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Crossmodal integration improves sensory detection thresholds in the ferret

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27 **Abstract**

28 During the last two decades ferrets (*Mustela putorius*) have been established as a highly
29 efficient animal model in different fields in neuroscience. Here we asked whether ferrets
30 integrate sensory information according to the same principles established for other species.
31 Since only few methods and protocols are available for behaving ferrets we developed a
32 head-free, body-restrained approach allowing a standardized stimulation position and the
33 utilization of the ferret's natural response behavior. We established a behavioral paradigm to
34 test audiovisual integration in the ferret. Animals had to detect a brief auditory and/or visual
35 stimulus presented either left or right from their midline. We first determined detection
36 thresholds for auditory amplitude and visual contrast. In a second step, we combined both
37 modalities and compared psychometric fits and the reaction times between all conditions. We
38 employed Maximum Likelihood Estimation (MLE) to model bimodal psychometric curves and
39 to investigate whether ferrets integrate modalities in an optimal manner. Furthermore, to test
40 for a redundant signal effect we pooled the reaction times of all animals to calculate a race
41 model. We observed that bimodal detection thresholds were reduced and reaction times
42 were faster in the bimodal compared to unimodal conditions. The race model and MLE
43 modeling showed that ferrets integrate modalities in a statistically optimal fashion. Taken
44 together, the data indicate that principles of multisensory integration previously demonstrated
45 in other species also apply to crossmodal processing in the ferret.
46

47 Introduction

48 During the last two decades ferrets (*Mustela putorius*) have become increasingly relevant as
49 an animal model in different fields in neuroscience [1–24]. Ferrets have been domesticated
50 for over 2000 years and are easy to handle and train on behavioral tasks [15,25–29]. As a
51 carnivore ferrets have excellent visual and auditory sensing and are well suited for cross-
52 modal integration studies. An additional advantage is that the ferret brain shows substantial
53 homologies with that of other animal models established in neuroscience, such as the cat
54 [10,11,18–20] and the primate [26]. Extensive work has been performed to map cortical and
55 subcortical regions of the ferret brain functionally and anatomically [3,11,17–20,22]. These
56 mapping studies have shown that ferrets have highly complex sensory cortical systems,
57 making them an interesting model for the study of sensory processing pathways, response
58 properties and topographies of sensory neurons. Several studies have addressed
59 multisensory response properties in anesthetized ferrets [2,4,8,14], but multisensory
60 interactions have not yet been studied in a behavioral preparation in this species.

61 Substantial effort has been made to uncover principles of multisensory integration in a
62 variety of species and paradigms [30–35]. Multisensory integration is crucial for animals and
63 influences behavior in synergistic or competitive ways. Sensory integration can lead to faster
64 reaction times, better detection rates and higher accuracy values in multi- compare to
65 unimodal conditions [33,36,37]. Specifically, sensory integration increases the reliability by
66 reducing the variance in the sensory estimate [36,38,39]. The consistent estimate with the
67 lowest variance is the Maximum Likelihood Estimate (MLE) [40], which can be derived from
68 the weighted sum of the individual sensory estimates, with weights being inversely
69 proportional to the variance of the unisensory signals [36,39]. A substantial number of
70 studies indicate that humans and animals indeed integrate information across sensory
71 modalities in this way [33,36,38,39,41–46]. For example, Ernst and Banks [36] used a MLE
72 model to predict the results of a visual-haptic experiment and showed that humans integrate
73 information in a statistically optimal fashion. Similar results were obtained by application of
74 MLE in a human audio-visual study [37] and in a vestibular-visual study in macaque monkeys
75 [47]. These studies demonstrate that the MLE is a robust statistical model to predict the
76 crossmodal response and to test whether subjects integrate information in a statistically
77 optimal fashion. As a results of the sensory integration process, the accumulation of
78 information in multimodal compared to unimodal conditions is faster, which in turn leads to
79 decreased reaction times (RT) [48–53].

80 In the present study, we investigated whether ferrets integrate sensory signals
81 according to the same principles established for humans [33,54] and non-human primates

82 [47]. Previous studies in behaving ferrets have used either freely-moving [13,15,55] or head-
83 restrained [26] animals. Here, we developed a head-free, body-restrained approach allowing
84 a standardized stimulation position and the utilization of the ferret's natural response
85 behavior. An additional demand was that the setup should be sufficiently flexible to allow
86 combination of the behavioral protocol with electrophysiological recordings. We established a
87 behavioral paradigm, requiring combination and integration in the auditory and/or visual
88 modality, to investigate features of uni- and multisensory integration in the ferret and
89 compare it to data reported from other species. Ferrets were tested in a 2-alternative-choice
90 task requiring them to detect lateralized auditory, visual, or combined audio-visual targets of
91 varying intensity. We expected the ferrets to perform more accurate and faster in the bimodal
92 cases, because congruent inputs from two modalities provide more reliable sensory
93 evidence. We first determined unimodal thresholds for auditory amplitude and visual contrast
94 detection. Subsequently, we combined both modalities and compared psychometric fits and
95 the RTs between all conditions. We used MLE to model psychometric curves and to probe
96 whether ferrets integrate visual and auditory signals in an optimal manner. Furthermore, to
97 test for a redundant signal effect (RSE) we pooled the RT of all animals in order to calculate
98 a race model and to investigate potential intensity- and modality-dependent effects
99 [49,56,57].

100

101 **Materials and Methods**

102 Ferrets were trained in a spatial detection paradigm, which was used to perform two
103 behavioral experiments. In the first experiment, the animals' auditory and visual unisensory
104 detection thresholds were determined. In the second experiment, unimodal and bimodal
105 thresholds were assessed in a combined approach, using the unimodal results from the first
106 experiment to adjust the test parameters.

