationship between age and inhibitory control in dogs may be task specific (Bray et al., 2014) and may differ between colony beagles and mixed-breed shelter-sourced dogs (Milgram et al., 1994).

Most studies on inhibitory control in pet dogs have observed deficits in older individuals (e.g., Mongillo et al., 2013; Wallis et al., 2014). However, only one study used a test which could be completed in a single session without specialized equipment. Piotti et al. (2018) assessed object and location reversal learning in pet dogs using a

Abbreviation: ARCD, age-related cognitive deficits.

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go-no-go paradigm. Dogs younger than eight years learned to approach the reinforced stimulus faster after each reversal than did older dogs. However, fewer than half of the older dogs learned the task within the cut-off of 100 trials. Thus, this task may be too difficult to rapidly assess reversal learning in older dogs.

In the present study, we designed a spatial serial reversal learning test to rapidly detect age-related cognitive decline in pet dogs. We examined whether age predicted performance after accounting for subject and test covariates. In addition, we developed an easily-interpretable test score to assay cognitive impairment. In doing so, we also examined whether age-related deficits in inhibitory control were characterized by bouts of poor performance in addition to poor overall performance.

2. Method

2.1. Subjects

Eighty pet dogs (39 male) of various breeds and ages (10–173 months, mean = 80.64) were tested (Table S1). To ensure accuracy of age reports, only dogs seen by a veterinarian before reaching one year of age were included in this study. All owners volunteered their dogs to participate.

2.2. Materials and procedure

The materials and layout were similar to Van Bourg et al. (2020). Additional information about the materials and layout are provided in supplementary material (S2.1).

This serial reversal learning task required dogs to choose which of two identical boxes contained a hidden food treat. Between trials, E1 hid a treat behind ("baited") one of the boxes while the dog waited with E2 in the holding room. In each trial, E2 released the dog into the testing room and the dog was allowed to search for a treat in one of the boxes. When the dog began to move away from the chosen box, E1 immediately ushered the dog back to the holding room. Thus, the dog was only allowed to retrieve the treat if it correctly choose to search the baited box.

The first box the dog oriented its head towards once the treat (or empty treat platform) was in view was scored as the dog's choice (Fig. S2.3). E1 was responsible for making this determination but E2 also watched the dog to provide confirmation or correction if needed. However, this was rarely the case as the dog almost always walked directly towards and brought its snout to within a few centimeters of the chosen box. In addition, all trials were verified from video recordings by a coder who was blind to the nature of the study.

E1 continued to bait the same box until the dog chose correctly in three consecutive trials. Each time the dog met this criterion, E1 repeated the procedure using the other box (a 'reversal'). If the dog failed to choose a box or retrieve the treat within two-minutes, E2 recorded an incorrect choice (per Gunter, 2018; for justification, see Udell and Wynne, 2010). The session ended when this occurred four times or when the dog completed 30 min of testing.

2.3. Analysis

All data were analyzed in R version 3.4.1. Generalized linear mixed models were constructed and tested using the package "lme4" (Bates et al., 2015).

2.3.1. Trial outcome

To test whether age predicted performance, we conducted a binomial regression analysis of trial outcome (correct or incorrect) using a generalized linear mixed model with a binomial error distribution (logit-link function). Recent studies indicate that cognitive performance in pet dogs may peak in middle age rather than decline linearly from adolescence (e.g., Watowich et al., 2020). Thus, to test both the linear and the nonlinear (quadratic) relationships between age and trial outcome we included fixed effects for age (in months) and age^2. To control for subject covariates, we included fixed effects for weight (kg), height (cm) and sex.

To test for evidence of learning, we included a fixed effect for trial number (a cumulative count of trials from the start of testing). If the dog completed reversals by learning to search for treats at the correct box rather than by random chance, we should expect an increase in performance with trial number. However, after each reversal the probability of choosing the correct box should abruptly drop. Thus, we also included a fixed effect for reversal number to control for variation between reversals (i.e., to account for this oscillating relationship between trial number and trial outcome).

If the assessment required inhibitory control, previously learned reward contingencies should interfere with the dog's ability to learn the current reward contingency. Such interference may be additive and thus the task may become more difficult with each additional reversal. Alternatively, dogs may learn to track reversing reward contingencies more rapidly with each additional completed reversal. The fixed effect for reversal number tested each of these hypotheses.

