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Research Paper

Is noise reactivity reflected in auditory response variables, including those that measure cognition, in dogs? Initial findings

Peter M. Scheifele [a,*], Kristine E. Sonstrom [b], Arthur E. Dunham [c], Karen L. Overall [c]

[a] Communication Sciences and Disorders Department, University of Cincinnati, Cincinnati, Ohio
[b] School of Speech-Language Pathology and Audiology, The University of Akron, Akron, Ohio
[c] Veterinary School/Biology Department, University of Pennsylvania, Philadelphia, Pennsylvania

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A B S T R A C T

Noise reactivity and noise phobia are anxiety- and panic-related conditions in dogs that may affect up to 50% of dogs across their lifetime. Affected dogs show a range of signs of distress including trembling, freezing, panting, social withdrawal, pacing, salivating, and escape behaviors. Noise reactivity and phobia have been shown to be comorbid conditions, and their presence may increase the risk and severity of other anxiety-related conditions. Anxiety disorders may interfere with dogs' abilities to perform problem-solving tasks or to interpret information that could be useful in such tasks, including tasks involving or affected by noise. The extent to which noise reactivity or phobia is related to auditory dysfunction or impairment is not known. In this study, we asked whether known noise reactivity in dogs was reflected in any of several measures of auditory function: the brainstem auditory-evoked response, auditory middle-latency response, and mismatch negativity. Most noise-reactive dogs in this study were mildly affected (mean anxiety intensity rank [noise] score 17.65, maximum = 64). Comparison of the major auditory measures of dogs who were noise reactive with those of dogs who were non–noise reactive revealed a significant difference in only one variable of the brainstem auditory-evoked response test, right ear wave-V (RE-V) (Welch's $t = 2.55$, df $= 22.41$, $P < 0.02$). Auditory middle- and late-latency responses were present in all dogs that allowed for the completion of this test, providing initial evidence of higher order auditory-cognitive function. Behaviorally, the group of noise-reactive dogs was significantly different from the group of non–noise-reactive dogs with respect to their ability to undergo this testing: 5 of the 17 noise-reactive dogs were too reactive to undergo or complete the test but none of the 14 non-noise dogs were unable to undergo and complete testing. This study suggests that the underlying pathology resulting in noise reactivity may not influence auditory middle-latency response or mismatch negativity related variables, but the study should be expanded to a larger and more severely affected population of dogs.

Introduction

Noise reactivity and phobia are common pathological behavioral conditions in pet dogs. Diagnostic criteria require that noise-phobic dogs exhibit a profound, nongraded, extreme response to noise, manifest as intense avoidance, escape, or anxiety and associated with the sympathetic branch of the autonomic nervous system. Dogs who are continuously and characteristically distressed when exposed to specified noises, including storms, but who do not meet the criteria for a "phobia" may be classified as "reactive" (Overall, 2013). Many surveys report that up to 50% of dogs may be affected by some extreme reaction to some noise during their lifetime (Blackshaw et al., 1990; Dale et al., 2010; Blackwell et al., 2013; Storengen and Lingaas, 2015; Tiira and Lohi, 2015, 2016). Reactions are most commonly reported for storms, fireworks, and guns, but noises associated with vehicles, machines, alarms, and so forth can also trigger fearful, anxious, or phobic responses in dogs (McCobb et al., 2001; King et al., 2003; Ley et al., 2007).

Nonspecific behavioral signs of distress associated with noise reactivity and phobia may include trembling, freezing, panting, social withdrawal, pacing, salivating, and escape behaviors (Beerda

* Address for reprint requests and correspondence: Peter M. Scheifele, University of Cincinnati, 3202 Eden Avenue, Cincinnati, Ohio 45267. Tel: 513-558-8519; Fax: 513-558-8500.
E-mail address: scheifpr@ucmail.uc.edu (P.M. Scheifele).

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et al., 1997, 1998; Overall et al., 2001; Hydbring-Sandberg et al., 2004; Overall and Dunham, 2016) and may be associated with both physical and behavioral debility and compromise (Overall et al., 2001; Dreschel and Granger, 2005; Dreschel, 2010; Siniscalchi et al., 2013). Noise reactivity and phobia interferes with performance in working dogs (Tomkins et al., 2011, 2012; Gazzano et al., 2007; Batt et al., 2008; Asher et al., 2013; Arvelius et al., 2014; Sherman et al., 2014; Evans et al., 2015) and interferes routine patterns of daily life in pet dogs (Overall et al., 2001). Treatment for noise reactivity and phobia focuses on redress of the associated behavioral and physiological signs. Interventions shown to be efficacious include avoidance, behavioral modification (Tuber et al., 1982; Shull-Selcer and Stagg, 1991), application of gentle pressure (Cottam et al., 2013), and medication Seksel and Lindemann, 2001; Crowell-Davis et al., 2003; Gruen and Sherman, 2008; Ogata and Dodman, 2011).

There are no studies investigating whether any aspect of auditory acuity and ability is related to measurable aspects of noise reactivity and phobia. Accordingly, as part of a larger study on factors affecting cognition and problem-solving ability in dogs, dogs reported to be reactive to or phobic of noises were tested for auditory function. A similarly sized group of dogs from the same larger study who were specifically reported to not react adversely to noises was also tested.

Auditory function was measured via the use of auditory-evoked potentials (AEPs). AEPs are electrical potentials produced by the brain in response to auditory stimuli (i.e., clicks) emitted through a transducer (i.e., inserts) and introduced into the dog's external auditory canal. The auditory/neural response is recorded from electrodes placed to the dog's scalp and connected to recording equipment. The resulting output is a waveform displayed on the computer which is interpreted and analyzed. Each AEP results in a waveform occurring at different times (latencies) following the onset of the auditory stimulus, measured in milliseconds.

AEPs are recorded using different stimulus and acquisition parameters. Stimulus parameters describe the characteristics of the stimulus. An air-conducted click stimulus and air-conducted tone burst stimulus are 2 types of stimuli, each representing a different frequency response from various regions of the cochlear basilar membrane within the inner ear. Click stimuli are less frequency specific than tone burst stimuli. Stimulus rate, measured per second, varies across AEPs. Slower stimulus rates are required for AEPs which measure higher order cortical function (i.e., 7.1 clicks per second, as was used with the auditory middle-latency response [AMLR] in this study), whereas faster stimulus rates are typically used to measure responses from the auditory nerve and brainstem (i.e., 33.1 clicks per second, as was used with the brainstem auditory-evoked response in this study). Stimulus intensity is the physical term that represents the volume or loudness of a stimulus perceptually. The intensity selected varies for different AEPs and is measured using a reference of peak-equivalent sound pressure level. When testing to estimate for degree of hearing loss, the clinician typically starts recording the response at a high intensity, incrementally dropping to lower intensities to determine the level at which the subject has a reliable auditory response and the level at which that response is no longer present.