107 **Animals**

108 Four adult female ferrets (*Mustela putorius*; Euroferret, Dybbølsgade, Denmark), aged 2
109 years (n=2) and 4 years (n=2), from two different litters were tested in the experiment. They
110 were individually housed in a standard ferret cage with enriched environment under
111 controlled ambient conditions (21°C, 12-h light/dark cycle, lights on at 8:00 a.m.). The
112 animals had ad libitum access to food pellets. Access to tap water was restricted 8h before
113 the experiments and the training procedure. All behavioral testing was done during the light
114 cycle between 10:00 a.m. and 2:00 p.m.

115 **Ethics statement**

116 All experiments were approved by the Hamburg state authority for animal welfare (BUG-
117 Hamburg; Permit Number: 22/11) and performed in accordance with the guidelines of the
118 German animal protection law. All sections of this report adhere to the ARRIVE Guidelines
119 for reporting animal research [58].

120 **Experimental setup**

121 The experiments were carried out in a dark sound attenuated chamber to ensure controlled
122 conditions for sensory stimulation. Once per day each ferret performed the experimental task
123 in a custom-build setup (Fig. 1A,D). We crafted a flat-bottomed tube to conveniently house
124 the animal during the experiment. The body of the ferret was slightly restrained by fixation to
125 three points in the tube via a harness, while the head remained freely movable outside the
126 tube throughout the session. The semi-circular tube was fixed on an aluminum pedestal to
127 level the animals' head at 20cm distance to the center of the LED screen used for visual
128 stimulation (BenQ XL2420T, Taipei, Taiwan). On the front ('head side'), two convex
129 aluminum semicircles were mounted horizontally below and above the animals' head,
130 respectively, at 150mm distance. They carried three light-barrier-fibers (FT-FM2), in the
131 center, left and right, respectively, connected to high-speed (sampling interval: 250µs)
132 receivers (FX301, SUNX, Aichi, Japan). This allowed the detection of the animal head during

133 the experiments. In addition, a waterspout was co-localized with each light-barrier source. On
134 both sides of the LED screen a speaker (T1; Beyerdynamic, Heilbronn, Germany) was
135 placed with a 45° angle to the screen surface and at the height of the horizontal screen
136 midline. A custom made 3-channel water-dispenser was installed outside the sound
137 attenuated chamber to avoid acoustical interference during the experiments. It consisted of
138 three valves from SMC Corporation (Tokyo, Japan), a Perfusor syringe (Melsungen,
139 Germany) as water reservoir and Perfusor tubing to connect it with the waterspouts. The
140 setup was controlled by custom-made routines using the Matlab environment (The
141 Mathworks Inc.; MA, USA) on a MacPro. Behavioral control (light-barriers) and reward
142 application (water-dispenser) were triggered through NI-PCI-cards (NI-6259 and NI-6251;
143 National Instruments GmbH, Munich, Germany). The Psychtoolbox and the custom-written
144 NI-mex-function referred to the same internal clock allowing the precise timing of behavior
145 and stimulation.

146 **Figure 1. Experimental setup and behavioral task.** (A) Schematic of the components of
147 the experimental setup in a top view: the LED-screen (a) with a speaker (b) on each side, the
148 aluminum pedestal (d), and the three light-barrier-waterspout combinations (c). The semi-
149 circular acrylic tube with a ferret (e) inside was placed on the pedestal. (B) Successive
150 phases in the detection task: The inter-trial window (I), the trial initialization window (II), the
151 event window (III) and the response window (IV). The three circles below each frame
152 represent the light-barriers (white = unbroken, red = broken). The center of the screen
153 displays a static visual random noise pattern. (C) Schematic of trial timing. When the ferret
154 broke the central light-barrier (II) for 500ms a trial was initialized and the event window
155 started (III), indicated by a decrease in contrast of the static random noise pattern. At a
156 random time between 0-1000ms during the event window the auditory and/or visual stimulus
157 appeared for 100ms either left or right from the center. After stimulus offset the ferret had a
158 response time window between +100-700ms (IV) to pan its head from the central position to
159 the light-barrier on the side of the stimulation. Subsequently, the inter-trial screen (I)
160 appeared again. During the whole session the screen's global luminance remained
161 unchanged. (D) Three-dimensional rendering of the experimental setup. Labeling of the
162 components as in (A).

163

164 **Sensory stimulation**

165 Auditory and visual stimuli were created using the Psychtoolbox (V3) [59] in a Matlab
166 environment (The Mathworks Inc.; MA, USA). A white noise auditory stimulus (100ms) with

167 up to 50dB sound pressure level (SPL) was used for auditory stimulation. It was generated
168 digitally at 96kHz sample rate on a high-end PCI-audio card (HDSPe AES, RME-Audio,
169 Germany) and delivered through two 'T1' Beyerdynamic speakers (Heilbronn, Germany).
170 Visual stimuli consisted of concentric moving circular gratings (22.5° , $0.2\text{cycles}/^\circ$, 5Hz) up to
171 0.38 Michelson contrast (Cm) shown for 100ms (6 frames @ 60 Hz monitor-refresh rate).
172 The background was set to half-maximum luminance to avoid global luminance changes at
173 stimulus onset. In the center of the screen, a static random noise pattern was displayed (7° ,
174 Cm between 0 and 1). During 'bimodal' trials, both visual and auditory stimuli were presented
175 synchronously as described below.