For random effects, we included only subject intercepts because subject slopes for trial and reversal number could not be reliably estimated (they created singularities and prevented convergence), did not improve model prediction, and did not account for any variance.

To test the significance of each predictor we conducted likelihood ratio tests of the difference in total prediction between the full model and the nested model without the predictor. To test overall model prediction, we compared the full model to an intercept-only model.

2.3.2. Total reversals

To test whether the total number of reversals completed during the test provided a stand-alone score which could be used to determine the dog's level of cognitive function, we constructed a generalized linear model of total reversals as a function of age and age^2. Because total reversals could take only a handful of discrete values, including zero, we used a Poisson error distribution. This better fit the data than other error distributions for count variables (e.g., negative-binomial, zero-inflated Poisson, etc.). To test the goodness of fit of the overall model, we compared the residual deviance and residual degrees of freedom to the chi-squared distribution (p-values $< .05$ indicate data do *not* fit the model). To control for minor violations of the Poisson distribution assumptions, we calculated robust standard errors for the predictors. We then calculated Z and p-values using the robust standard errors to test the significance of the parameters.

2.3.3. Longest streak of perseverative errors

To assess the severity of the dog's worst bout of performance, we measured the longest streak of perseverative errors committed during the test. Given that the dog was not informed when a reversal occurred, only incorrect choices in trials after the first of each reversal were considered perseverative errors. To test the relationship between age and bouts of poor performance, we tested the regression of age and age^2 on the longest streak of perseverative errors, which was normalized with a square root-transformation. We then conducted an F-test for the overall prediction of the model and two-tailed t tests for the prediction of the individual parameters. Satisfying the assumption of equal variances required removing a strong outlier. Importantly, this did not change the outcome of the analysis (see Supplementary material S3).

2.3.4. Age-weight interactions

Although we are unaware of any evidence that the rate of cognitive aging in dogs varies as a function of body size, lifespan is inversely related to body size in dogs and physiological deterioration may progress more rapidly in large breeds (Kraus et al. 2013). To control for potential effects of body size on lifespan changes in inhibitory control, we tested a large enough sample to ensure that age was not related to weight ($R^2 < 0.0001$). In addition, we repeated each analysis with additional coefficients for the interaction between weight and age, and the interaction between weight and age^2. These effects were not significant in any analysis and did not meaningfully change the outcome of any analysis (see supplementary material S4).

3. Results

Shaping required an average of 20 trials and all dogs that completed shaping also completed the assessment (n = 62). Sixteen dogs failed to complete shaping. Additionally, one dog would not eat treats and one dog would not approach the left box.

Dogs made a choice in all but 30 of the 2878 trials suggesting that they were highly motivated to participate. Moreover, no-choice trials were approximately uniformly distributed among 16 dogs (mean = 1.88 trials) indicating that low motivation was not a major problem for any dog. Although dogs may become less active with age (Salvin et al. 2011b) and may lose interest in cognitive tests more quickly (Salvin et al. 2011a), age was not correlated with the number of 'no-choice' trials during our test ($R^2 = 0.001$). Thus, these shaping and exclusion criteria may effectively control for motivation.

3.1. Trial outcome

The model significantly predicted trial outcome, $X^2(8) = 29.70$, $p = .0002$ (Table 1). The effects of age, $X^2(1) = 4.88$, $p = .027$, and age^2 were significant, $X^2(1) = 6.76$, $p = .009$. Middle-aged dogs chose correctly more often than younger and older dogs. The probability of choosing the correct box increased with trial number, $X^2(1) = 7.66$, $p = .006$, and decreased with reversal number, $X^2(1) = 12.39$, $p = .0004$ (Fig. S5). Random variation among subjects predicted trial outcome, $X^2(1) = 6.96$, $p = .008$.

The effects of height, weight, and sex were not significant. Therefore, to confirm the significance of the other predictors, we constructed a final model without these covariates. This did not change overall prediction and all remaining predictors were significant (Table 1).

The variance inflation factors of the coefficients for trial (7.0) and reversal number (7.1) suggested multicollinearity. Thus, the standard errors of these terms may be overestimated and the strength of their prediction, underestimated.