Acquisition parameters are characteristics of the recording, such as the transducer, electrode montage, or filter settings. The transducer is the equipment that delivers the stimulus to the ear. Examples of different transducers include ear inserts, supra aural headphones, or a bone conductor, with the latter used when middle ear disorder is suspected (i.e., otitis media). The bone conductor, placed over the mastoid, delivers the stimulus directly to the inner ear via vibration of the skull, bypassing the middle ear space. Electrode montage describes the location on the head where the electrodes are placed. Filter settings are chosen within the software and allow specific frequency responses of interest to be measured while excluding those that are undesirable, typically due to contamination of the waveform response (i.e., that from electrical interference or myogenic interference). It is important to note that chosen stimulus and acquisition parameters have a direct effect on the waveform response output, thus must be selected appropriately (Scheifele and Clark, 2012). Likewise, subject parameters may also result in a varied output waveform response. Examples of subject parameters include medical disorders, age, or gender. Last, the auditory and/or neural generator sites differ for each AEP measured, as described in the following.

The following AEPs were measured in the dogs: (1) the brainstem auditory-evoked response (BAER), (2) AMLR, and (3) mismatch negativity (MMN).

The BAER or Auditory Brainstem Response test is an electrophysiological test which objectively assesses auditory function and estimates hearing acuity in dogs (Scheifele and Clark, 2012). This measure represents activity within the auditory system (the ear, auditory nerve, or auditory regions of the brain) that are stimulated by auditory or acoustic stimuli (Hall, 2007). The overall integrity of the auditory system is assessed with this measure, specifically the pathway from the auditory nerve to the brainstem. The BAER test is commonly used to test for congenital deafness in puppies and presbycusis in older dogs. The BAER includes a series of up to 7 waves that occur within the first 10 ms following the onset of the stimulus, with the first 5 waves being clinically relevant in small animals (Scheifele and Clark, 2012). The positive peaks are labeled with Roman numerals, as I, II, III, IV, and V. This routine technique has been used with humans since the 1960's and slowly introduced into the animal industry since the 1980's (Hall, 2007; Kay et al., 1984; Sims & Moore, 1984a). The BAER test is the currently accepted measure of objectively assessing auditory function and estimating hearing acuity in dogs.

The AMLR was performed to measure cortical responses from the canine brain regions responsible for higher order, auditory-cognitive function. The AMLR is an event-related potential (ERP) that results from interaction between responses from the auditory cortex, thalamus, and frontal cortex. These regions connect to and interact with the hypothalamus, hippocampus, and amygdala, regions responsible for cognitive function. Hence, the AMLR provides a direct measurement of auditory-cognitive function. The subject need not attend to the stimulus in this test because the response is derived from auditory discrimination processing in the primary auditory and association areas. Middle-latency responses are preattentive, so it is not required for the subject to perceive that they heard (or attended) to the sound stimulus in order for a response to be obtained. This is unlike certain late AEPs, in which a conscious perception to the sound stimulus is required in order for a response to be obtained. AMLR testing assays central auditory perception, auditory memory, and preattentional processes associated with auditory sensory input to conscious perception and higher forms of memory. When combined with BAER test to measure auditory acuity, it is an excellent tool for assessing auditory aspects of cognitive function in dogs. An assessment of problem-solving behavior combined with AMLR assessment may be useful for predicting the ability to work with sounds and/or in noisy environments, or those in which dogs may react adversely to specific auditory stimuli.

AMLRs are thought to emanate from regions at the thalamic, precortical (extralemniscal), and cortical levels of the prefrontal, frontal, and temporal lobes of the brain (Deiber et al., 1988; Kraus et al., 1982; Scherg and von Cramon, 1986). The response generated from this ERP includes a series of waves 12-80 ms following the stimulus onset and has 3 vertex-positive and negative points

(N_0, P_0, N_a, P_a, N_b, and P_b with P_a) (Luck and Kappenman, 2012). The P_b component of the AMLR provides evidence of “sensory gating,” the process of habituating to repeated stimuli and differentiating repeated from novel stimuli. When identical stimuli are presented, the amplitude of the P_b component is reduced for the second stimulus when compared to the first stimulus, indicating sensory gating and reflecting the preattentive activity of the brain (Hall, 2007). The P_b component of the AMLR occurs at a latency of approximately 50 ms following the onset of the stimulus (P50 component).

To our knowledge, there is only one published article on AMLR testing in dogs (Sims and Moore, 1984b). The AMLR has also been performed on other species (Arezzo et al., 1975; Buchwald et al., 1981; Kileny et al., 1987). In nonanesthetized dogs, waveform morphology of the AMLR is similar to that of humans (Sims and Moore, 1984b); however, the use of the AMLR to assess higher order cognitive function has not been investigated.

MMN is an ERP that presents as a negative wave, elicited by a combination of a frequent standard stimuli and infrequent deviant or “odd-ball” stimuli (Näätänen et al., 1978). The oddball stimulus deviates from the standard stimulus in terms of frequency, intensity level, or stimulus type (2 separate frequencies used for current study). The response occurs within the latency range of 100-300 ms after the onset of the stimulus. The negative response is most evident when the standard stimuli waveform is subtracted from the deviant stimuli waveform, as it was in the present study. Neural generator sites of the MMN response include the primary and secondary auditory cortices within the temporal lobe, with contributions from the frontal lobe, thought to reflect memory. MMN is a reflection of a number of sequential and fundamental brain processes, including a preattentive analysis of sound features (frequency, intensity, duration), cognitive processes, sensory memory, and a continuous comparison and perception of the 2 types of presented stimuli (standard and deviant) (Näätänen, 2007).

Two parameters analyzed within the MMN recording were N1 (N100) and P2 (P200), both of which represent auditory late-latency responses (ALLRs). N1 and P2 occur within the range of 50-250 ms after the onset of the stimulus and are labeled as a negative trough (N1) and positive peak (P2). Generator sites of ALLRs include the primary and secondary auditory cortices within the temporal lobe, the mesencephalic reticular activating system and the planum temporale (Folmer, 2011). Similar to the AMLR and MMN, the ALLR represents higher order auditory-cognitive function.

Event-related potential testing measures changes in auditory-cognitive brain activity in direct response to differing stimuli, one function of a cognitive response. We evaluated the use of different AEPs in dogs as a potentially useful objective method for recording event-related potentials from neural regions believed to be affected by excessive noise and adverse reactions to noise (e.g., noise reactivity, noise phobia, canine post-traumatic stress disorder) (Overall et al., 2001; Overall, 2013; Burghardt, 2013). Abnormalities of the AMLR may also assist in the detection of auditory issues at cortical levels and problems with auditory scene analysis.

Materials and methods

Behavioral assessment

As part of a larger study on problem-solving behavior and cognition in dogs, 35 dogs of various ages and breeds were chosen for auditory testing based on their reactivity to noises and their availability during the testing period. All owners completed a 33-page questionnaire, adapted for pet dogs from one developed to assess working dog behavioral reactivity and environmental exposure (Working Dog Questionnaire—Pet Version/WDQ-PET; Supplemental Materials). The WDQ-PET contains topical questionnaires validated in other studies (Overall et al., 2001; Hsu and Serpell, 2003; Tiira et al., 2014; 2015). We also obtained information on significant health problems and training. Several dogs were rescued so their history was incomplete.