176 **Detection task**

177 The ferrets were trained to solve a spatial detection task, as shown in Figure 1B and C. To
178 initialize a trial the ferret had to maintain a central head position by breaking the central light-
179 barrier for 500ms. This caused the random noise pattern in the center of the screen to
180 decrease contrast and indicate to the animal that the stimulus-window (up to 1000ms) had
181 started. During this interval the animal had to further maintain a central head position. A
182 stimulus was presented for 100ms on the left or on the right side, respectively, starting at a
183 random time in this window. The stimulus could be a unimodal visual (circular grating),
184 unimodal audio (white noise burst) or temporally congruent bimodal stimulus (further details
185 see below). After stimulus offset, the animal had to respond within 600ms by panning its
186 head to the respective side. If the response was correct the animal received a water reward
187 ($\sim 80\mu\text{l}$) at that position and could immediately start the next trial. If the response was too
188 early (before stimulus onset or within 100ms after stimulus onset), incorrect (wrong side) or
189 omitted (no response), the trial was immediately terminated, followed by a 2000ms interval
190 during which no new trial start was allowed.

191 **General procedure**

192 Following the habituation to the harness, tube and setup all ferrets learned to detect
193 unimodal stimuli. Two of the animals were trained in the auditory task first and then the
194 visual; the other two were trained in reverse order. After completion of the training and
195 reaching of sufficient performance, we presented stimuli of both modalities during the same
196 sessions and determined the individual detection threshold. Twenty different stimulus
197 amplitudes (0-50dB SPL; 0-0.38Cm) were chosen in a 1down/3up staircase procedure [60],
198 i.e., if the animal solved the trial correctly (hits) the stimulus amplitude decreased by one step
199 for the next trial, down to the minimum, whereas false responses (misses, or omitted
200 responses) led to a 3 step increase. No change occurred for responses that were issued too

201 early (rash trials). In each trial either the auditory or the visual stimulus was presented in a
202 pseudo-randomized fashion with individual staircases. To avoid a side- or modality-bias,
203 each modality-side-combination was titrated to an equal number of hits within each session.
204 Due to the huge combinatorics of conditions, each ferret had to complete 10-15 sessions to
205 accumulate a sufficient number of trials per amplitude level. The data of each animal were
206 pooled and treated as one sample, i.e., session information was discounted during further
207 analysis. Sensory thresholds were determined by fitting a Weibull function to the data for
208 each ferret individually.

209 In a subsequent set of measurements, we combined simultaneous stimulus
210 presentation in both modalities. To this end, we fixed the stimulus in one modality at the
211 amplitude where the tested animal had an accuracy of 75% during the unimodal testing and
212 varied the amplitude in the other modality according to the staircase procedure described
213 above. In these bimodal sessions we again included the unimodal conditions, such that we
214 obtained four different stimulation classes: unimodal auditory (A), unimodal visual (V),
215 auditory supported by visual (Av), visual supported by auditory (Va). These four stimulation
216 conditions were presented in a pseudo-randomized fashion and separate staircases during
217 the sessions. All ferrets completed 10-12 sessions and the threshold was determined for
218 each ferret by fitting a Weibull function to the data.

219 Data Analysis

220 All offline data analysis was performed using custom written scripts in Matlab (The
221 Mathworks Inc., MA, USA).

222 Psychometrics

223 We evaluated the accuracy values (P) for all N stimulus amplitude classes (a) with at least 6
224 hit trials in total on both sides using equation (1).

$$225 \quad P_a = \frac{N_{a,h}}{(N_{a,o} - N_{a,r})} \quad (1)$$

226 Here, a denotes the amplitude of the stimulus, $N_{a,h}$ (*hit trials*) was defined as the number of
227 correct response trials for stimulus amplitude a , $N_{a,o}$ (*onset trials*) was the number of trials for
228 stimulus amplitude a where the animal reached stimulus onset time, and $N_{a,r}$ (*rash trials*) as
229 the number of trials for stimulus amplitude a where the animal gave a response before the
230 response window had started (up to 100ms after stimulus onset), assuming the animal was
231 guessing and not responding based on sufficiently collected sensory evidence. We estimated
232 the detection threshold by fitting a Weibull function to P_a .

233
$$F_a = 1 - \exp^{-(\lambda a)^k} \quad (2)$$

234 here k signifies the form-parameter and λ represents the scale-parameter. The number of
235 trials were used as weights during the fitting procedure. Due to the fact that every animal had
236 different thresholds in the respective modalities, we calculated the standard deviation of each
237 fit by using a delete-d jackknife method, where $d = 20\%$ corresponds to the number of
238 sessions excluded per run, i.e. 2 or 3, respectively.

239 **Modeling cross-modal interaction**

240 In order to quantify the cross-modal interaction, we used the MLE approach. Therefore we
241 utilized the audio and visual accuracy from the multimodal experiment for all existing stimulus
242 intensities. Assuming a model of a hidden Gaussian representation of the sensory input in
243 the brain we estimated the variance (σ) for all points based on the F_a values from the
244 Weibull function,

245
$$\sigma = \frac{\sigma_0}{\text{inverf}(F_a)} \quad (3)$$

246 where ‘*inverf*’ equates to the inverse error function and σ_0 an unknown scale factor. As in
247 the following calculation of σ_{bi} it drops out we can set it arbitrarily to a value of 1. The next
248 step was to combine both unimodal variances to derive the bimodal variance (σ_{bi}) according
249 to

250
$$\sigma_{bi} = \frac{\sigma_{mod} \cdot \sigma_{fix}}{\sqrt{\sigma_{mod}^2 + \sigma_{fix}^2}} \quad (4)$$

251 where σ_{mod} represents the variance for the modality which intensity were modulated and
252 σ_{fix} for the modality that was fixed at 75% threshold. Subsequently, we used the inverse
253 value of the bimodal variance in an error function (*erf*) to determine the bimodal accuracy (5).