3.2. Total reversals

Although the goodness-of-fit test was not significant, $X^2(59) = 74.55$, p = .08, neither age, ß = 4.05e^{-03}, $SE = 7.22e^{-03}$; $p(>|Z|) = .58$, nor age^2, ß = -2.97e^{-05}, $SE = 4.52e^{-05}$; $p(>|Z|) = .51$, significantly predicted total reversals.

3.3. Longest streak of perseverative errors

The overall model significantly predicted the longest streak of perseverative errors, $F(2,58) = 8.30$, $p = .0007$; $r^2 = 0.22$. The effects of both age, ß = -0.013, $SE = .004$; $t(58) = -3.20$, $p = .002$, and age^2 were significant, ß = 8.99e^{-05}, $SE = 2.41e^{-05}$; $t(58) = 3.73$, $p = .0004$. Perseverative streaks ($\bar{y} = 3.49$, $SEy = 0.19$) were shorter in middle-aged dogs than in young and old dogs (Fig. 1).

4. Discussion

In this sample of pet dogs, the ability to correctly respond to serially reversing reward contingencies peaked in middle-age and this finding could not be attributed to subject covariates. After accounting for reversal number, performance improved with trial number indicating

Table 1
Analysis of Trial Outcome.

Predictor	Coefficients		LRT (Nested)		Model Fit			LRT (vs. Null)		LRT (vs. Full)	
	ß	*SE*	X^2	*p*	*AIC*	*BIC*	$\frac{r^2}{r(df)}$	X^2	*p*	X^2	*p*
Null Model					3912	3918	1.004				
Intercept	0.11	0.04	–	–							
Full Model					3898	3952	0.978	29.70	0.0002		
Age	0.55	0.25	4.88	0.027							
Age^2	−0.65	0.24	6.76	0.009							
Trial	0.29	0.11	7.66	0.006							
REV	−0.45	0.13	12.39	0.0004							
Height	0.08	0.15	0.27	0.60							
Weight	−0.19	0.15	1.55	0.21							
Sex	−0.09	0.12	0.63	0.43							
Intercept	0.15	0.08	–	–							
Rnd.Sbj.Int	–	0.07	6.96	0.008							
Final Model					3898	3933	0.975	24.38	0.0002	5.33	0.15
Age	0.50	0.25	3.95	0.047							
Age^2	−0.59	0.25	5.63	0.018							
Trial	0.30	0.10	8.31	0.004							
REV	−0.45	0.13	13.04	0.0003							
Intercept	0.10	0.06	–	–							
Rnd.Sbj.Int	–	0.05	9.19	0.002							

The three sections of the table identify the three generalized linear mixed models of trial outcome (correct or incorrect choice) with binomial error distributions. The first row of each section, in which the model is named, provides information about the fit and significance of the overall model. Each subsequent row provides information about a predictor in the model. The full model was constructed based on a priori predictions and included fixed effects for test and subject variables, a fixed intercept, and random subject intercepts (Rnd.Sbj.Int). Likelihood Ratio Tests (LRTs) of nested models were used to assess the significance of each predictor. The final model with only the significant predictors from the full model was constructed to address potential overfitting. To determine whether these models accounted for significant variation in trial outcome, each was compared to the null model using an LRT. A third LRT was used to compare overall prediction between the full and final models. Akaike & Bayesian Information Criterion (AIC and BIC) were used to compare model fit. The ratio of the sum of the squared Pearson residuals to the residuals degrees of freedom ($r^2/r(df)$) was used to assess dispersion. REV: reversal number.

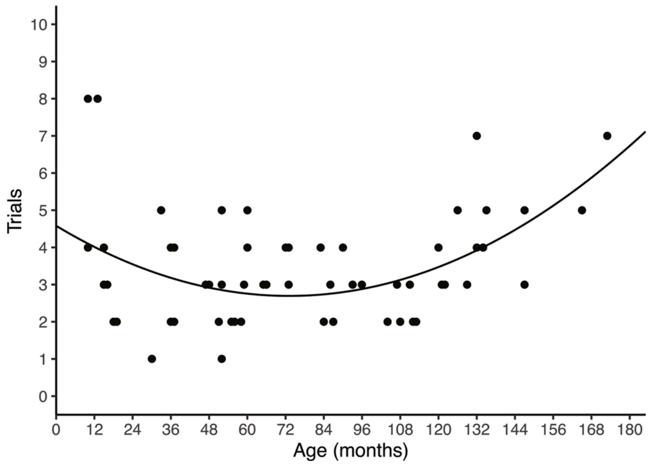

Fig. 1. Longest streak of perseverative errors by age. A square root transformation was used for analysis. The displayed values and regression line are back-transformed.

that dogs completed reversals by learning the correct location rather than choosing at random. Dogs were less likely to choose the correct box after each reversal suggesting that previously learned reward contingencies increasingly interfered with the dog's ability to learn the current reward contingency. In turn, this indicates that completing reversals required inhibitory control. Together, these findings provide evidence that this test detected age-related deficits in inhibitory control.