Included in the WDQ-PET was information about whether the dog reacted to (1) storms/thunderstorms, (2) gunshots, (3) fireworks, and (4) other noises. Additionally, owners were asked to specify the noise and to describe and quantify their dog’s reaction using a benchmarked assessment tool. The latter was essential because not all reactions to all noises are pathological, and not all pathological responses occur only in these 3 scenarios. Dogs who herded or played with vacuum cleaners were not considered to have noise reactivity or phobia, as defined here.

Response choices to questions about contextual reactivity were as follows: (1) yes, (2) no, or (3) unknown/I don’t know. If the owners ticked “yes,” they were asked to estimate with what frequency the dog reacted to that particular noise stimulus. Choices were as follows: (1) 100% of the time, (2) <100% but >60% of the time, (3) 40%-60% of the time, (4) >0% but <40% of the time.

Owners were also asked how often the dog was exposed to each of the noises. Choices were as follows: “never,” “occasionally/a few times per year,” “regularly/about once a month or so,” “frequently/a few times a month or more in some seasons.” This question was asked to ensure we were studying dogs for whom adequate information was available. No one answered “never.”

For each noise to which the dog reacted, owners were asked to specify the type(s) of response: salivate, hide, defecate, tremble, urinate, vocalize, destroy, pace, escape, freeze, and/or pant. These signs are not equally obvious to all owners, but the most common signs reported are clear.

All dogs had anxiety intensity ranks (AIRs scores) for noise and separation anxiety intensity rank scores calculated based on the response to the questionnaire, allowing us to compare dogs identified by the owner as reacting badly to noise and those not reacting to noise. Anxiety intensity rank (AIR) and separation anxiety intensity rank scores were calculated by multiplying the number of signs any dog showed by a weight determined by frequency of reaction, with the frequencies above receiving a weight of 4, 2.5, 1.5, 1, and 0, respectively, and summed for all provocative stimuli (Overall et al., 2001; Overall, 2013; Overall and Dunham, 2016).

Questionnaires were reviewed before testing for completion and errors. If any questionnaire was unclear or there were additional questions, owners were asked for clarification.

All dogs were tested with the complete 13-subtest canine intelligence test protocol (CITP), a cognitive testing protocol that evaluates the 4 most commonly defined cognitive domains (e.g., social/interactive learning; physical/spatial learning/memory; executive function/complex memory including sustained attention, task perseverance, and inhibition; and spontaneous behavior including laterality and responses to stressors) (Lezak et al., 2004; Strauss et al., 2006; Gabowitz et al., 2008). Additionally, dogs at least the size of a beagle were fitted with VOYCE bands (http://voyce.com/) employing custom firmware that recorded movement in 3 dimensions every second. Results from the CITP and VOYCE bands will be reported elsewhere.

Auditory assessment

Selection of dogs for the auditory testing was based on a combination of the WDQ-PET, CITP performance, and owner availability. An attempt was made to obtain a range of breeds and skill sets in the dogs tested during the limited time of the auditory portion of the study. All dogs in this study underwent cognitive and auditory testing over an 8-week period during which no storms involving thunder were expected or occurred. Cognitive testing preceded auditory testing for each dog. All auditory testing was performed blinded to whether the dog reacted to noise, and the assessment of whether the dog reacted to noise was performed blinded as to auditory test outcome. The statistician (Arthur E. Dunham) unblinded the results and groups.

Nineteen of 35 dogs were identified by their owners as reacting fearfully to the 3 main classes of noises commonly assessed (storms, fireworks, and guns). Sixteen dogs were identified as nonreactive.

All auditory testing was performed on all dogs while they were awake, not sedated, and unrestrained. Sedation has been found to influence specific components of AEP responses (Hall, 2007), therefore, was not used. All dogs were asked to lie in sternal or lateral recumbence on 2 stacked extra-large memory foam dog beds. Owners were asked to sit or lie with their dogs and gently hold and calm them throughout testing. Topical lidocaine ointment (2%; Hi-Tech Pharmaceutical, Amherst, NY) or lidocaine/prilocaine cream (2.5%/2.5%; Hi-Tech Pharmaceutical) was applied to the regions of the dog's head where the electrodes were inserted. Lidocaine was applied 10 minutes before electrode insertion. Dogs were permitted to sleep through the study if they wished. Refer to Figure 1 for an example of the test setup during data collection for a bull terrier.

The BAER test was performed first to assess the integrity of the auditory system at the level of the auditory nerve and brainstem. The AMLR was performed to measure cortical responses from the canine brain regions responsible for higher order, auditory-cognitive function. Finally, an MMN test was performed.

Visual observation of the external ear, external auditory canal, and overall aural condition was performed at the onset of testing. The auditory stimulus for AEP testing was delivered using ER3A disposable 13-mm polyurethane ear insert transducers. Three subdermal needle electrodes (Rhythmlink Corp.; Columbia, SC) were applied subcutaneously at 3 cranial locations, according to the international 10/20 system of electrode placement (Klem et al., 1999). We used the A1 Cz A2 electrode montage for all auditory testing. Cz represents the top of the head, and A1 and A2 represent the right and left ears, respectively. The positive (noninverting) electrode was placed at the vertex (Cz), or top cranial midline. The negative (inverting) electrode (A1) was placed at the tragus, rostral to the opening of the external auditory canal and the ground electrode (A2) was placed rostral to the tragus of the nontest ear. The electrode montage was selected to enable the recording of all auditory responses without electrode removal and replacement after the BAER test was completed. The stimulus and acquisition parameters are consistent with recommendations for each AEP measured. Stimulus parameters were adjusted for the AMLR and MMN as recommended for each measure (Hall, 2007), indicated in Table 1. All dogs used for AMLR and MMN testing passed the BAER screen, suggesting normal peripheral auditory function. A single-channel Intelligent Hearing System (Intelligent Hearing Systems; Miami, FL) was used to run the test and for data collection. The BAER and AMLR tests were performed at least twice for comparison, ensuring that the results were repeatable. Important factors considered when evaluating and interpreting the BAER include waveform morphology (robustly present waves with appropriate latency and amplitude), waveform repeatability (waveform overlap), appropriate absolute and interpeak latency (within reference range), appropriate interaural comparison, and appropriate wave amplitude (within reference range; however, variability with this measure exists) (Wilson & Mills, 2005; Scheifele & Clark, 2012).

The presence of the BAER and AMLR was established using both waveform latency and overall morphology (Hall, 2007). Latency is defined as the time from the stimulus onset to the positive peak and/or negative trough of the waves of interest, represented in milliseconds. Latencies were confirmed by repeatability and the respective latency range. Morphology was assessed by the presence of the peaks of interest; for the BAER test, this included waves I-V, and for the AMLR test, this included N_a-P_a and N_b-P_b components, each of which are unlikely to be coincidental with BAER components and are more readily seen due to larger amplitude than N_o-P_o components. For analysis, amplitude was not considered due to subject variability. Such variability can occur due both to disparities in movement of the subject and to stimulus and acquisition parameters (Hall, 2007). All waveforms were analyzed by at least 2 experienced clinicians to ensure reliability.