254
$$\text{accuracy}_{bi} = \text{erf}\left(\frac{1}{\sigma_{bi}}\right) \quad (5)$$

255 **Reaction time**

256 The RT was defined as the time difference between stimulus-onset and the time point when
257 the animal panned its head out of the central light-barrier. Only intensity classes with at least
258 6 successful responses (hits) were included in the RT analyses. To quantify the RT

259 differences between the corresponding amplitudes from uni- and bimodal stimulation we
260 computed the Multisensory Response Enhancement (MRE) [49] as follows:

$$261 \quad MRE = \frac{\min(\overline{RT_A}, \overline{RT_V}) - \overline{RT_{AV}}}{\min(\overline{RT_A}, \overline{RT_V})} \quad (6)$$

262 with $\overline{RT_A}$ and $\overline{RT_V}$ referring to the observed mean RT for the auditory and visual stimuli,
263 respectively. $\overline{RT_{AV}}$ is the mean RT for the corresponding bimodal stimulus.

264 We calculated a race model [56] to evaluate potential RSE. In our study, accuracy
265 varied across subjects and sensory conditions. In order to compare reaction times across
266 subjects and compute the race model for all related modality combinations we introduced
267 'subjective intensity classes' (SIC) as determined by the accuracy fit in different unimodal
268 conditions (0-74%, 75-89% and 90-100% indicating low, medium and high performance
269 accuracy, respectively). This ensured a sufficient number of trials per SIC and additionally
270 normalized for inter-individual differences in the range of stimulus amplitudes. Intensity and
271 modality effects on the RT were tested applying the same grouping approach and computing
272 a two-way ANOVA.

273

274 Results

275 Four ferrets were trained in a lateralized audiovisual spatial detection task until they
276 accomplished to solve the detection task in both modalities at high supra-threshold stimulus
277 amplitudes (audio = 50dB SPL, visual = 0.38 Cm). The training was discontinued once the
278 animals showed a stable baseline performance (>90%) across 5 consecutive days with high
279 accuracy levels (audio = 92±1%, visual = 92±1%; mean±SEM). Two of the animals learned
280 first the auditory (26 and 16 days training, respectively) and then the visual task (training for
281 28 days in both animals). The two other ferrets acquired the modalities in the opposite
282 sequence (11 and 19 days for the visual and 14 and 14 days for the auditory modality,
283 respectively). All animals achieved high performance levels demonstrating the viability of the
284 training paradigm.

285 In all experiments for the determination of sensory thresholds we pooled results from
286 left and right stimulation sides to calculate the accuracy values for all amplitudes. Testing for
287 a laterality bias by comparing hit performance on both sides with a paired *t*-test revealed no
288 significant bias (unimodal experiment: all animals = $p > 0.05$; bimodal experiment: all animals
289 = $p > 0.05$).

290 Determination of unimodal thresholds

291 In the first experiment we determined the 75% accuracy threshold for detection of visual and
292 auditory stimuli in a unimodal setting for each individual ferret (Fig. 2), with an individual
293 range of stimulus amplitudes for each animal. Ferrets performed on average 12 (±2)
294 sessions (104±26 trials±SEM/session) in the unimodal experiment. Before pooling the
295 sessions, we tested each ferret for non-stationarity effects across sessions by comparing the
296 variance of the first three sessions at 84% accuracy threshold against the one of the last
297 three sessions. We used three sessions as a minimum to ensure a sufficient number of trials
298 for a proper Weibull function fit. No animal showed a non-stationarity in any modality ($p > 0.05$
299 Two-sample *t*-test, 2-sided). The pooled data could well be described by a Weibull function
300 ($r^2 = 0.56 - 0.92$, Fig. 2).

301 **Figure 2. Detection task performance of the unimodal experiment.** (A) Data for
302 performance in the unimodal auditory detection task. (B) Data for the unimodal visual
303 detection task. Each row represents one animal (1-4). Each dot represents the average
304 performance of *N* trials (diameter) for the tested auditory amplitudes (dB SPL) or visual
305 contrasts (Cm). The data are fitted by a Weibull function. Numbers within the panels indicate
306 the amplitude values corresponding to the 75% and 84% thresholds, respectively. The blue

307 shaded area around the fit indicates the standard deviation. The unmasked parts of the
308 graphs indicate the range of the actually tested stimulus amplitudes.

309 Determination of uni- and bimodal thresholds

310 In the second experiment, the two crossmodal stimulation conditions were added to the
311 sessions. One modality's intensity was fixed at 75% threshold, as determined from the
312 unimodal experiment (Fig. 2) while the other modality was varied in amplitude according to a
313 staircase procedure. All ferrets participated in 12 (± 1) multimodal sessions (111 ± 37
314 trials \pm SEM/session). Like for the unimodal sessions, we again tested for non-stationarity
315 effects between the first and the last sessions by comparing the 84% accuracy threshold
316 variance as determined by the Weibull fit. Since the introduction of bimodal classes reduced
317 the relative number of unimodal stimulus presentations during each session, we had to pool
318 minimum across the first and last 5 sessions, respectively, to generate a proper Weibull fit.
319 No animal showed non-stationarity across the bimodal sessions (2-sided two-sample *t*-test; *p*
320 > 0.05). Subsequently, we calculated the accuracy for each amplitude where at least 6 trials
321 had been performed and the psychometric curves were fit using a Weibull function (Fig. 3).
322 The pooled data could well be described by a Weibull function ($r^2 = 0.39 - 0.90$, Fig. 3).