Importantly, these deficits were also detected with a stand-alone score (the longest streak of perseverative errors) that can be easily measured and interpreted by clinicians and dog owners. In addition, this test required only two visually-separated areas, two identical objects large enough to hide food treats, and 30 min for testing. Thus, this assessment may provide a viable clinical or in-home assessment for ARCD.

The positive association between age and cognitive flexibility and the negative association between age and perseveration in dogs between 10 and 72 months of age provided additional support for recent indications that executive functions continue to develop until middle-age in pet dogs. Watowich et al. (2020) observed a quadratic relationship between age and performance in a broad range of cognitive assessments implemented by citizen scientists. Experimental studies on pet dogs also align with these findings. Wallis et al. (2014) found that selective attention and sensorimotor coordination peaked in middle-age. Using the same two-box paradigm as the present study, Van Bourg et al. (in press) found that middle-aged dogs could recall the location of a hidden treat more accurately and after longer retention intervals. In addition, young and old dogs displayed stronger box preferences suggesting that the ability to inhibit incorrect responses to a preferred location does not fully develop until midlife.

Given that age and age^2 predicted the dog's longest streak of perseverative errors but not the number of reversals completed during the test, older and younger dogs may be prone to more severe bouts of perseveration but not deficits in average efficiency of serial reversal learning. More generally, ARCD in dogs may be better characterized by severe bouts of cognitive dysfunction rather than temporally-consistent cognitive deficits. Worst performance and other measurements related to intra-individual variability are underutilized tools which can complement scores for overall performance and may improve prediction of cognitive decline (Hultsch and MacDonald, 2004). Indeed, studies on humans indicate that an individual's worst performance in a multi-trial psychometric test may serve as a useful indicator of ARCD (Wallert et al., 2017, 2018). To our knowledge, the present study is the first to examine the relationship between age and worst performance in a cognitive assessment for dogs. Thus, future studies are needed to confirm this hypothesis.

The finding that age did not predict total reversals completed suggests that this measurement was not a useful assessment score. Particularly in rapid assessments which must be completed in fewer trials, integer scores may be limited to a small number of potential outcomes. Although such measurements may be used to detect average performance differences between age groups, they provide little resolution and therefore, may be less useful for identifying ARCD in individual dogs. This further highlights the importance of analyzing age as a continuous variable rather than grouping dogs into age categories (see Van Bourg et al., 2020; Watowich et al., 2020).

The apparently counterintuitive decrease in performance across reversals displayed by dogs in the present may stem from methodological constraints. When animals are trained in many sessions on spatial serial reversal learning tasks, performance generally improves across reversals as subjects learn the "principal of reversal" or simple strategies like the Win-Stay and Lose-Shift rules (Shettleworth, 1998, 2010). In the present study, dogs were tested in only one short session. Thus, nearly one third of the dogs completed only one reversal and over half of the dogs were unable to complete a third reversal, which is usually the first reversal that subjects complete faster than the initial side-learning event (e.g., Warren, 1966).

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Ethics approval

This research was approved by the Arizona State University Institutional Animal Care and Use Committee (Protocol Number: 19-1681R).

Consent

Informed consent was received from the owners of all dogs that participated in this study and all participation was voluntary.

CRediT authorship contribution statement

Joshua Van Bourg: Conceptualization, Methodology, Formal analysis, Investigation, Data curation, Writing - original draft, Writing - review & editing, Visualization, Supervision, Project administration. **Lisa M. Gunter:** . **Clive D.L. Wynne:** Conceptualization, Methodology, Resources, Writing - review & editing, Supervision, Project administration.

Declaration of Competing Interest

The authors report no declarations of interest.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.beproc.2021.104375.

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