The BAER was analyzed using descriptive statistics, including the absolute latency of Wave V, standard deviation, and range for the Wave V component, along with overall morphology and repeatability. The AMLR was analyzed using descriptive statistics which included the absolute latency of identified peaks and troughs, standard deviation, and range for all waveform components (N_a-P_a and N_b-P_b). In humans, the overall response of the AMLR occurs within the range of 15-65 ms following stimulus presentation (Hall, 2007; Folmer et al., 2011). Sims and Moore (1984b) calculated ranges for the AMLR in dogs that were

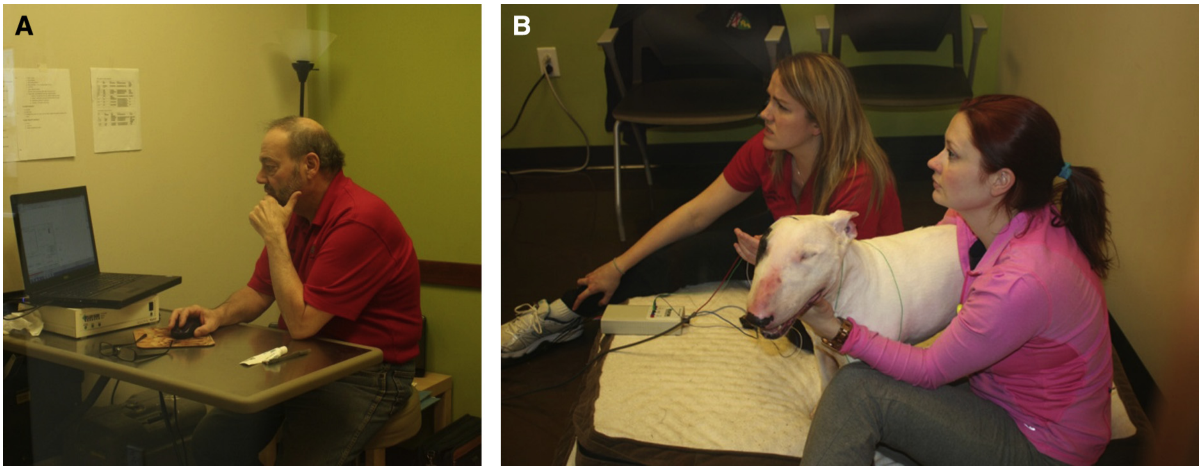

Figure 1. Test apparatus and set up, including electrode montage, during auditory testing of a bull terrier.

Table 1
Acquisition parameters used for AMLR testing

Stimulus parameter	BAER settings	AMLR settings	MMN settings
Intensity	102-dB peSPL	102-dB peSPL	90-dB SPL
Sweeps	500	500	100
Rate (clicks/s)	33.1	7.1	1.1
Stimuli type	100-μs click	100-μs click	100-μs click Standard: 4000 Hz (80%) Deviant: 1000 Hz (20%)
Time window (ms)	12	100	510
Polarity	Rarefaction	Alternating	Alternating
Window	Rectangular	Rectangular	Rectangular
High-pass filter	100 Hz	10 Hz	1 Hz
Low-pass filter	1500 Hz	1500 Hz	30 Hz
Electrode montage	A1 Cz A2	A1 Cz A2	A1 Cz A2

AMLR, auditory middle-latency response; BAER, brainstem auditory-evoked response; MMN, mismatch negativity; peSPL, peak-equivalent sound pressure level; SPL, sound pressure level.

relatively consistent with human findings. The accepted normal latency for each component in humans is as follows: N_a occurs approximately 15-25 ms following the stimulus presentation, P_a occurs approximately 25-35 ms following the stimulus presentation, N_b occurs approximately 35-45 ms following the stimulus presentation and P_b occurs approximately 40-65 ms following the stimulus presentation (Folmer et al., 2011).

All cognitive and auditory testing occurred at a large specialty and referral veterinary hospital in suburban greater Philadelphia, PA, USA (https://hopevs.com). This study was approved by the University of Pennsylvanian IACUC, the US Army IACUC, and the clinical studies committee at HOPE VS.

Statistical analysis

Parametric, Welch two-sample *t* tests were used to evaluate the null hypotheses of no association between any of the auditory variables and the noise-reactive and separation anxiety status of dogs tested. Noise-reactive status was blinded to the researcher carrying out the hearing tests and was only unblended at the time of the analysis. Although there is no evidence that the distributions of the response variables violate any of the assumptions of the Welch two-sample *t* test, because of the relatively small sample sizes, we also computed 2-sided Wilcoxon exact tests on the same data. *G* tests for independence were also used where appropriate to evaluate the likelihood that the noise-phobic status of individuals was associated with any of the independent variables in the study. Power analysis was not performed because baseline data were lacking. Finally, Spearman correlation tests were also used to explore associations between all variables in the study. Significance levels for every statistical analysis performed in this study were determined by permutation (exact) procedures.

All analyses were performed using R statistical software (R Core Team, 2015), and a result was considered significant if $P < 0.05$.

Results

Behavioral results

The dogs initially enrolled in the auditory part of the cognition study are listed in Table 2. Because all auditory testing was done on unrestrained, nonsedated dogs, those dogs who would have required restraint or sedation to comfortably undergo testing were excused from the study. Of the 19 dogs who reacted to noise, 3 of these dogs were too anxious to be able to test without restraint or sedation and were excluded from the study. None of the 16 non–noise-reactive dogs were excused from the study because they would have required restraint or sedation to complete testing.

Of the remaining 16 noise-reactive dogs, 2 were not assessed with the AMLR due to an abnormal BAER test, suggesting hearing impairment or deafness.

Finally, 1 of the noise-reactive dogs was excused because she was so exquisitely sensitive to the testing that further testing would have caused profound distress. A low hearing threshold indicates that the dog could detect sounds at unusually low intensities. This trait may be normal for this individual dog or may be indicative of hyperacusis.

Two of the 16 non–noise-reactive dogs were excused from the study: 1 was diagnosed with auditory dysfunction from the BAER test, and 1 had sufficiently severe otitis media that AMLR testing was not possible. Hearing loss can have an effect on the AMLR (Hall, 2007).

One of the dogs originally classified as non–noise reactive reacted to an extreme summer storm 3 months after his original auditory testing, and 4 months after his CITP and WDQ-PET. For this analysis, he was considered as non–noise reactive.

The remaining 13 noise-reactive and 14 non–noise-reactive dogs underwent AMLR testing. Eleven of the 13 noise-reactive dogs completed AMLR testing, and all 14 of the non–noise-reactive dogs completed AMLR testing.

Regardless of the reasons already discussed, as a group, 4 of the 17 nondeaf, noise-reactive dogs were too reactive or sensitive to the sounds involved to undergo the test. An additional 2 noise-reactive dogs could not complete the test because their behaviors interfered with interpretation of all test parameters. Of the 14 non–noise-reactive dogs who did not have otitis and were not deaf, none were unable to undergo and complete testing because they were too sensitive to the sounds or too behaviorally reactive. A comparison of these groups (G test; $P < 0.0294$) suggests that regardless of the outcome of any auditory parameter comparison, the groups of dogs differ behaviorally.