323 **Figure 3. Detection task performance of the bimodal experiment.** (A) Data for the
324 stimulus conditions auditory-only (A) and auditory stimulation supported by a visual stimulus
325 (Av). (B) Data for the stimulus conditions visual-only (V) and visual stimulation supported by
326 an auditory stimulus (Va). Each row represents one ferret (1-4). Each dot represents the
327 average performance of N trials (diameter) at a given auditory amplitude (dB SPL) or visual
328 contrast (Cm). The data are fitted by a Weibull function. The uni- and bimodal fit is
329 represented by the blue and red line, respectively. The shaded area around the fit indicates
330 the standard deviation. Δ_{84} displays the relative amount of threshold shift of the bimodal
331 compared to the unimodal psychometric function at a performance of 84%. A positive shift
332 indicates a threshold decrease. The black curve represents the MLE model. The unmasked
333 parts of the graphs indicate the range of the actually tested stimulus amplitudes.

334 The comparison of the unimodal 75% thresholds between both experiments revealed a slight
335 increase from the uni- to the multimodal experiment, except in animal 2 which showed a
336 decrease (Table 1). However, the differences were smaller than one of the respective
337 amplitude steps in the staircase procedure. Furthermore, two of the animals (1 and 4) did not
338 reach a performance above $90 \pm 5\%$ in the highest intensities in one modality (audio and

339 visual, respectively). These findings indicate that the bimodal experiments were slightly more
 340 demanding, presumably because four stimulation conditions were presented compared to the
 341 unimodal experiment with only two stimulation conditions.

342 **Table 1. Comparison of threshold values for uni- and bimodal experiments.**

	Amplitude values @ 75%		Amplitude values @ 84%		
	unimodal Exp.	bimodal Exp.	unimodal Exp.	bimodal Exp.	
	A	A	A	A	Av
1	39	40	42	45	41
2	27	30	29	32	26
3	25	28	27	33	31
4	31	31	33	34	25
	V	V	V	V	Va
1	0.08	0.08	0.10	0.10	0.09
2	0.09	0.08	0.11	0.09	0.09
3	0.07	0.10	0.09	0.18	0.12
4	0.15	0.19	0.19	0.25	0.10

343 The amplitude values at the 75% and 84% thresholds (in dB SPL for A and Av; Cm for V and
 344 Va) in the unimodal and bimodal experiments (columns) for all animals (rows 1-4).

345 Because different values were used for the lower bounds in uni- (50%) and crossmodal
 346 (75%) fitting, we employed the 84% threshold for comparison of performance between uni-
 347 and crossmodal settings. All fits to the bimodal psychometric functions showed a left shift
 348 compared to their unimodal complements, except for animal 2 in the V-Va comparison
 349 (amplitude decrease \pm SEM: A-Av = 5.3 \pm 1.5; V-Va = 0.06 \pm 0.03; for absolute values see Table
 350 1). This demonstrates a decrease in detection thresholds in all ferrets, except for animal 2 in
 351 the Va condition where the auditory stimulus had no augmenting effect. For quantification we
 352 calculated the relative shifts at the 84% performance-level between the uni- and bimodal
 353 psychometric fit (Δ_{84} in Fig. 3). A positive number indicates a lower threshold as determined
 354 by the bimodal fit, i.e., an increase in bimodal detection performance. On average, there was
 355 a shift (\pm SEM) of 15 \pm 5%, indicating an effective bimodal integration.

356 Maximum likelihood estimates

357 To investigate whether ferrets integrate the two sensory modalities in a statistically optimal
 358 fashion, we computed a MLE model and compared the r^2 -difference between the empirical
 359 data (Fig. 3, red) and model (Fig. 3, black). The range of the difference $\Delta_{bimodal-MLE}$ was -1 to
 360 49% (mean difference \pm SEM 14 \pm 6). In four cases the MLE matched the bimodal
 361 psychometric function and the difference of the explained variance between the empirical fit

362 (Fig. 3) and the MLE was 10% or less (A1: $\Delta_{Va-MLE} = 8\%$; A2: $\Delta_{Va-MLE} = 2\%$; A3: $\Delta_{Av-MLE} =$
363 1% and $\Delta_{Va-MLE} = -1\%$). For one condition (animal 1: $\Delta_{Av-MLE} = 11\%$) the MLE underestimated
364 the empirical fit at the highest stimulus amplitudes (Fig. 3A). This may be caused by the low
365 unimodal performance at high stimulus amplitudes, since the MLE model depends on the
366 unimodal performance. This argument also holds true for the Va case ($\Delta_{Va-MLE} = 15\%$) of
367 animal 4 (Fig. 3B, bottom panel). If the animal had shown a unimodal performance
368 comparable to that previously measured in the unimodal experiment, the MLE model would
369 be similar to the empirical bimodal fit. In the other two cases the MLE underestimated the
370 empirical fit in the intermediate amplitude ranges (animal 2: $\Delta_{Av-MLE} = 25\%$ and animal 4: =
371 49% , Fig. 3). Overall, the MLE modeling results support the conclusions drawn from the
372 comparison of the 84% performance threshold between uni- and bimodal conditions. The
373 results indicate that ferrets integrated the two modalities as good or even better than
374 predicted by the MLE estimator (Fig. 3).

375 Reaction time analysis

376 One of the most important benefits of multisensory integration is the reduction of RTs for
377 bimodal stimuli compared to unimodal stimulation. The measured RT varied during the
378 multisensory experiment with target amplitude in all modality types. In all stimulus conditions
379 and all animals, RT showed a significant negative correlation with stimulus amplitude (range
380 A: $r = -0.17$ to -0.41 ; V: $r = -0.25$ to -0.45 ; Av: $r = -0.21$ to -0.44 ; Va: $r = -0.34$ to -0.46 ; all
381 correlations: $p < 0.01$; Fig. 4). RT significantly increased with decreasing amplitude (ANOVA
382 $p < 0.05$) in all but one condition (animal 1: audio-alone, ANOVA $p > 0.05$). This is an
383 expected finding, because the signal-to-noise ratio (SNR) decreases with decreasing
384 stimulus amplitude and the internal signal processing is slower for low SNR.

385 **Figure 4. Reaction time data from the bimodal experiment.** (A) Data for the stimulus
386 conditions auditory-only (A) and auditory stimulation supported by a visual stimulus (Av). (B)
387 Data for the stimulus conditions visual-only (V) and visual stimulation supported by an
388 auditory stimulus (Va). Each row represents one ferret (1-4). RT \pm SEM are shown as a
389 function of stimulus amplitude (red = bimodal, blue = unimodal). Each data point represents
390 the RT average for all hit trials recorded at that amplitude. Asterisks indicate significant
391 differences between uni- and bimodal conditions (t -test: * = $p < 0.05$, ** = $p < 0.01$, *** = $p <$
392 0.001). Below each pair of uni- and bimodal RTs the Multisensory Response Enhancement
393 (MRE) is shown as numerical values. In each panel, Pearson correlation coefficient and

394 regression line for both data sets are shown. The two vertical lines mark the borders between
 395 the subject intensity classes (left of first line: 0-74%, between the lines 75-89%; right of the
 396 second line 90-100% performance).

397 To reduce the dimensionality and compare reaction times across subjects we used
 398 'subjective intensity classes' (SIC) (see Material and Methods). To quantify RT changes
 399 reflecting potential multimodal enhancement effects, we calculated the MRE for all uni- and
 400 bimodal stimulus pairs and summed these according to the SICs. The average MRE of both
 401 modalities was slightly positive ($A_v = 3.59\%$; $V_a = 0.06\%$). However, about one-third of the
 402 cases (7 out of 24, Table 2) showed a negative MRE. Such negative MRE values, which
 403 indicate that the average unimodal RT is faster than the average RT of the bimodal condition,
 404 occurred only in the low and medium SIC. In the highest SIC, the MRE was consistently
 405 positive. Overall, the MRE results suggest a multimodal enhancement effect in the high and
 406 medium and an interfering effect in the lower SIC.

407 **Table 2. Reaction time: average MRE.**

	0-74%	75-89%	90-100%	0-74%	75-89%	90-100%
	MRE A_v			MRE V_a		
1	-6.00	4.33	8.00	1.00	-0.67	2.22
2	5.50	6.33	5.50	-20.50	-19.00	4.40
3	-9.40	-3.00	3.63	-18.75	3.00	8.50
4	15.00	4.00	9.20	10.00	12.50	18.00

408
 409 Multisensory Response Enhancement (MRE) computed for the RTs from all animals (rows)
 410 and stimulus conditions of the bimodal experiment according to equation 6. (see Methods).
 411 The MRE's were sorted by the subjective intensity classes (SIC; columns from left to right).
 412 A_v : auditory supported by visual; V_a : visual supported by auditory.

413 To investigate a potential RSE we calculated a race model on the pooled RTs
 414 according to the SICs. The race model assumes that during multimodal stimulation no
 415 modality integration happens, but that signals of either modality are processed
 416 independently. Whichever of the two leads to a result first triggers and determines the
 417 response, i.e., the head movement towards the detected stimulus. Therefore, the bimodal
 418 cumulative distribution function (CDF) of the RT can be modeled by sampling from the
 419 unimodal RT CDFs. Afterwards the modeled bimodal RT CDF can be compared with the
 420 empirical bimodal RT CDF (see Fig. 5). If the empirical RT CDF is faster in 20-50% of the
 421 percentiles compare to the modeled RT CDF the race model can be rejected and modality

422 integration is suggested [61]. For a detailed explanation of the race model see Ulrich et al.
423 [56].

424 **Figure 5. Race model example.** Analysis of RT CDFs from animal 4. High visual SIC CDFs
425 are shown for unimodal visual stimulation (V, blue), auditory stimulation at 75% (A75%,
426 green), auditory stimulus supported by visual stimulation (Av, red) and the combination of
427 both unimodal CDFs (V+A75%, black). In this case the race model gets rejected, because
428 the empirical bimodal CDF (red) is 'faster' than the modeled CDF (black).

429 We computed the relative (%) deviation from the linear unimodal combination for all
430 stimulus conditions (Fig. 6) for each SIC. If this difference for the empirical bimodal CDF is in
431 20-50% of the cases negative the race model can be rejected (Miller and Ulrich, 2003). The
432 biggest effect of the supportive value occurred in the highest intensity group, because there
433 the change was negative compare to the combined unisensory CDF in the lower percentiles
434 (upper row, Fig. 6). In the 75-89% SIC no percentile of the crossmodal combinations was
435 negative (middle row Fig. 6) and in the lowest intensity-group the bimodal and the supportive
436 value RTs were similar (bottom row Fig. 6), i.e., the benefit of the redundant signal seems to
437 diminish with decreasing intensity group. However, in the medium and high performance
438 classes the bimodal RT seemed to be closer to the combined CDF than each of the unimodal
439 distributions. For the high SICs, the distributions suggest that the race model can be rejected
440 at a descriptive level. Overall, these results are compatible with the notion that, for higher
441 SICs, multisensory integration processes are leading to RT gains beyond what can be
442 predicted from the fastest unimodal responses.

443 **Figure 6. Reaction time: race model results.** The RTs were sorted by the SICs (rows) and
444 both modalities (A: audio, B: visual) pooled across all animals. The X-axis displays the
445 cumulative reaction time differences to the race model for each modality (\pm SEM). A value of
446 0 at the X-axis corresponds to the prediction from the combination of both unimodal CDF's.
447 The blue curve displays the unimodal condition, the green curve the RTs at the supportive
448 value and the red curve the bimodal class, respectively.