AIR scores for dogs who reacted to noise in this study ranged from 1.5 to 64.0 with a mean of 17.65 ($N = 20$) and a standard deviation of 17.82. Comparable data for the dogs tested who were reported by their owners to not react to noise were 0-4.0, 0.31 ($N = 13$, 1.11). The AIR scores for these 2 groups of dogs were highly significantly different ($t = 4.34$, df $= 19.23$, $P < 0.0004$).

Auditory results

Ranges established for the AMLR in dogs from this study were similar to those in the current literature (Folmer, 2011; Hall, 2007; Sims and Moore, 1984b). Examples of the AMLR are displayed in Figures 2-4.

Statistical results

The statistical summaries for auditory-related variables and for noise-reactive and non–noise-reactive dogs are presented in Tables 3 and 4. Comparison of the major auditory measures of dogs who were noise reactive with those of dogs who were non–noise reactive revealed a significant difference in only 1 variable, right ear wave-V (RE-V) (Table 5, Welch's $t = 2.55$, df $= 22.41$, $P < 0.02$).

Spearman correlation analysis (Table 5 and Figure 5) revealed 8 significant correlations among major auditory variables and noise reactivity or AIR scores. The RE-V–left ear wave-V (LE-V) correlation is not unexpected because they are the same measurements taken on different ears. Likewise, the AIR–noise reactivity is expected because the AIR score is a measure of noise reactivity. The RE-V–noise reactivity correlation is interesting because there is no known causal mechanism to explain this finding. The relatively high correlation between LE-V and RE-V

Table 2
Demographics of dogs tested and reported noise-reactive status in order of testing; dogs with an * were excluded from the AMLR analysis for the reasons listed

Dog	Sex	Breed	DOB	Auditory test date	Age at testing (years)	Noise reactive	Comments
1	FS	Cocker spaniel	9/18/2008	3/14/2015	6.5	Yes	
2	MC	Jack Russell terrier	10/15/2006	3/14/2015	8.41	Yes	
3	FS	French bulldog mix	4/16/2009	3/14/2015	5.92	No	
4*	MC	Golden retriever	1/30/2007	3/14/2015	7.71	Yes	Unable to record AMLR; multiple tries
5*	MC	Basenji	1/3/2010	3/14/2015	5.21	Yes	Excluded—too reactive to test
6	FI	Labrador retriever	1/6/2014	3/14/2015	1.19	No	
7*	FS	Labrador retriever	5/7/2002	3/14/2015	12.85	Yes	Bilateral moderate hearing loss unequivocal
8	MC	Golden retriever	4/9/2003	3/15/2015	11.94	Yes	
9*	MC	Golden retriever mix	3/30/2011	3/15/2015	3.96	Yes	Excluded—too reactive to test
10	MC	Mixed breed	3/1/2010	3/15/2015	4.95	Yes	
11	MC	Borzoi	8/10/2010	3/15/2015 OR 4/26/2015	4.58 OR 4.68	Yes	Tested twice due to technical malfunction first time
12	MC	Australian shepherd	3/19/2005	4/18/2015	10.08	No	
13	MC	Greyhound	8/25/2009	4/18/2015	5.60	Yes	
14	FS	Golden retriever	3/6/2013	4/18/2015	2.10	No	
15	FS	Border collie × Labrador retriever	9/22/2012	4/18/2015	2.58	Yes	
16	FS	Labrador retriever	5/14/2006	4/18/2015	8.92	No	
17	M	Keeshond	3/4/2014	4/18/2015	1.13	No	
18*	MC	Mixed breed	4/26/2013	4/18/2017	3.98	Yes	Incomplete reliable data; cyclical waveforms due to electrical interference; no AMLR data
19	MC	Golden retriever	11/13/2014	4/19/2015	0.50	No	
20	MC	Standard poodle	7/13/2013	4/19/2015	1.75	Yes	
21	MC	Australian shepherd	2/14/2007	4/19/2015	8.17	No	Not at test time—reacted to a series of severe storms months later
22	MC	Australian shepherd	3/15/2008	4/26/2015	7.10	No	
23	FS	German shepherd	8/30/2014	4/26/2015	0.67	No	
24	MC	Golden retriever	2/10/2012	4/25/2015	3.21	No	Mild hearing loss left ear; data exists for AMLR and MMN
25	FS	Australian shepherd	10/26/2010	4/25/2015	4.50	Yes	
26	MC	Australian shepherd	7/14/2007	4/25/2015	7.77	No	
27*	MC	Bull terrier	3/11/2007	4/25/2015	8.13	No	Incomplete test; otitis media; too much myogenic artifact
28*	FI	Miniature dachshund	12/12/2013	4/25/2015	1.38	Yes	Only able to get BAER test; no cognitive data because wave forms too cyclic and unreliable (multiple tries); BAER down to 30-dB peSPL so likely very keen hearing but could not repeat and match waveforms or fully evaluate because of her distress.
29*	FS	Labrador retriever	12/23/2006	4/25/2015	8.41	No	Incomplete reliable data; cyclical (electrical interference) unclear cognitive data
30	FS	Labrador retriever	3/21/2003	4/25/2015	12.08	No	
31	FS	Mixed breed	5/25/2011	4/25/2015	3.92	Yes	
32	FS	Labrador retriever	4/19/2011	4/25/2015	4.08	No	
33	MC	Golden retriever	9/9/2006	4/26/2015	8.63	Yes	
34*	MC	Mixed breed	3/1/2012	4/26/2015	3.15	Yes	Excluded—too reactive to test
35*	MC	Australian shepherd	5/1/2002	4/26/2015	12.99	Yes	Mild hearing loss in right ear; moderate-severe loss in left ear

AMLR, auditory middle-latency response; MMN, mismatch negativity.

suggests that the effect may be bilateral but that sample size issues and relatively high variability coupled with the fact that many of the affected dogs were only mildly affected may preclude significance.

Discussion

Ranges established for the AMLR in dogs from this study were similar to those established for humans and dogs from previous

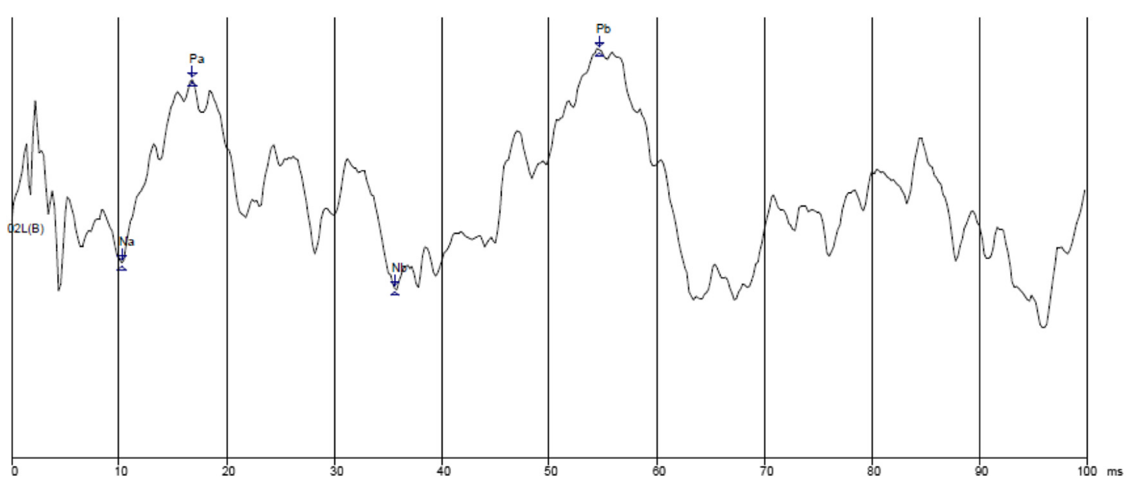

Figure 2. AMLR from a 2-year-old Golden retriever, dog 14; components are labeled as Na-Pa, Nb-Pb. AMLR, auditory middle-latency response.

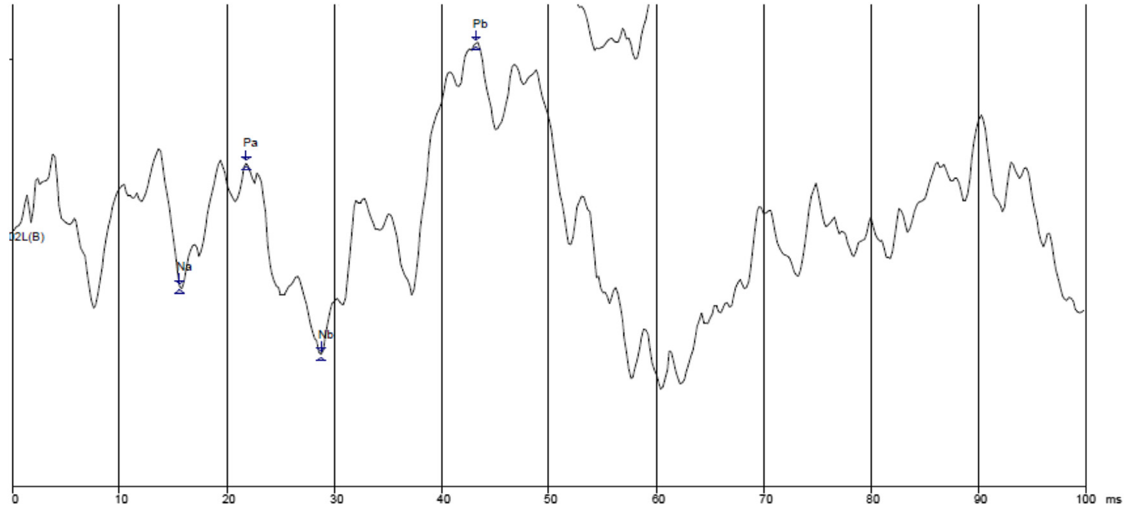

Figure 3. AMLR in an 8-year-old Australian shepherd, dog 21. AMLR, auditory middle-latency response.

studies (Sims and Moore, 1984b; Folmer, 2011; Hall 2007). There was more variability with the N_b-P_b complex than with the N_a-P_a complex. In some cases, the absolute latency of N_a-P_a was earlier in the dogs than in humans. This result is expected because the absolute latencies of the BAER components occur earlier in dogs when compared to humans (Shelton et al., 1993). The range of each analyzed AMLR component for dogs was greater than the range for the same components in humans. The explanation for this could be related to movement during testing; the none of the tested dogs were sedated or anesthetized. Excessive movement that occurs during the recording results in myogenic interference and is known to affect AEP waveform amplitude, substantially more than latency. However, this may explain the increased latency ranges.

The overall hearing ability of dogs in this study did not differ based on whether they were fearful of and reactive to noises. The finding that dogs that reacted to noise in this study had a lateralized BAER is interesting. Lateralization has been shown to covary with noise reactivity and phobia in some studies (Branson and Rogers, 2006; Siniscali et al., 2008; Tomkins et al., 2012). Lateralization may also affect other sensory modalities (Siniscali et al., 2011) and has been reported to be a risk factor for some forms of mental illness (Francks et al., 2007). Here, the applicability of the finding is unclear.

Statistical analysis of the data presented is complicated by 2 considerations. First, we have a relatively small sample size and the associated reduction in power. The dogs tested in this study were chosen from the overall study population on the basis of their availability to be tested within a specific 8-week period. As a result, we did not select for dogs that were severely affected with noise phobia or reactivity, nor do we have substantial population variation (see Overall and Dunham, 2016, for comparison). Additionally, some of the more severely affected noise-reactive dogs could not undergo or complete auditory testing. Another study of severely affected noise-reactive dogs may produce different results and be informative.

As noted, comparison of the major BAER scores of dogs who were noise reactive with those of dogs who were non–noise reactive revealed a significant difference in RE-V. Nonparametric (Spearman) correlation analysis revealed only 8 significant correlations among major auditory variables and noise reactivity or AIR

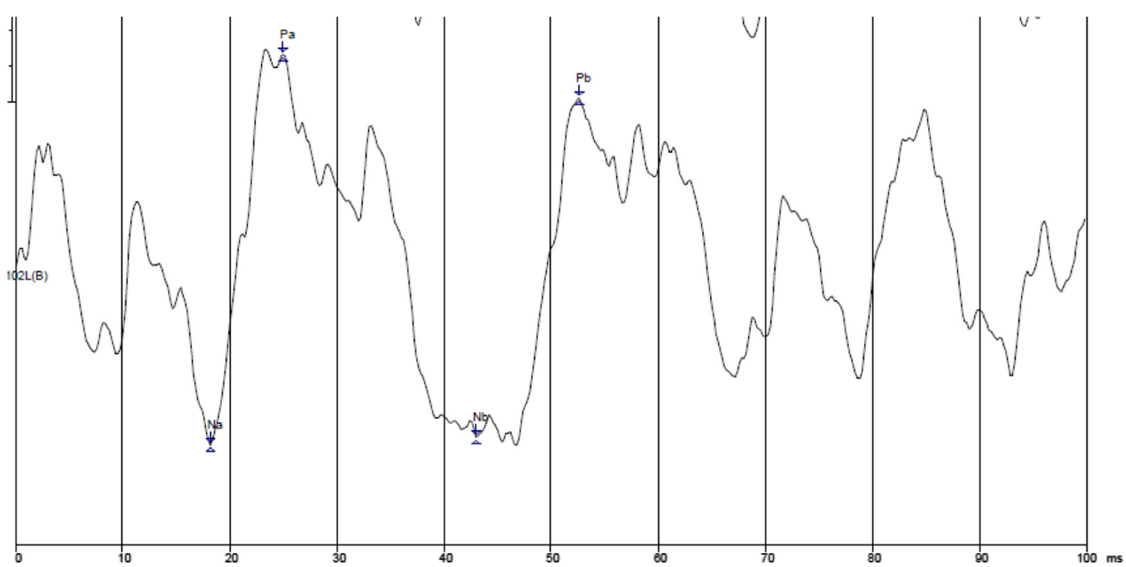

Figure 4. AMLR in an 8-month-old German shepherd, dog 23. AMLR, auditory middle-latency response.