449 To investigate intensity, modality and interaction effects on a more global scale we
450 pooled the RT of all animals according to subjective intensity classes and calculated a two-
451 way ANOVA, with modality and intensity as main factors (Fig. 7). This revealed main effects
452 in both factors (Modality: $F(3, 4632) = 18.84$ ($p < 0.001$); Intensity: $F(2, 4633) = 310.65$ ($p <$

453 0.001)) and an interaction effect (Modality*Intensity: $F(6, 4624) = 3.93$ ($p < 0.01$)). A post hoc
454 t -test (Holm-Bonferroni corrected) revealed significant differences between and within
455 performance classes (Fig. 7), respectively. The post hoc t -tests between the intensity groups
456 and modalities were all highly significant ($p < 0.001$). This result suggests that the ferrets'
457 RTs increase as the intensity of the stimulus gets weaker and significantly decrease in the
458 multimodal compared to the unimodal classes.

459 **Figure 7. Reaction time: two-way ANOVA results.** The reaction times (RT) pooled by
460 subjective intensity classes (0-74%, 75-89%, 90-100%). The X-axis displays the three
461 performance classes and the Y-axis shows the RT in milliseconds \pm SEM. The solid lines
462 represent the unimodal, the dashed lines the bimodal, red indicates the audio and blue the
463 visual modalities (*: $p < 0.05$; **: $p < 0.01$; ***: $p < 0.001$; Holm-Bonferroni corrected). +++,
464 significant differences between performance classes within each modality (Holm-Bonferroni
465 corrected); red and blue asterisks, significant differences between uni- and bimodal
466 conditions in one performance class (Holm-Bonferroni corrected); green asterisk, significant
467 difference between the two unimodal conditions.
468

469 Discussion

470 How information from different modalities is integrated has been a subject of intense
471 research for many years. Here we asked if ferrets integrate sensory signals according to the
472 same principles established for other species [31,33,35–39,47,62,63]. We expected the
473 ferrets to perform more accurately and with lower RTs in the bimodal cases, because
474 congruent inputs from two modalities provide more reliable sensory evidence [62,64–66]. As
475 predicted, bimodal detection thresholds were reduced and RTs were faster in the bimodal
476 compared to unimodal conditions, demonstrating multimodal integration effects. Furthermore
477 our results on MLE modeling suggest that ferrets integrate modalities in a statistically optimal
478 fashion.

479 Methodological considerations

480 Previous studies in behaving ferrets have used either freely-moving [1,13,15,55] or head-
481 restrained [26] animals. Here, we developed a head-free, body-restrained approach allowing
482 a standardized stimulation position and the utilization of the ferret's natural response
483 behavior. The setup is especially suited for psychometric investigations because the distance
484 between animal and the stimulus sources remains constant across trials. The high inter-trial-
485 consistency and the fixed animal position allow the combination of behavioral protocols with
486 neurophysiological recordings comparable to head-restrained approaches [26]. An additional
487 advantage is the usage of a screen instead of a single light-source for the visual stimulation
488 [1,31], enabling the spatially flexible presentation of a broad variety of visual stimuli. Similar
489 to other ferret studies [13,55], one limitation of our approach lies in the relatively low number
490 of trials collected per session. We therefore had to pool data from different sessions to obtain
491 a sufficient number of trials for the fitting of psychometric functions. Merging of sessions was
492 justified by the absence of non-stationarity effects and the high amount of variance explained
493 by the fits. This also indicates a low day-to-day variability of perceptual thresholds. Our
494 results complement that of an earlier study in ferrets demonstrating that measured thresholds
495 were not affected by trial-to-trial fluctuations in the animals' decision criterion [1]. Overall,
496 these findings suggest that the experimental design presented in this study is well suited for
497 psychophysical investigations.

498 Establishing links across species, our behavioral paradigm was inspired by previous
499 human psychophysical studies which showed that temporally congruent crossmodal stimuli
500 enhance detection [62,64–66]. Frassinetti et al. [62] adopted an animal approach [51] to
501 humans and obtained similar results in terms of multisensory enhancement effects. Another

502 study from Lippert and colleagues [64] showed that informative congruent sounds improve
503 detection rates, but this gain disappears when subjects are not aware of the fact that the
504 additional sound offers information about the visual stimulus. They concluded that cross-
505 modal influences in simple detection tasks are not exclusively reflecting hard-wired sensory
506 integration mechanisms but, rather, point to a prominent role for cognitive and contextual
507 effects. This contrasts with more classical views suggesting that information from different
508 sensory modalities may be integrated pre-attentively and substantially rely on automatic
509 bottom-up processing [35]. Our observation of the inter-experiment threshold increase for the
510 unimodal conditions might suggest possible contextual effects. A possibility is that, in the
511 second experiment, the inclusion of the bimodal conditions may have created a contextual, or
512 motivational, bias of the animals towards solving the bimodal trials because more sensory
513 evidence was provided. This could also explain why the performance in the unimodal
514 conditions of the bimodal experiment did not reach 95-100% accuracy even at the highest
515 intensities, unlike in the unimodal experiment.

516 Taken together, our study demonstrates that the implemented behavioral paradigm is
517 suitable to determine uni- and bimodal thresholds and to operationalize multisensory
518 integration processes. Possible contextual and attention-like effects seem hard to elucidate
519 by pure psychometrics, but simultaneous electrophysiological recordings could provide
520 valuable insights into the underlying brain processes during the task.