Table 3
Summary statistics for non–noise-reactive and noise-reactive dogs in this study

Variable	N	Mean	Standard deviation	Minimum	Maximum
Non–noise reactive					
N_a	12	15.38	3.35	10.40	20.60
N_b	12	36.75	4.33	29	44
P_a	12	24.95	3.97	17.00	30.60
P_b	12	51.63	5.8	42	59.4
N1S	11	68.18	18.59	45	97
P2S	11	154.09	18.81	122	185
N1D	11	66.18	15.8	49	100
P2D	11	156.09	17.04	133	185
N1MMN	11	69	21.16	41	100
P2MMN	11	157.36	20.58	120	187
LE-V	13	5.07	0.48	4.53	6.1
RE-V	13	4.24	0.63	3.63	6
AIR	13	0.31	1.11	0	4
SAIR	13	1	2.74	0	10
Noise reactive					
N_a	14	16.50	3.38	11.20	23.00
N_b	14	36.26	5.76	27.8	45.6
P_a	14	27.06	3.70	22.00	34.00
P_b	14	47.37	6.59	36	57.4
N1S	16	68.69	20.44	42	110
P2S	16	151.88	23.89	115	204
N1D	16	71.31	18.37	44	100
P2D	16	156	27.32	105	205
N1MMN	16	67.44	18.63	41	100
P2MMN	16	150.31	19.94	113	185
LE-V	16	5.18	0.6	4.15	6.13
RE-V	15	4.39	0.61	3.75	5.85
AIR	20	17.65	17.82	1.5	64
SAIR	20	1.65	3.58	0	16

AIR, anxiety intensity rank; SAIR, separation anxiety intensity rank; LE, Left ear; RE, right ear.
Refer to Glossary to reference abbreviations and waveform components.

scores. Of these, only the correlation of noise reactivity with RE-V is not unexpected for reasons detailed above. The RE-V–noise reactivity association is interesting because there is no known causal mechanism to explain it. The relatively high correlation between LE-V and RE-V suggests that the effect may be bilateral but that sample size issues and relatively high variability coupled with the fact that many of the affected dogs were only mildly affected may preclude significance of an LE-V–noise reactivity association.

Conclusions

AMLR and MMN data show the presence of inattentive cognitive and intelligence processes (e.g., stimulus anticipation) at the level

Table 4
Comparison of BAER and MMN parameters for dogs who reacted to noise compared with those who did not

Variable	Welch's *t*	df	*P*	95% confidence interval
AIR	4.34	19.226	0.0004	8.984 to 25.701
LE-V	1.292	19.447	0.2116 NS	−0.173 to 0.735
RE-V	**2.551**	**22.413**	**0.0179**	**0.087 to 0.837**
N_a	0.843	23.446	0.4076 NS	−1.620 to 3.853
N_b	−0.248	23.645	0.3857 NS	−4.591 to 3.61
N1MMN	−1.5001	22.412	0.1476 NS	−25.643 to 4.104
N1D	0.7753	23.619	0.4459 NS	−8.539 to 18.801
N1S	0.0667	22.957	0.9474 NS	−15.190 to 16.201
P2MMN	0.2108	23.992	0.8348 NS	−12.892 to 15.826
P2D	−0.106	24.846	0.9916 NS	−17.701 to 17.519
P2S	−0.269	24.441	0.7901 NS	−19.196 to 14.765
SAIR	0.5887	30.061	0.5605 NS	−1.605 to 2.905

AIR, anxiety intensity rank; LE, left ear; RE, right ear; BAER, brainstem auditory-evoked response; MMN, mismatch negativity; SAIR, separation anxiety intensity rank.
The only significant result (noise-reactive dogs have higher RE-V measures) is bolded. Refer to Glossary to reference abbreviations and waveform components.

Table 5
Statistically significant ($P < 0.05$) Spearman rank correlations among major auditory variables, noise reactivity status, AIR, and SAIR scores

Variables	R_s (*P*)
LE-V–RE-V	$r_s = 0.62$ ($P = 0.001$)
Noise reactivity–RE-V	$r_s = -0.40$ ($P = 0.001$)
Noise reactivity–AIR	$r_s = 0.62$ ($P = 0.003$)
N_a–P_a	$r_s = 0.44$ ($P = 0.03$)
N_b–P_b	$r_s = 0.66$ ($P = 0.00$)
N1–P2S	$r_s = 0.46$ ($P = 0.02$)
N1D–P2D	$r_s = 0.43$ ($P = 0.02$)
P2D–P2MM	$r_s = 0.62$ ($P = 0.000$)

AIR, anxiety intensity rank; SAIR, separation anxiety intensity rank; LE, left ear; RE, right ear.
Refer to Glossary to reference abbreviations and waveform components.

of the auditory cortex. The AMLR measures brain processes responsible for the shift from attentional gating to conscious perception of sounds. The presence of a valid AMLR in our canine subjects is indicative of functional responses from cortical regions of the canine auditory pathway where primary and secondary processing and integration of auditory information occur, specifically the thalamic and cortical levels of the prefrontal, frontal, and temporal lobes of the brain. Accordingly, the AMLR is indicative of the dogs' ability to process and integrate auditory information related to echoic memory. Likewise, MMN is a reflection of sequential and fundamental brain processes, including a pre-attentive analysis of sound features, cognitive processes, sensory memory, and a continuous comparison and perception of different acoustic stimuli. The presence of the ALLR within the MMN response is additional preliminary evidence of higher order cognitive function within the central auditory nervous system, though further research is needed to validate these measures and see how they correlate to noise phobia and/or behavioral reactivity. There is evidence that noise stress impairs prefrontal cortical cognitive function in monkeys (Arnsten and Goldman-Rakic, 1998) and furthermore affects the feedback-related negativity component within the ALLR response in humans (Banis and Lorist, 2012). A further investigation into the use of higher order auditory

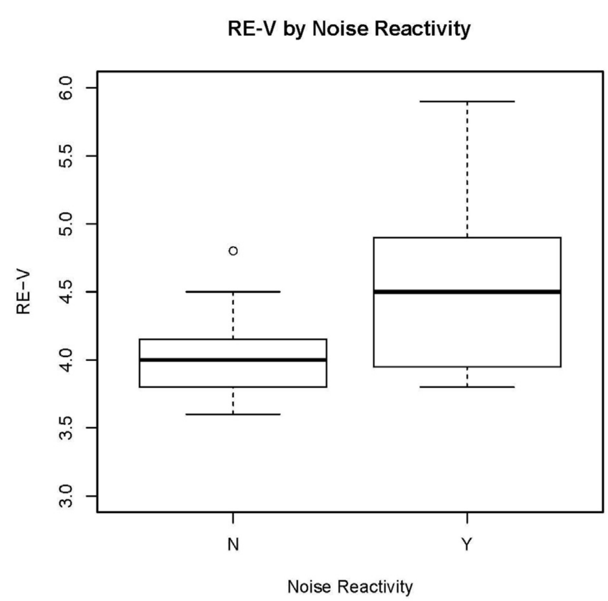

Figure 5. Box and whisker plot of the distribution of RE-V measures for dogs who reacted to noise and those who did not. Whiskers indicate 2 standard errors; means are heavy horizontal bars.

electrophysiologic measures in noise-reactive dogs may address questions regarding how they use feedback information from the internal and external environment to assess and modify their behaviors in response to noise.