521 **Optimal modality integration**

522 This is the first study on behaving ferrets to quantify multimodal enhancement effects and to
523 test for optimal modality integration. The results of our bimodal experiment show clear
524 multisensory enhancement effects. The left shift of the psychometric function and the
525 variance reduction, derived at 84% accuracy, demonstrate increased detection rates and
526 enhanced reliability for lower test-intensities in the bimodal stimulation conditions, indicating
527 that the ferrets indeed integrate information across modalities as shown for other species
528 [31,35,37,47,54,63–65]. MLE modeling is typically used in multisensory integration to test the
529 hypothesis that the integrative process is statistically optimal by fitting the parameters of the
530 model to unisensory response distributions and then comparing the multimodal prediction of
531 the model to the empirical data. Studies on humans have shown that different modalities get
532 integrated in a statistical optimal fashion. For example, Battaglia et al. [37] found that human
533 subjects integrate audio and visual modalities as an optimal observer. The same is true for
534 visual and haptic integration [36], and integration of stereo and texture information [39,67].
535 Furthermore, Alais and Burr [38] could show that the ventriloquist effect is based on near-
536 optimal sensory integration. Rowland and colleagues showed statistical optimal integration in

537 the cat for audio-visual perception [63] and Gu et al. [47] could demonstrate the same
538 principle in macaques for visual and vestibular sensory integration. Similar to the
539 abovementioned studies, our results on MLE modeling suggest that ferrets integrate
540 modalities in a statistically optimal fashion. Surprisingly, in two of our cases the MLE
541 underestimates the empirical fit, which is counterintuitive because the MLE provides already
542 the maximum estimate. A potential explanation might be that multisensory benefit is larger
543 for some modalities compared to others, as suggested by the modality precision hypothesis
544 by Welch and Warren [68]. These hypotheses states that discrepancies are always resolved
545 in favor of the more precise modality, i.e. the modality with the highest SNR gets weighted
546 higher in the final sensory estimate. Battaglia and coworkers [37] showed that humans have
547 a bias towards the visual modality in a multisensory spatial detection task. Finally, it could be
548 caused by a low unimodal performance in the intermediate intensities since the MLE model
549 depends on the unimodal performance. In summary, the MLE model provides evidence that
550 ferrets merge modalities in a near-optimal fashion, similar to other species [36–38,47,67].

551 **Multisensory response enhancement**

552 In a second analysis approach we compared RTs of the uni- and bimodal stimulation
553 conditions and computed a race model to test a RSE. Our main results are in line with
554 findings from other species. Previous work in humans revealed that subjects respond faster
555 to bimodal compared to unimodal stimuli [49,64]. Miller [53] showed that this RT gain is a
556 result of a modality integration effect and not only a product of the fastest processed
557 modality. Gleiss and Kayser [31] demonstrated that additional non-informative white noise
558 decreases RT in a visual detection task in rats. The effect size of the RT gain increased
559 when the light intensity decreased. In our study the influence of amplitude on RT is directly
560 related to the SNR, i.e., the internal signal processing is faster for high SNR. For high
561 intensities of the varying modality (>75% unimodal performance), the SNR should be higher
562 compared to the fixed supporting modality. Decreasing the intensity of the variable modality
563 leads to a continuous decrease of its SNR (until 0), such that for low intensities the RT is
564 completely determined by the amplitude of the supporting modality. Interestingly, some MRE
565 values were negative in the lower and intermediate subjective intensity classes. This is due
566 to the fact that the MRE model uses the fastest unimodal RT for calculation and the RT of the
567 supporting values is faster than the average bimodal RT. The variable modality seems to
568 have a competitive effect on the RT at low intensities, because the average bimodal RT is
569 slower than the RT of the supportive value.

570 In addition to the MRE analysis, we computed a race model for the RT data. The race
571 model tests RT effects in a more sophisticated way, by comparing a modeled bimodal RT

572 CDF with the empirical bimodal RT CDF. In our dataset, the benefit of the redundant signal
573 increased from low to high SIC. Data reached the criterion to reject the race model only in the
574 high SIC. In the intermediate and low SIC the linear unimodal combination was faster
575 compared to the empirical bimodal conditions. Nevertheless, in the intermediate SIC the
576 bimodal percentiles were closer to the linear combination than the unimodal groups,
577 indicating a minor gain of the supportive value and therefore a multisensory enhancement
578 effect. In contrast, in the low SIC the bimodal group matches the supporting value group,
579 implying that the supportive value is the driving modality in the sensory process [57,61].

580 **Conclusions**

581 In conclusion, our data demonstrate that basic principles of multisensory integration, such as
582 enhancement effects of bimodal stimuli on detection rates, precision and RT apply to
583 crossmodal processing in the ferret brain. The race model and MLE modeling provide
584 evidence that ferrets integrate modalities in a statistically optimal fashion. To quantify this in
585 more detail more advanced behavioral paradigms would be required where the stimulus
586 onset varies across modalities and a broader range of stimulus amplitudes of supporting
587 modality can be covered.

588 The setup we have developed to test ferrets in uni- and bimodal conditions is similar
589 to human and non-human primate tasks, and can be combined in future research with
590 approaches for the study of the underlying neural processes. Our behavioral paradigm could
591 be combined with neuroscientific approaches such as, e.g., optogenetics or *in vivo* imaging
592 [69]. Furthermore, the same setup could be used to implement more complex behavioral
593 paradigms such as discrimination or go/no-go tasks [26]. Moreover, the setup would also be
594 suitable to investigate aspects of sensory processing other than multisensory integration
595 relating, e.g., to altered developmental conditions [7,12,24], to top-down influences on
596 sensory processing, or to large-scale communication across distinct sensory regions during
597 different behavioral paradigms. Altogether, our results describe a highly multifunctional
598 experimental approach, which may further enhance the viability and suitability of the ferret
599 model.

600

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604

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790 **Supporting Information**

791 **S1 ARRIVE Guidelines.** Completed “ARRIVE Guidelines Checklist” for reporting animal data
792 in this manuscript.

793 **S2 Dataset. Raw data of the unimodal detection task for all animals.**

794 **S3 Dataset. Raw data of the multimodal detection task for all animals.**