Perhaps, the most overarching conclusion from statistical analysis of these data may be that the underlying pathology resulting in noise reactivity, at least in mildly affected dogs, may not influence AMLR- or MMN-related variables to any large degree. It is likely important that even in this mildly affected and small study population, dogs with noise reactivity were statistically less likely, behaviorally, to be able to tolerate and complete the auditory testing than were non–noise-reactive dogs. All of the non–noise-reactive dogs were able to complete the testing and none exhibited behaviors that were a concern for them or the researchers. This observation suggests that even at low levels, noise reactivity may affect many social and daily behaviors, including those involved in problem-solving behavior, in which dogs engage, and may contribute to a level of mental and behavioral discomfort with respect to these behaviors that is underappreciated and warrants redress.

This study, when combined with more detailed studies, may be used as a basis for an auditory neurodiagnosis in dogs exposed to excessive noise or exhibiting a phobia to noise. Future work needs to focus on establishing norms for amplitude components of each of the auditory waveforms measured and on any variation in response seen across the entire range of noise reactivities/phobias. The AMLR waveform measure is sensitive to identifying auditory dysfunction at the level of the central auditory nervous system and will reflect the ability of the cortical auditory system to accurately conduct auditory scene analysis (Hall, 2007). Establishing normative AMLR and MMN data for a larger population of adult dogs is warranted. This normative data can then be compared to a potentially more severally affected group of noise-reactive dogs.

It is interesting that the only dogs—8/19 or 42.11%—who were excluded from the auditory portion of the study (1 for profoundly sensitive hearing, 2 for deafness, 3 because they were too reactive to lie still for the test, 2 because they could not complete all test components) were dogs from the noise-reactive group. While 2 non–noise-reactive dogs also had evidence of deafness or auditory disease which precluded complete auditory testing, none were excluded from the auditory portion of the test because they were behaviorally too reactive to test.

Noise reactivity and noise phobia have been shown to be comorbid behavioral conditions in dogs (Overall et al., 2001; Tiira and Lohi, 2016). Noise reactivity/phobia is a common condition, and various sources suggest that nearly 50% of dogs may be affected by some extreme reaction to some noise during their lifetime (Blackshaw et al., 1990; Dale et al., 2010; Blackwell et al., 2013; Storengen and Lingaas, 2015; Tiira and Lohi, 2015, 2016). Twenty-one percent (4/19) of our noise-reactive dogs could not undergo any degree of unsedated auditory testing because they were distressed when handled and could not calm sufficiently to permit the 30-minute test. It is likely that this distress when handled may be a commonly comorbid, but underreported condition in pet dogs. Given the prevalence of noise reactivity/phobia, this finding suggests that routine screening, early and effective intervention, and client education are all serious quality-of-life issues for pet dogs that may be currently escaping redress.

Our study shows that there are neurodiagnostic differences represented with auditory (or BAER) testing in dogs who react adversely to noises and those who do not. As such, this is the first report linking neurophysiological changes to the behavioral pathology of noise reactivity/phobia. Because some of our more reactive dogs could not calm sufficiently to undergo testing, we cannot know if these dogs had a more profound neurophysiological response or had greater shifts in the BAER waveform pattern. However, their inability to undergo testing demonstrates that dogs who experience noise reactivity and phobia suffer from their condition and, even when they are not working dogs, experience profound alterations in the behavioral performance. Such alterations may well be accompanied by alterations in problem-solving and cognitive ability.

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Conflict of interest

Dr. Overall is the editor-in-chief of the Journal of Veterinary Behavior: Clinical Applications and Research. A guest editor was appointed for this special volume. This study was conceived by Art Dunham, Karen Overall, and Peter Scheifele. The study was conducted by Karen Overall, Peter Scheifele, and Kristine Sonstrom, with help from Jess Lydon. The statistical analysis was performed by Art Dunham with the other authors contributing to data analysis. All authors contributed to the writing of the article. This research was funded by DoD ARO grants W911NF-14-1-0574 565053 and 65366-LS to KLO and AED.

Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.jveb.2016.09.002.

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Appendix. Glossary

Term	Abbreviation	Definition
Event-related potential	ERP	Electrical potentials produced by the central auditory nervous system in response to complex endogenous stimuli from within high cognitive levels.
Auditory-evoked potential	AEP	Electrical potentials produced by the peripheral or central auditory nervous system in response to or evoked by brief duration auditory stimuli, such as click or tonal stimuli.
Brainstem auditory-evoked response; aka auditory brainstem response	BAER; ABR	An auditory-evoked potential generated by the auditory nerve and brainstem in response to acoustic stimuli; commonly used to estimate hearing and auditory acuity and function. Waveform peaks occur within the first 10 ms following stimulus onset and are labeled as I, II, III, IV, and V. Peaks of wave V for the right and left ears are reported as RE-V and LE-V, respectively, throughout this article.
Auditory middle-latency response	AMLR	An event-related potential generated by the thalamic, precortical and cortical levels of the frontal and temporal lobes of the brain in response to acoustic stimuli; commonly used to assess higher order cognitive function. Waveform peaks occur within the range of 12-80 ms following stimulus onset and are labeled as N_0, P_0, N_a, P_a, N_b, and P_b.
Auditory late-latency response	ALLR	An event-related potential generated by the primary and secondary auditory cortices of the temporal lobe, the mesencephalic reticular activating system and the planum temporale, in response to acoustic stimuli; commonly used to assess higher order cognitive function. Waveform peaks occur within the range of 50-250 ms following stimulus onset and are labeled as N1, P1, N2, P2, and P3.
Mismatch negativity	MMN	An auditory late-latency response generated by the primary and secondary cortices of the temporal lobe with contributions from the frontal lobe; commonly used to assess sequential and fundamental brain processes, including preattentive analysis of sound features, cognitive processes, sensory memory, and the continuous comparison and perception of acoustic stimuli. Waveform peaks occur within the latency range of 100-300 ms following stimulus onset. The negative waveform response is most evident when the standard stimuli waveform is subtracted from the deviant stimuli waveform.
Canine post-traumatic stress disorder	C-PTSD	A disorder in which canines exhibit physical and psychological behaviors that mimic the behaviors seen in humans diagnosed with post-traumatic stress disorder.
Stimulus parameters		Used to describe characteristics of the acoustic stimulus that produce an AEP or ERP; examples include stimulus type (click vs. tone burst), stimulus rate (7.1/s vs. 33.1/s), and stimulus intensity (50-dB peSPL vs. 90-dB peSPL).
Acquisition parameters		Used to describe characteristics of the AEP or ERP recording; examples include electrode montage (i.e., A1, Cz, A2), transducer (i.e., ear inserts, bone conductor), and filter settings (i.e., 1-30 Hz vs. 30-1500 Hz).
Latency		The time at which the waveform response peak or trough occurs following onset of the stimulus, measured in milliseconds.
Amplitude		The distance from the waveform response peak to trough or trough to peak, measured in microvolts.